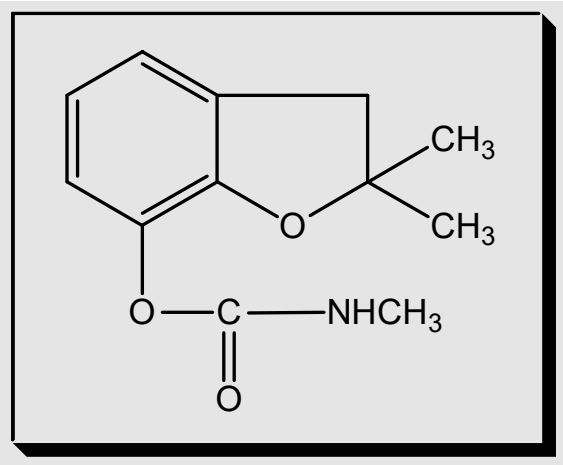
RISK CHARACTERIZATION DOCUMENT

CARBOFURAN



Medical Toxicology Branch
Department of Pesticide Regulation
California Environmental Protection Agency

January 23, 2006

CONTRIBUTORS AND ACKNOWLEDGMENTS

Primary author:	Andrew L. Rubin, Ph.D., D.A.B.T. Staff Toxicologist Health Assessment Section Medical Toxicology Branch
Secondary author: (Environmental Fate section only)	Summer Evert Environmental Monitoring Branch
Toxicology reviews:	Marilyn Silva, Ph.D., D.A.B.T. Charles Aldous, Ph.D., D.A.B.T. Staff Toxicologists SB 950 Data Review Section Medical Toxicology Branch Joyce Gee, Ph.D. Senior Toxicologist SB 950 Data Review Section Medical Toxicology Branch
Exposure assessment:	Sheryl Beauvais, Ph.D. Staff Toxicologist Exposure Assessment Group Worker Health and Safety Branch Josh Johnson, M.A. Associate Environmental Research Scientist Exposure Assessment Group Worker Health and Safety Branch
Peer reviews:	Keith Pfeifer, Ph.D., D.A.B.T. Senior Toxicologist Health Assessment Section Medical Toxicology Branch Jay Schreider, Ph.D. Primary State Toxicologist Medical Toxicology Branch

The advice of Dr. Nu-may R. Reed regarding the hazard identification and risk characterization aspects of this document, as well as that of Drs. Svetlana Koshlukova and Nu-may R. Reed regarding the dietary assessment, is gratefully acknowledged. We are also grateful to the Office of Environmental Health Hazard Assessment, Cal-EPA, for their review of this document.

TABLE OF CONTENTS

CONTRIBUTORS AND ACKNOWLEDGMENTS i

I. SUMMARY 1

II. INTRODUCTION 10
- A. CHEMICAL IDENTIFICATION 10
- B. REGULATORY HISTORY 10
- C. TECHNICAL / PRODUCT FORMULATIONS 11
- D. USAGE 11
- E. ILLNESS REPORTS 11
- F. PHYSICO-CHEMICAL PROPERTIES 12
- G. ENVIRONMENTAL FATE 13
  - 1. Air 13
  - 2. Water 14
  - 3. Soil 14
  - 4. Biota 16

III. TOXICITY PROFILE 19
- A. PHARMACOKINETICS 19
  - 1. Overview 19
  - 2. Absorption (oral exposure) 19
  - 3. Distribution (oral exposure) 21
  - 4. Biotransformation (oral exposure) 21
  - 5. Excretion (oral exposure) 22
  - 6. Special studies 22
    - a. Inhalation exposure 22
    - b. Dermal penetration 23
    - c. Enterohepatic circulation and conjugation 24
    - d. Metabolism in lactating animals 24
    - e. Enzymes involved in carbofuran metabolism 27
    - f. Formation of *N*-nitroso carbofuran 27
- B. ACUTE TOXICITY 31
  - 1. Overview 31
  - 2. Human studies (controlled exposures) 31
  - 3. Human studies (poisoning incidents) 33
  - 4. Laboratory animal studies 34
    - a. Technical carbofuran 34
    - b. Carbofuran formulations 37
- C. SUBCHRONIC TOXICITY 41
  - 1. Overview 41
  - 2. Laboratory animal studies 41
    - a. Rat - dietary 41
    - b. Mouse - dietary 41
    - c. Rabbit - dermal 42
    - d. Dog - dietary 43

D. CHRONIC TOXICITY AND ONCOGENICITY 46
1. Overview 46
2. Human studies (epidemiology) 46
3. Laboratory animal studies 47
a. Rat - dietary 47
b. Mouse - dietary 49
c. Wild mouse - dietary 50
d. Dog - dietary 51
E. GENOTOXICITY 57
1. Overview 57
2. Gene mutation 57
3. Chromosomal aberrations 57
4. DNA damage 58
5. Genotoxicity and cytotoxicity of *N*-nitrosocarbofuran 58
F. REPRODUCTIVE TOXICITY 64
1. Overview 64
2. Laboratory animal studies 64
a. Rat - dietary 64
b. Rat - gavage 64
c. Rabbit - gavage 67
d. Rat - dietary 68
e. Mouse - gavage 68
G. DEVELOPMENTAL TOXICITY 69
1. Overview 69
2. Human studies (poisoning incidents) 69
3. Laboratory animal studies 70
a. Rat - gavage 70
b. Rat - dietary 71
c. Rat - gavage 72
d. Rat - gavage 75
e. Rat and mouse - gavage 80
f. Rabbit - gavage 81
H. NEUROTOXICITY 83
1. Overview 83
2. Human studies (poisoning incidents) 83
3. Laboratory animal studies 83
a. Rat - dietary 83
b. Rat (developmental neurotoxicity) - dietary 83
I. MISCELLANEOUS STUDIES 87
J. TOXICITY OF CARBOFURAN METABOLITES 89
1. Overview 89
2. 3-OH-carbofuran 89
3. 3-keto carbofuran 90
4. 7-phenol 90
5. 3-OH-7-phenol 90
6. 3-keto-7-phenol 90

IV. RISK ASSESSMENT 92
A. HAZARD IDENTIFICATION 92
1. Non-oncogenic effects 92
a. Acute toxicity 92
b. Subchronic toxicity 95
c. Chronic toxicity 96
2. Oncogenicity 97
B. EXPOSURE ASSESSMENT 97
1. Overview 97
2. Occupational exposure 98
a. Handlers 98
b. Fieldworkers 102
3. Ambient air exposure 103
4. Application site (bystander) air exposure 104
5. Dietary exposure 105
a. Introduction 105
b. Consumption data and dietary exposure 105
c. Exposure to carbofuran in food 106
d. Residue data sources 107
e. Acute exposure 108
f. Chronic exposure 110
C. RISK CHARACTERIZATION 121
1. Overview 121
2. Occupational exposure 122
a. Handlers 122
b. Fieldworker reentry scenarios 123
3. Ambient air exposure 124
4. Bystander (application site) exposure 125
5. Dietary exposure 125
a. Acute risk estimation - deterministic and distributional approaches 125
b. Chronic risk estimation 126
6. Aggregate exposure 126

V. RISK APPRAISAL 129
A. HAZARD IDENTIFICATION 129
1. Acute toxicity 129
a. Oral and inhalation exposure 129
b. Dermal exposure 131
2. Subchronic toxicity 131
a. Oral and inhalation exposure 131
b. Dermal exposure 132
3. Chronic toxicity 132
a. Oral exposure 132
b. Dermal exposure 133

B. EXPOSURE ASSESSMENT 133
1. Occupational and resident / bystander exposure 133
2. Dietary exposure 135
a. Parameter uncertainty 135
b. Model uncertainty 136
c. Scenario uncertainty 137
C. RISK CHARACTERIZATION 137
D. CRITICAL TOXICITY ENDPOINTS - USEPA *vs.* DPR 138

VI. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT 140

VII. REFERENCE DOSES AND CONCENTRATIONS 141
A. REFERENCE DOSES (RfDs) - oral exposures 141
B. REFERENCE CONCENTRATIONS (RfCs) - inhalation exposures 142

VIII. TOLERANCE ASSESSMENT 145
A. ACUTE EXPOSURE 145
B. CHRONIC EXPOSURE 146

IX. CONCLUSIONS 148

X. REFERENCES 151

Attachment I. Benchmark dose calculations for chewing behavior incidence in pregnant females (WARF, 1978a) 163

Attachment II. Benchmark dose calculations for teeth grinding incidence in females (FMC, 2002) 168

Attachment III. DEEM Acute Point Estimate Dietary Exposure Assessment 171

Attachment IV. DEEM Acute Distributional (Monte Carlo) Dietary Exposure Assessment . . 193

Attachment V. Chronic Dietary Exposure Estimate 217

APPENDIX I. Estimation of exposure of persons in California to pesticide products that contain carbofuran (HS-1803) 220

I. SUMMARY

Carbofuran (2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate; MW, 221.26) is a broad spectrum, systemic insecticide, acaricide and nematicide. It is used in a wide variety of crops against a large number of target species. As a member of the carbamate class of pesticides, the action of carbofuran is largely based on its ability to inhibit acetylcholinesterase (AChE) in the nervous system and motor endplates of the target species. Carbofuran's toxicity in mammalian systems is also based on this property, though other mechanisms of toxicity may be operative. Carbofuran inhibits other cholinesterases (ChEs) besides nerve-localized AChE, including the plasma-localized butyryl ChE and the red blood cell-localized AChE.

Carbofuran became available for agricultural use in 1968. By the 1980s and early 1990s it was clear that soil-applied granular formulations were responsible for numerous bird kill incidents. As a result, the USEPA and FMC, the manufacturer, agreed to ban all granular carbofuran formulations. The ban was effective in September 1994 following a special review, though some uses on rice were permitted until August 1999. Liquid formulations remain in use throughout the country. They are classified as Restricted Use Pesticides due to their toxicity to humans by the oral and inhalation routes. At the time of this report, only a single product, Furadan 4F (a 44% liquid concentrate), is registered for use in California.

Between 1992 and 2003, a total of 77 reports of illnesses, injuries, or death associated with exposure to carbofuran, alone or in combination with other pesticides, were received by DPR's Pesticide Illness Surveillance Program (PISP). Sixty nine of the 77 cases were systemic in nature, with complaints of nausea, vomiting, abdominal cramps, headache, and dizziness. The other eight incidents comprised injuries or irritation to eyes, skin or throat. There were two reported cases of hospitalization, one in 1994 and one in 1998, and 37 cases involving disability ranging from one to twenty-eight days. A single reported death in 1999 followed ingestion of carbofuran; no other deaths are known to have been associated with carbofuran exposures in California.

Pharmacokinetics

Hydroxylation (oxidation) and hydrolysis, along with polar conjugations, comprise the major metabolic transformations of carbofuran, creating esters or ester cleavage products. In the rat, data using carbonyl-^{14}C-carbofuran indicate rapid absorption by the oral route, followed by carbamate hydrolysis and excretion, either through the lungs ($^{14}CO_2$) or through the urine and feces. The data using ring-^{14}C-carbofuran indicate rapid excretion, predominantly in urine. One bile cannulation study demonstrated carbofuran entry into the enterohepatic circulation. In this manner, appreciable cholinesterase inhibiting activity is maintained in the blood after the disappearance of the parent molecule.

In the most informative study to date, single doses of carbonyl-^{14}C-carbofuran (0.4 mg/kg) or ring-^{14}C-carbofuran (4 mg/kg) were administered orally to rats. By 24 hours, 43.4% of the administered carbonyl-^{14}C-carbofuran dose had appeared as $^{14}CO_2$, suggesting that hydrolysis of the carbamate ester bond was relatively rapid. At 32 hours, this proportion was 44.6%, remaining stable at that level through 120 hours. Urine accounted for 36.8% and 38.4% of the dose at 24 and 32 hours, respectively, while 1.9% and 2.4% of the dose appeared in feces. Thus by 24 hours, 82.1% of the administered carbonyl-^{14}C-carbofuran had been excreted. By 32 hours excretion had risen to 85.6% and by 120 hours to 87.4%. The urinary and expired air data indicated that oral carbofuran was rapidly absorbed. A similar conclusion was suggested by the

ring-^{14}C-carbofuran data: 74.5% of the dose had been excreted by 24 hours (72.2% in the urine, 2.3% in the feces), 90.1 % by 32 hours (87.7% in the urine, 2.4% in the feces), and 94.9% by 120 hours (91.6% in the urine, 3.3% in the feces). Tissue analysis conducted at 1, 2, 4 and 8 hours after exposure to 4 mg/kg ring-^{14}C-Furadan showed, at 1 hour, the highest proportions of radioligand in the liver (1.43 ppm/mg dry weight), followed by blood (0.47 ppm/mg), kidney (0.38 ppm/mg), brain (0.30 ppm/mg), leg muscle (0. 19 ppm/mg) and bone (0.08 ppm/mg). By 8 hours, notable declines had occurred. The liver still contained the greatest quantity of radioligand at that time (0.78 ppm/mg), followed by blood (0.30 ppm/mg), kidney (0.14 ppm/mg), brain (0.09 ppm/mg), leg muscle (0.06 ppm/mg) and bone (0.06 ppm/mg).

One study investigated the possibility that *N*-nitrosocarbofuran could be formed in the stomach. This mutagenic and cytotoxic derivative was formed more readily in the guinea pig stomach, with its pH of 1-2, than in the rat stomach, with its pH of 3-5. As the guinea pig stomach pH approximates that of the human, formation of this mutagenic derivative is considered plausible.

Dermal penetration. As dermal exposure to carbofuran was the predominant occupational exposure route, it was important to determine the extent of penetration. Percutaneous penetration of ring-labeled carbofuran in young and adult rats was studied at 4 dose levels, 28, 285, 535 and 2680 nmol/cm^2, applied to ~2.3% of the body surface area. Absorption at 285 nmol/cm^2, the only dose at which timed measurements were made, was 5.2% and 2.2% in young and adult animals, respectively, at 6 hours, and 43.0% and 17.8% at 120 hr. In both age groups the bulk of the applied dose remained at the treatment site, even after 120 hr. The absorption $T_{O.5}$ was 128 hours for the young and 400 hours for the adult animals. In general, penetration in young animals was ~3-fold higher than that in adults. More than 75% of the absorbed dose was excreted in the urine by 6 hours in both groups. By 120 hours, 40% and 17% of the total applied dose was excreted in the urine in young and adults. Corresponding fecal excretion was 2.3% and 0.4%. Because of the rapid excretion, only very low amounts of radioligand were detected in tissues. The maximum tissue load was about 1% of the dose in the young and 0.4% in adults, measured at 6 and 24 hours. In general, kidneys had the highest levels among the tissues tested. Dose had a large effect on the fraction of carbofuran absorbed. Percent absorption in young animals at 72 hours was 24.5%, 36.3%, 9.2% and 3.7% at increasing doses. In adults it was 83.4%, 13.0%, 8.3% and 6.0%. The Worker Health and Safety Branch of DPR determined that this study did not adequately characterize the extent of dermal penetration for the purposes of risk assessment. Consequently, they adopted a default value of 50% absorption in order to estimate human systemic doses by the dermal route.

Hazard identification

Acute toxicity, oral. The acute toxicity of carbofuran is thought to result largely from its ability to carbamylate, and thus inhibit, acetyl cholinesterase (AChE) at synapses and neuromuscular junctions. Consequent local accumulations of acetylcholine (ACh) generate a plethora of cholinergic signs and symptoms. Due to the reversibility of the carbamate-AChE bond, recovery is expected when exposures are low. However, higher levels of carbofuran exposure can lead to death by respiratory failure.

An acute regulatory LED_{05} value (the lower bound on the effective dose at the 95% confidence limit) of **0.01 mg/kg** (ED_{05}=0.02 mg/kg), was derived using benchmark dose methodology. This value was used in this analysis to characterize acute risk after oral, dermal and inhalation exposure to carbofuran. It was calculated from maternal incidence data in a developmental toxicity study conducted in CD rats. Statistically significant, dose-dependent induction of

chewing behavior in pregnant dams was observed at doses as low as the low dose of 0.1 mg/kg. The acute nature of this sign was explicit in the study report. Other signs, including lacrimation, pale eyes, increased salivation, rough coat, trembling and convulsions, were seen in several animals at the high dose of 1 mg/kg. Lethargy was observed at both the mid dose of 0.3 and at the high dose. Except for the chewing behavior, the report did not indicate if the latter signs were acute responses. However, recognizing that the exposure regimen was for 10 days only (gestation days 6-15), it is apparent that these signs also resulted from short term, if not strictly acute, exposures.

Support for this critical LED_{05} determination came from at least two other studies. Pregnant female Wistar rats exposed by daily gavage to 0.2 mg/kg carbofuran (low dose) on gestation days 1-5 exhibited statistically significant, dose-dependent decreases in number of rears, locomotive activity, and number of head dips on day 5. Application of benchmark dose methodology to both the head dip and locomotor activity data resulted in LED_{05} and ED_{05} values of 0.01 and 0.02 mg/kg, respectively, precisely the same as those obtained in the critical CD rat developmental toxicity study. In a study in CD rats, clinical signs, including teeth grinding and possible slight tremors were recorded at a low dose of 0.5 mg/kg after acute oral gavage.

Acute toxicity, inhalation. There was insufficient observational detail from the acute inhalation toxicity studies to establish a critical inhalation no-observed-effect-level (NOEL). Acute inhalation risk was thus gauged by the critical oral LED_{05} of 0.01 mg/kg.

Acute toxicity, dermal. One human dermal toxicity study was reviewed for this document. It was found to be inadequate for risk assessment purposes. Nonetheless, evidence from that study indicated that humans may be substantially more sensitive by the dermal route than rabbits, for which an acceptable 21-day repeat-dose dermal study was available. On this basis it was decided that the potential for dermal toxicity should be evaluated using the health-protective rat critical oral LED_{05} of 0.01 mg/kg, which was lower than the lowest dose at which RBC cholinesterase inhibition was noted in the human study (0.5 mg/kg) or at which overt toxicity was noted (4 mg/kg).

Subchronic toxicity, oral. The critical subchronic oral NOEL was set at 0.1 mg/kg/day based on testicular toxicity and suppression of body weight gain in Druckrey rats. These animals were subjected to gavage dosing with carbofuran for 60 days at a LOEL dose of 0.2 mg/kg/day. The testicular toxicity was manifested as reductions in the absolute and relative weights of epididymides, seminal vesicles, ventral prostate and coagulating gland, reduced epididymal sperm motility and counts, morphologic sperm abnormalities, changes in testicular enzyme levels, vacuolization of Sertoli cells and spermatids, and testicular congestion. Higher doses caused even more severe responses.

Subchronic toxicity, dermal. No adequate subchronic dermal study was available to derive a critical NOEL. The critical subchronic oral NOEL of **0.1 mg/kg/day**, based on testicular effects in rats in the 60-day study, was substituted for a subchronic dermal NOEL in the risk calculations.

It might be argued that the rabbit 21-day repeat dose dermal study discussed above offered a more appropriate critical subchronic NOEL, particularly as it was route specific. However, evidence presented above suggested that the rabbit was not as sensitive as the human to the adverse effects of carbofuran by the dermal route, and thus may be inappropriate to use in a carbofuran risk assessment. In addition, the strong evidence for testicular effects in the oral

study made it unwise to ignore the possibility of such effects by the dermal route. The rabbit 21-day study did not address the possibility of male reproductive pathology.

Chronic toxicity. Risks from chronic oral and dermal exposure to carbofuran were evaluated using the rat subchronic oral NOEL value of **0.1 mg/kg/day** (see above). A subchronic study was chosen to represent chronic toxicity in this assessment as a health protective measure. The lowest chronic NOEL was 0.3 mg/kg/day, based on testicular degeneration and clonic convulsions at 0.6 mg/kg/day in the 1-yr dog feeding study. The concordance of testicular effects in the rat and dog studies supported use of the rat study in this context. As there were no available chronic dermal studies by which the risk from such an exposure scenario could be evaluated, the oral study was used to represent the risk of chronic dermal toxicity.

Oncogenicity. There was no indication from the chronic toxicity studies in laboratory animals that carbofuran induced tumors. However, one prospective epidemiologic study indicated a positive correlation between reported carbofuran exposure and incidence of lung cancer in pesticide applicators from Iowa and North Carolina (RR≈3). Possible confounding factors and conflicting results using different referent populations suggested that caution be exercised in the interpretation of this study. It should nonetheless be recalled that, in view of evidence that *N*-nitrosocarbamates are oncogenic, formation of *N*-nitrosocarbofuran has been demonstrated in the guinea pig stomach.

Genotoxicity. *In vivo* tests indicated that carbofuran induced chromosome abnormalities and micronucleus formation in mice. Furthermore, sperm abnormalities were induced in mice upon intraperitoneal injection. The latter observation was consistent with similar observations in the male reproductive systems of several species subjected to chronic, reproductive, and/or developmental toxicity tests. Data from four additional studies indicated that the *N*-nitroso derivatives of carbofuran were genotoxic in several *in vitro* tests.

Reproductive and developmental toxicity. Carbofuran by the oral route adversely affected the male reproductive system in several species. In the critical subchronic study in rats, impacts on sperm counts, motility and sperm structure were noted at the mid low dose of 0.2 mg/kg/day, becoming more severe at the higher doses (0.4 and 0.8 mg/kg/day). These observations resulted in a NOEL of 0.1 mg/kg/day. Changes in testicular enzyme activities, decreases in absolute and relative weights of epididymides, seminal vesicles, ventral prostate and coagulating gland, and decreases in total body weights were also noted. In a later study by the same authors, similar degenerative changes were demonstrated in 90-day old rats that had been exposed to 0.4 mg/kg/day carbofuran, either throughout gestation or for the lactational period of 21 days. The NOEL for that study was 0.2 mg/kg/day. In view of the fact that the affected animals had been exposed indirectly through placental blood or mother's milk, and the testicular exams were carried out as long as 90 days after carbofuran administration had ended, the slightly higher NOEL was not surprising.

Testicular degeneration was noted at the mid dose of 0.6 mg/kg/day in the 1-year dog dietary study in the absence of other overt toxicity in males (one female showed clonic convulsions at that dose). Additional evidence for sperm toxicity came from rabbit and mouse studies. Finally, one study in pregnant female rats showed that oral carbofuran caused pre-implantation loss at doses as low as 0.4 mg/kg/day, though cholinergic effects were present at even lower doses (0.2 mg/kg/day). Thus carbofuran has the potential to disrupt both spermatogenesis in males and embryo implantation in pregnant females.

Neurotoxicity. To the extent that many of the acute oral and dermal effects noted above may be driven by inhibition of brain or peripheral neural AChEs, they are classifiable as neurotoxic. A rat 13-week neurotoxicity study provided evidence for gait impairments and reduced limb grip strength after dietary exposure to carbofuran. A separate rat developmental neurotoxicity study produced possibly CNS-related neural disruptions in pups exposed during gestation, though the doses were higher than those eliciting frank cholinergic signs or ChE inhibition in other studies.

Toxicity of carbofuran metabolites. Scant data were available on the toxicity of carbofuran metabolites, though a series of summaries of acute and subchronic studies were provided by FMC. LD_{50}s in rats after gavage dosing for carbofuran metabolites were as follows: 3-OH-carbofuran (LD_{50}=17.9 mg/kg), 3-keto carbofuran (LD_{50}=69.0 mg/kg), 3-keto-7-phenol (LD_{50}=295 mg/kg), 3-OH-7-phenol (LD_{50}=1350 mg/kg), and 7-phenol (LD_{50}=1800-2200 mg/kg). For purposes of comparison, the oral LD_{50} of carbofuran fell between 2 and 20 mg/kg. As noted above, the nitroso derivatives of carbofuran proved mutagenic in several *in vitro* assays.

Exposure assessment and risk calculations

The potential for non-oncogenic health effects resulting from exposure to carbofuran was expressed as the Margin of Exposure (MOE). The MOE is defined as the ratio of the critical NOEL or LED value divided by the estimated exposure. An MOE of >100 was considered to be protective of human health when the relevant adverse effects were observed in animal studies, as was true in the present case.

Handlers. Dermal and inhalation exposures for five occupational handler categories were estimated using the Pesticide Handlers Exposure Database (PHED), a surrogate approach. The five categories included the groundboom, aerial, chemigation, low-pressure handwand and dip/slurry (mixer/loader only) tasks. Within those categories, exposures were estimated for different tasks, including (where appropriate) mixer/loader, applicator, mixer/loader/applicator and flagger. For each task, assumptions were made regarding the influence of protective gear. The period of seasonal use was estimated by reference to the DPR Pesticide Use Report. The dermal component of the total systemic exposure was greater than the inhalation component. The handler category receiving the highest exposures by both the dermal and inhalation routes and under all exposure length scenarios was the aerial applicator.

Exposure estimates for dip/slurry applicators were generated using two models. For dermal estimates, the equations in the Risk Assessment Guidance for Superfund, Part E (RAGS-E) were used. For inhalation estimates, the estimated air saturation level for carbofuran was used.

The acute dermal absorbed daily dosages (acute ADDs) for handlers ranged between 0.002 and 6.36 mg/kg/day, generating acute dermal MOEs of <1-5 (LED_{05}=0.01 mg/kg). The acute inhalation absorbed daily dosages ranged between 0.00003 and 0.041 mg/kg/day, generating acute inhalation MOEs of <1-333 (LED_{05}=0.01 mg/kg).

The seasonal dermal average daily dosages (SADDs) for handlers ranged between 0.0006 and 2.12 mg/kg/day, generating seasonal dermal MOEs of <1-167. The seasonal inhalation absorbed daily dosages ranged between 0.00002 and 0.016 mg/kg/day, generating seasonal inhalation MOEs of 6-5000.

The annual dermal average daily dosages (AADDs) for handlers ranged between 0.0001 and 0.354 mg/kg/day, generating annual dermal MOEs of <1-1000. The annual inhalation absorbed

daily dosages ranged between 0.00001 and 0.003 mg/kg/day, generating annual inhalation MOEs of 33-10,000.

Fieldworkers. Fieldworker exposures were predicted to occur only upon reentry into treated fields and only by the dermal route. Three scenarios, scouting cotton, scouting alfalfa and scouting potatoes, were examined as plausible sources of dermal contact to fieldworkers.

Acute ADDs for all of these activities ranged between 0.007-0.099 mg/kg/day. These exposures generated acute MOEs of <1-1. SADDs ranged between 0.0009-0.070 mg/kg/day, generating seasonal MOEs of 1-111. AADDs ranged between 0.0001 and 0.012 mg/kg/day, generating annual MOEs of 8-1000.

General public, ambient air. Inhalation exposure of the general public to carbofuran was predicted via the ambient air, *i.e.*, air distal to an application site that was not associated with a particular application. Ambient air estimates were based on measurements in Imperial County and Sacramento County. Acute ADDs ranged between 0.0014 and 0.070 µg/kg/day for infants and between 0.0007 and 0.034 µg/kg/day for adults. These estimates generated MOE values between 143 and 7143 for infants and 294 and 14,286 for adults. SADDs ranged between 0.0004 and 0.020 µg/kg/day (infants) and between 0.0002 and 0.010 µg/kg/day (adults), resulting in MOEs of 5000-250,000 and 10,000-500,000, respectively. AADDs ranged between 0.0001 and 0.003 µg/kg/day (infants) and between 0.00007 and 0.002 µg/kg/day (adults), resulting in MOEs of 50,000-1,000,000.

General public, application site (bystander) air. Inhalation exposure of the general public was also predicted via application site air, *i.e.*, air close to an application site that was associated with a particular application. Application site estimates were based on air monitoring 20 meters west of an Imperial County alfalfa field in 1993. They were associated with a groundboom application for 1 hour at a rate of 1 lb ai/acre.

Acute 1-hr ADDs were estimated at 0.550 µg/kg/hr in infants and 0.099 µg/kg/hr in adults, generating 1-hr MOEs of 18 and 101, respectively. Acute 24-hr ADDs were estimated at 0.454 in infants and 0.216 in adults, generating 24-hr MOEs of 22 and 46, respectively. Seasonal and annual exposures were not estimated because application site air levels were expected to approach ambient levels within a few days of the application.

Dietary exposure and risk. Dietary pesticide exposure is the product of the amount of food that is consumed and the concentration of the pesticide residue in that food. DPR dietary assessments consider only those commodities that carry a tolerance for the pesticide in question. For carbofuran, this includes 26 commodities, in addition to drinking water. Two distinct pieces of information are required to assess the dietary exposure using the DEEM package: (1) the amount of the pesticide residue in food, which is established in the USDA's Pesticide Data Program and other databases, and (2) the food consumption, which is determined by the USDA's 1994-1998 Continuing Survey of Food Intake by Individuals (CSFII).

For estimating acute exposure, either the highest residue values at or below the tolerance or the distribution of residues were considered. For chronic exposure, the mean residue values were used. Acute exposure was calculated on a per-user basis, *i.e.*, including only the days of survey in which at least one commodity with potential pesticide residues was consumed in the distribution of exposures. Chronic exposure was calculated using per-capita mean consumption

estimates.

A tiered approach was used to estimate acute dietary exposure. For tiers 1-3, point estimates were established for each food group. Such a “deterministic” approach employed the tolerance (Tier 1), the upper bound value (Tier 2) or the mean residue value (Tier 3) to estimate residues for individual food groups. Tier 4 comprised the distributional (Monte Carlo) approach. Monte Carlo was used to refine the assessment by taking into account the *distribution* of the residue values for a particular commodity, rather than relying on a single point estimate. Only data from Tiers 2 and 4 were expressed in the current assessment, as Tiers 1 and 3 were not considered to contribute substantially to the analysis.

The lowest MOEs were associated with infants and children, as predicted by their relatively higher exposure values. For the Tier 2 (point estimate) analysis, MOEs at the 97.5^{th} user day percentile ranged between 6 (children 1-2 yr) and 22 (females 13+ preg./not lactating). At the 99^{th} percentile, point estimate MOEs ranged between 4 and 16. At the 99.9^{th} percentile, point estimate MOEs ranged between 2 and 16. For the Tier 4 (distributional) analysis, MOEs at the 97.5^{th} user day percentile ranged between 16 (non-nursing infants <1 yr) and 60 (adults 50+). At the 99^{th} percentile, the distributional MOEs ranged between 11 and 47. At the 99.9^{th} percentile, the distributional MOEs ranged between 5 and 35. As the MOEs for the acute dietary analysis fell well below the benchmark of 100 for both the Tier 2 and Tier 4 analyses, an acute dietary health concern was indicated.

The chronic dietary analysis produced lower exposure values and utilized a 10-fold higher critical NOEL. Correspondingly, the chronic MOEs were notably higher, 427 - 1623. A chronic dietary health concern was, therefore, not indicated for carbofuran.

Reference doses (RfDs). Reference doses for potential oral exposures to the general population were calculated by dividing the critical acute oral LED_{05} or the critical subchronic oral NOEL by an uncertainty factor of 100 to account for possible intra- and interspecies variations in sensitivity. The resulting oral RfD_{acute} was 0.1 µg/kg and the $RfD_{s/a}$ was 1 µg/kg/day. The predicted acute dietary exposure for each of the examined subpopulations exceeded the RfD_{acute} even when the distributional (Monte Carlo) refinement was used to estimate exposure. Conversely, chronic dietary exposures did not exceed the $RfD_{s/a}$ (the DEEM dietary exposure module did not estimate seasonal dietary exposures). Dermal and inhalation exposures sustained under occupational scenarios were not considered for this analysis.

Reference air concentrations (RfCs). In the absence of appropriate inhalation toxicity studies, RfC values for the general population were based on the critical oral acute and subchronic studies. Consequently, they required both an uncertainty factor of 100 to ensure health protection and the use of default respiratory rate values relevant to infants and adults. The resultant 1-hr acute RfCs were 0.4 and 2.22 µg/kg for infants and adults, respectively, while the 24-hr acute RfCs were 0.17 and 0.36 $\mu g/m^3$. The seasonal / annual RfCs were 1.7 and 3.6 $\mu g/m^3$ for infants and adults. For acute scenarios, both the 1-hr and 24-hr application site exposures exceeded the relevant infant RfCs. The 24-hr application site exposures also exceeded the adult 24-hr RfC, while the 1-hr application site exposure level was equal to the 1-hr adult RfC level. Ambient exposures did not exceed the infant or adult RfCs under any exposure duration. Inhalation exposures sustained under occupational scenarios were not considered for this analysis.

Risk appraisal

The reliability of this risk evaluation is dependent on the reliability of the underlying toxicity and exposure data, as well as the applicability of the toxicity data to the anticipated exposure scenarios.

Acute toxicity, oral and inhalation. The very low acute oral LED_{05} of 0.01 mg/kg (used to assess dietary and inhalation exposure scenarios), based on induction of chewing behavior in rats at 0.1 mg/kg, was not unexpected in light of the low LD_{50}s noted for carbofuran relative to other cholinesterase inhibiting pesticides. In addition, it was consistent with cholinergic signs at similar doses in a published study, only slightly lower than doses causing pregnancy termination in that same study, and only slightly lower than a similar abnormal chewing behavior observation in yet another study. Even so, there were several reasons to question the appropriateness of the LED_{05} for this analysis: (1) the chewing behavior observations, established in a rangefinding study, were not reproduced in the complete study, (2) the toxicologic significance of this behavior was unclear, particularly in view of the fact that the animals were not otherwise compromised at that dose, (3) the LED_{05} (benchmark dose) determination depended on choice of incidence curve algorithm and benchmark response level, both of which had inherent uncertainties, and (4) the gavage bolus dose used in the critical study probably resulted in higher temporal pesticide body burdens than could be obtained by "real world" dietary or inhalation exposure; thus the LED_{05} may be unrealistically low.

Acute toxicity, dermal. In the absence of an appropriate dermal toxicity study, the rat critical oral toxicity study was used to assess the risks from human dermal exposure to carbofuran. A route extrapolation of this nature carried similar uncertainties to the oral-to-inhalation extrapolation, particularly those associated with using an oral bolus exposure to assess systemic toxicity by the dermal route, where the pharmacokinetics are very different.

Subchronic toxicity. The critical subchronic oral NOEL of 0.1 mg/kg/day (based on damage to the rat male reproductive system following gavage dosing at 0.2 mg/kg/day) was supported by similar observations in at least three other species (mouse, rabbit, and dog), and in human sperm *in vitro*. Moreover, testicular effects were noted in rat offspring after exposure of the mother during gestation or lactation. The wide species distribution minimized concern that, as a non-FIFRA open-literature study that utilized a less common rat strain (Druckrey rats), it was not relevant in a regulatory framework. However, as was the case for the acute oral LED_{05}, introduction of the pesticide by oral gavage may have produced higher internal concentrations than those attainable by the dietary route, resulting in an underestimation of the critical NOEL (overestimation of risk). The same consideration would apply to the evaluation of seasonal dermal risk, for which the subchronic oral NOEL was also used. Finally, there was uncertainty involved with using an oral bolus study to evaluate the risks associated with inhalation exposure.

Chronic toxicity. Choice of a subchronic NOEL to evaluate chronic risk injected a clear uncertainty into the analysis, as chronic exposure might be expected to result in lower NOELs than subchronic. However, in the present case the lowest NOEL from a chronic study was higher than that determined in the subchronic study. The subchronic NOEL was therefore adopted in the chronic case as a health-conservative measure.

Exposure assessment, occupational and resident / bystander. There are many uncertainties inherent in the occupational and resident / bystander exposure assessment for

carbofuran. Most prominent among them are the fact that specific occupational monitoring data were not used to estimate exposure. Consequently, the handler estimates were derived from surrogate data in the Pesticide Handler's Exposure Database (PHED). These incorporated values for acres treated per day which were based on USEPA defaults or Deputy Agricultural Commissioner estimates. As such, the handler estimates were expected to be conservative - however, there were insufficient data to evaluate their accuracy. The lack of monitoring data also affected the fieldworker dermal exposure estimates, which were perforce dependent on chemical-specific dislodgeable foliar residue values and crop-specific transfer coefficients. The accuracy of the resultant exposure estimates was subject to many factors and contributed greatly to the risk estimate uncertainty.

As no biomonitoring was available, ambient and application site exposures were based both on measured air concentrations and on assumptions about carbofuran uptake by adults and infants from the air. In addition, while ambient monitoring sites were selected based on anticipated nearby carbofuran use, actual applications were not confirmed. The fact that a number of samples were negative for carbofuran even in Imperial County where use was high, suggests the possibility that carbofuran levels were occasionally not measured at sites and times of peak use. This would result in underestimates of potential ambient levels.

Dietary exposure. Sources of uncertainty in the dietary exposure assessment included the completeness of the food residue database, the use of surrogate data, the possible presence of sampling or reporting errors, the representativeness of the food consumption survey database CSFII, particularly for some undersampled populations, and the routine summing of carbofuran plus 3-OH-carbofuran residues for all estimates. The vast majority of residue assays in the USDA Pesticide Data Program (PDP) were negative, resulting in the setting of those levels at the limits of detection (LOD) for the point estimate approach. This probably resulted in overestimation of residue levels (and thus risk) because the *actual* residue level could be anywhere between zero and the LOD. This was less of a problem with the Monte Carlo approach, which, for non-blended commodities, set only a fraction of the non-detects at the LOD depending on the percentage of the crop that was treated (PCT). In contrast, estimates based on field trial data were likely to be high because such studies were conducted to determine the highest residue level that can result from maximal legal use of the pesticide.

Tolerance assessment

A separate acute tolerance assessment was conducted for each "high-contributor" commodity (*i.e.*, those commodities providing greater than ~5% of the total carbofuran + 3-OH-carbofuran consumption in the DEEM Tier II point estimate) using the DEEM dietary exposure software and CSFII. The acute tolerance assessment did not address simultaneous consumption of multiple commodities at tolerance levels. The probability of consuming multiple commodities at such levels significantly decreases as the number of commodities included in the assessment increases. Consumption of even two commodities at tolerance was considered unlikely. Excluded from the tolerance assessment were those subgroup-commodity pairs with less than 25 user days.

MOEs of less than 100 were indicated for every commodity and population group examined, indicating a health concern in each case. Squash, with its high projected exposures (1.480 - 17.288 µg/kg/day) and high tolerance (0.6 ppm) resulted in very low MOEs (<1 - 6) at tolerance. Similarly low MOEs for grapes-juice were more consumption-driven, as it exhibited a lower tolerance (0.2 ppm).

II. INTRODUCTION

A. CHEMICAL IDENTIFICATION

Carbofuran (2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate; MW, 221.26) is a broad spectrum, systemic insecticide, acaricide and nematicide. It is used against a large number of target species, including aphids, beetles, chinch bugs, corn rootworm, grasshoppers, greenbugs, leafhoppers, lygus bugs, nematodes, sugarcane borers, thrips, weevils and wireworms. Treated crop systems include alfalfa, field corn, cotton, grapes, potatoes, small grains, sorghum, soybeans, strawberries, sugarcane, sunflowers, sweet corn and tobacco (Farm Chemicals Handbook, 2002).

As a member of the carbamate class of pesticides, the action of carbofuran is based largely on its ability to inhibit acetylcholinesterase (AChE) in the nervous system and motor endplates of the target species. Carbofuran's toxicity in mammalian systems may also based on this property. Nonetheless, carbofuran inhibits other cholinesterases (ChEs) as well, including the plasma-localized butyryl ChE and the red blood cell-localized AChE. Possible contributions of the latter effects to the overall toxicologic picture are obscure, though this assessment is cognizant that adverse outcomes could theoretically arise from inhibition of these enzymes or by mechanisms currently unknown.

In contrast to the organophosphates, carbamates do not form irreversible inhibitory bonds with ChE molecules. Because of the relatively fast carbamate-ChE dissociation rate, standard methods of preparing tissue samples for assay may underestimate the extent of inhibition. This is because such assays utilize extended incubation times and large dilutions in buffer, both of which favor the dissociation and consequent reactivation of the enzyme. Efforts have been made over the past decade to develop ChE assay techniques that take into account the carbamate dissociation problem (Padilla and Hooper, 1992; Nostrandt *et al.*, 1993). Unfortunately, such techniques have not been utilized in the analysis of carbofuran-treated tissues. This methodological conundrum must be viewed as a limitation to the interpretation of the ChE data in the present assessment.

B. REGULATORY HISTORY

Carbofuran was discovered and developed by the Niagara Division of FMC Corporation, becoming available for agricultural use in 1968 (Tobin, 1970; Spencer, 1981; OEHHA, 2000). By the early 1990s it was clear that soil-applied granular formulations were responsible for numerous bird kill incidents (see section I.G. below). As a result, the USEPA and FMC agreed to ban all granular carbofuran formulations, with the ban taking effect in September 1994 following a special review (Extoxnet, 1996). Some uses on rice were permitted until August 1999. Liquid formulations remain in use throughout the country, though they are classified as Restricted Use Pesticides due to their toxicity to humans by the oral and inhalation routes.

In 2000, California's Office of Environmental Health Hazard Assessment promulgated a Public Health Goal (PHG) of 1.7 ppb in drinking water (OEHHA, 2000). This was based on testicular toxicity observed in the study of Pant *et al.* (1995). Previously, the State of California (OEHHA) and the USEPA had set Maximum Containment Levels (MCLs) of 18 ppb and 40 ppb, respectively. These were based on results from the same chronic study in dogs (Toxigenics,

1982), though OEHHA's lower value relied on plasma ChE depression, while the USEPA's higher value relied on ChE depression, clinical signs and testicular toxicity (OEHHA, 2000). The USEPA issued a Revised Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) Document (Phase 2) on September 1, 2005 (USEPA, 2005) (see section V.D. for a comparative review of the toxicity endpoints). USEPA is scheduled to issue an Interim Reregistration Eligibility Document (IRED) on carbofuran in March 2006.

Carbofuran is not currently listed by the State of California under Proposition 65 as a chemical known to cause cancer or reproductive toxicity.

C. TECHNICAL / PRODUCT FORMULATIONS

As of the time of this report, only a single product, Furadan 4F, is registered for use in California. Furadan 4F is a flowable liquid concentrate which contains 44% carbofuran.

D. USAGE

Ninety five percent of the carbofuran applied in California is directed toward four crops: alfalfa, rice, grapes and cotton. Use on three of these crops, alfalfa, rice and grapes, declined markedly over the 1996-2001 period, accounting for an overall decline in use, from 220,622 pounds in 1996 to 95,863 pounds in 2001. Use on cotton actually increased over this period, while use on rice was cancelled after 2000. Other crops registering minor amounts of use in California over this period include artichokes, nursery plants and bermuda grass.

E. ILLNESS REPORTS

The following is quoted directly from the Exposure Assessment document (DPR, 2006; attached to this report as Appendix I). References cited can be found in that document:

> Reports of illness and injury with definite, probable, or possible exposure to pesticide products are recorded in a database maintained by the Pesticide Illness Surveillance Program (PISP) at DPR. The PISP database contains information about the nature of the pesticide exposure and the subsequent illness or injury...
>
> Between 1992 and 2003, a total of 77 reports of illnesses, injuries, or death associated with exposure to carbofuran, alone or in combination with other pesticides, were received by PISP (Verder-Carlos, 2005). Most of the illnesses were systemic in nature (69 of 77, about 90% of the total cases), with complaints of nausea, vomiting, abdominal cramps, headache, and dizziness (Verder-Carlos, 2005). The other eight incidents consisted of injuries or irritation to eyes, skin or throat. There were two reported cases of hospitalization, one in 1994 and one in 1998, and 37 cases involving disability that ranged from one to twenty-eight days. A single reported death in 1999 followed ingestion of carbofuran; no other deaths have been associated with carbofuran exposures in California.
>
> Of the 77 total illness reports received by PISP, 56 came from occupational

exposures, in which the subjects were working with or near carbofuran (or multiple pesticides that included carbofuran), or were working in treated areas. Of the individuals reporting illness following occupational exposures, three were mixer/loaders and five were applicators. Thirty-six workers reported illness after entering a field treated with carbofuran. Most of the other exposures occurred when carbofuran drifted from a nearby application.

Two incidents resulted in multiple illness reports to PISP. Following a drift incident in 1993, 19 residents from a single neighborhood reported symptoms including headache, dizziness, nausea, and irritated throat and eyes (Verder-Carlos, 2005). In 1998, 34 field workers began weeding a treated cotton field two hours after an application of carbofuran, mepiquat chloride, and abamectin (Das *et al.*, 1999; Edmiston *et al.*, 1999b). The exposure duration was approximately 3.5 hours; shortly afterward, the workers developed symptoms including headache, nausea, vomiting, diarrhea, eye irritation, repiratory problems, salivation, and muscle weakness. Carbofuran and 3-hydroxycarbofuran residues were detected in foliage samples collected from the field, as well as in clothing and urine samples taken from the affected workers. Additionally, red cell cholinesterase activity was below the normal range for all ten workers from whom blood samples were drawn (Edmiston *et al.*, 1999b).

F. PHYSICO-CHEMICAL PROPERTIES

The physico-chemical properties of carbofuran are listed below in Table II-1.

Table II-1. Physico-chemical properties of carbofuran

Molecular weight, Molecular formula [1]	221.26, $C_{12}H_{15}NO_3$
Melting point [2]	150-152°C
Water solubility [3]	351 ppm (25˚C)
Vapor pressure [4]	6 x 10^{-7} mm Hg (25˚C)
Octanol-water partition coefficient (K_{ow}) [3]	17 - 26
Henry's Law constant [1]	3.9 x 10^{-9} atm m^3/mol
Hydrolysis half-lives (days) [3]	27.7 (pH 7, 25˚C); 2.73 (pH 8, 25˚C); 0.54 (pH 9, 25˚C)
Aqueous photolysis half-life (days) [3]	7.95 x 10^3 (pH 7, 28˚C)
Soil photolysis half-life (days) [3]	138 (27˚C, pH 5.7, sandy-loam, 2.1% organic carbon, 21% moisture)
Aerobic degradation half-life (days) [3]	22 (25˚C, pH 5.7, sandy-loam, 2.1% organic carbon, 21% moisture)
Anaerobic degradation half-life (days) [3]	30.0 (25˚C, pH 5.7, sandy-loam, 2.1% organic carbon, 21% moisture)
Field dissipation half-life (days) [3]	13.0 (pH 7.3, sandy-loam, 0.38% organic carbon)
Adsorption coefficient (K_{oc}) [5]	22

[1] HEFED, 1991
[2] Lewis, 1996
[3] DPR, 2002a
[4] Alvarez, 1989
[5] Extoxnet, 2001

G. ENVIRONMENTAL FATE

1. Air

Carbofuran's low vapor pressure and low Henry's Law constant (Table II-1) indicates that it has a correspondingly low tendency to volatilize from water or moist soils (Deuel *et al.*, 1979). Low concentrations of carbofuran were found in air when samplers were placed 20 yards from the edge of an agricultural field in Imperial County, California. Reported concentrations ranging from 0.03 to 0.66 µg/m^3 were observed after a 44-hour sampling period following an application of a 44% formulation (Shibamoto *et al.*, 1993).

Once in the air, carbofuran is subject to vapor-phase photooxidation by reacting with hydroxyl radicals. The half-life under this reaction was estimated to be 4.6 hours in a typical atmosphere (HEFED, 1991).

2. Water

Base-catalyzed hydrolysis to carbofuran phenol is the major carbofuran degradation pathway in both water and sediment (Yu *et al.* 1974, Seiber *et al.* 1978, Brahmaprakash *et al.*, 1987, Talebi and Walker, 1993). Other degradation products include 3-OH-7-phenol carbofuran (Chiron *et al.*, 1996), carbofuran phenol and *N*-methylcarbamic acid (via hydroxylation of the benzofuranyl moiety) (Yu *et al.*, 1974). The aqueous hydrolysis rate of carbofuran increases dramatically with increasing pH. One laboratory study reported 80-95% recoveries of initial carbofuran spikes at pH 3 after 1, 3, and 6 hours (25ºC). In contrast, at pH 10 only 65% of the original amount was recovered after 1 hour, 35% remained after 3 hours, and 10% remained after 6 hours (Bailey *et al.*, 1996).

Seiber *et al.* (1978) found that the hydrolysis of carbofuran was more than 700 times faster at pH 10 than at pH 7 in rice paddy water treated with the granular formulation; the reported decomposition $t_{1/2}$s were 1.2 hours and 864 hours, respectively. In addition, hydrolysis was observed to be more rapid in natural paddy water than in deionized water. Half lives at pH 7 were 240 hours and 864 hours in paddy water and deionized water, respectively. It was not clear what dissolved or suspended impurities were responsible for this effect. However, the effect decreased with increasing pH. Thus at pH 8.7 the $t_{1/2}$s were 13.9 hours and 19.4 hours in paddy water and deionized water, while at pH 10 the $t_{1/2}$s were 1.3 and 1.2 . Overall, the mean laboratory half life in paddy water at pH 8 was 40 hours. This agreed well with the 57-hour average observed in the field at the same pH, especially considering that such factors as variations in sunlight, pH, temperature, microbial degradation and the presence of impurities certainly influence the process (Seiber *et al.*, 1978)**.**

Photolysis of carbofuran appears somewhat less important than hydrolysis as a degradation pathway, though it does occur. Photometabolites include 2,3-dihydro-2,2 dimethyl benzofuran-4,7-diol and 2,3-dihydro-3 keto-2,2 dimethyl benzofuran-7-yl carbamate (or 3-ketocarbofuran) (Raha and Das, 1990). Deuel *et al.* (1979) compared recovery of carbofuran in deionized water exposed to summer sunlight to carbofuran exposed to laboratory light. After 96 hr the mean recovery was 75.6% for the sunlight-exposed carbofuran and 93.3% for carbofuran in artificial light. Seiber *et al.* also reported that sunlight decreased the carbofuran decomposition time, showing that the $t_{1/2}$ decreased from 753 hr to 660 hr in deionized water (pH 7, 29°C for 16 hr, 21°C for 8 hr to mimic day and night temperatures) from dark to sunlight, and from 224 hr to 173 hr in rice paddy water.

3. Soil

Because of its high water solubility (351 ppm at 25˚C) and low adsorption coefficient (K_{oc}= 22, Table II-1), carbofuran is relatively mobile in soil and in surface runoff. It thus has the potential to contaminate lakes, streams and groundwater. Indeed, carbofuran has been detected in the Sacramento River (Nicosia *et al.*, 1991), although concentrations were below U.S. Health Advisory Levels (HALs) and Maximum Contaminant Levels (MCLs) (Cohen, 1996).

A study by Kumari *et al.* (1987) on the movement of carbofuran found a slight difference between adsorption coefficients in 2 soil types. In clay loam (OC content 0.53%, pH 8.6), carbofuran was found to have a K_d value of 22.4, while in silt loam (OC content 0.18%, pH 8.4) a K_d value of 19.9 was registered. Less movement and higher adsorption were seen in the clay loam, due presumably to the presence of a greater organic matter and/or clay content. Leaching studies also demonstrated increased sorption and less mobility in the clay soil (Kumari *et al.*, 1987). Sharom *et al.* (1980) compared leachability of carbofuran from sand (OC content 0.7%,

pH 7.0) and organic soil (OC content 75.3%, pH 6.1) using 10 successive rinses with 200 ml of distilled water. Carbofuran was almost completely leached out of the sand within the first two rinses (1st rinse recovered 94.8%, 2nd rinse recovered 4.1%). Amounts recovered from organic soil were less, with 73.8% from the 1st rinse, and 16.3% from the 2nd rinse (Sharom *et al.*, 1980).

Carbofuran is expected to partition into the water from soil (Johnson and Lavy [1995]). Immediately following granular application to paddy soil, 54% of the carbofuran was found in the water while 46% was found remaining in soil. However, data from Nicosia *et al.* (1991) contradicted this finding - the mass recovered from paddy soil was 5 times greater than mass recovered in paddy water immediately after application. Seventy days after flooding, the mass recovered in soil was 98 times greater than the mass recovered in water. They noted that low pH levels in soil compared to the water may have contributed to persistence in the soil (organic carbon content in this study ranged from 2.2% to 2.8%).

The effect of pH on hydrolysis rates in soil is similar to that observed in water, where, as noted, carbofuran degradation rates are increased under alkaline conditions. Getzin (1973) reported a 10-fold difference in DT_{50} (time required for 50% breakdown) between soils at pH 4.3 and 7.8. He concluded that while hydrolysis was the major route of degradation in alkaline soils, the slower degradation in acidic and neutral soils was dominated by microbial and chemical mechanisms. Breakdown products in soil include carbofuran phenol (Getzin, 1973), 3-OH-carbofuran, and 3-ketocarbofuran (Johnson and Lavy, 1995).

Other studies indicate that microbial degradation is an important route of carbofuran degradation in neutral soils. Miles *et al.* (1981) compared dissipation rates in two soil types, sandy loam (organic matter 3.3%, pH 7.3) and muck (organic matter 36%, pH 7.3), under sterile and nonsterile conditions. Carbofuran was persistent in sterile soils, with 77% remaining in sterile muck and 50% in sterile sandy loam after 8 weeks. In contrast, 25% remained in the nonsterile muck while carbofuran was undetectable in the nonsterile sandy loam after 8 weeks (Miles *et al.*, 1981). Degradation of the metabolites 3-OH- and 3-ketocarbofuran was also more rapid in non-sterile soils.

A study using soil previously treated with carbofuran granules found a dissipation half life of 58 days in one field (2.4% organic carbon), and 43 days in another (2.2% organic carbon) (Nicosia *et al.*, 1991). Szeto and Price (1991) found 78 µg/g of carbofuran in Canadian silt loam soils nearly a year after the application of granular material. The pH of similar soils from this area (the Frasier Delta of British Columbia) has been reported to be 5.0 - 5.9 (Mineau, 1993). Caro *et al.* (1973) reported a soil dissipation half life of 117 days in a corn field. Low soil pH (5.3) and lower soil moisture content may explain the relatively slow rate of dissipation.

There is general consensus among researchers that repeated application of carbofuran to soils can result in enhanced rates of microbial degradation (Harris *et al.*, 1984; Turco and Konopka, 1990; Scow *et al.,* 1990). Enhanced degradation of a soil-applied pesticide may occur when a population of soil microorganisms develops the ability to catabolize the chemical after repeated exposures (Parkin and Shelton, 1994). Singh and Sethunathan (1999) found much lower recovery rates (*i.e.*, higher degradation rates) in soils previously treated with carbofuran than in untreated soils. Two days after treating *Azolla* plots, 55.5% of the carbofuran was recovered, compared to 89.4% from untreated plots. After 5 days, 29.8% was recovered from the treated plot, while 87.3% was recovered in the uninoculated plot. Getzin and Shanks (1990) found

enhanced degradation rates with as little as one or two applications of carbofuran. Volatilization also contributes to the dissipation process, though it is not as important as microbial degradation. Under laboratory conditions, 4.4, 10.3 and 14.4 µg of carbofuran evolved after 20, 40, and 60 days of application of carbofuran to a concentration of 7.3 ppm in sandy loam (5.8% water). In sand, amounts of carbofuran evolved were 216, 466, and 842 µg (initial concentration applied was 5.8 ppm, 0.7% water) (Caro *et al.*, 1976). Carbofuran volatilization rates are more rapid under flooded soil conditions than under non-flooded conditions. This is likely due to co-evaporation with the water on the surface of the soil (Lalah *et al.*, 1996).

Photodegradation is generally considered a minor route of carbofuran degradation from soil. One study found that carbofuran adsorbed onto silt loam had a half life of 13.6 days when exposed to a light intensity of 2400 mW/cm^2 at 26˚C (though the corresponding half life in the absence of light was not reported (NRCC, 1979). The rate of dissipation in soil is also strongly affected by temperature (Yen *et al.*, 1997). One laboratory study found that carbofuran's half life in silty clay loam (pH 6.7, organic matter 2.9%) decreased from 105 days to 35 days when the temperature was increased from 15ºC to 35ºC (Yen *et al.*, 1997).

4. Biota

In 1991, the EPA and the FMC Corporation agreed to ban granular formations of the chemical, though use was permitted on rice until August of 1999 (USEPA, 2002). The primary factor in this decision was the toxicity of the granular form to birds. Numerous reports of bird kills are documented as the result of direct ingestion of carbofuran after field applications. In all probability, the granular form is mistaken by birds as grit or food, or is ingested by waterfowl while sifting sediments (Erwin, 1991). Over 80 separate bird kill incidents have been reported. These involve more than 40 species of birds, including robins, larks, sparrows, cardinals, goldfinches, bluebirds, blackbirds and doves. Secondary poisoning (*i.e.*, resulting from ingestion of poisoned insects and small birds) has been reported in owls, hawks and eagles (Erwin, 1991). Flowable carbofuran is as toxic to birds as the granular form, but exposure to the flowable form is less likely.

The principal metabolite of carbofuran in plants is 3-OH-carbofuran (NRCC, 1979). 3-OH-carbofuran is subsequently oxidized to 3-ketocarbofuran, which is then rapidly hydrolyzed to the less toxic 3-ketocarbofuran-7-phenol. The latter compound is not likely to occur in plants above trace levels (Eisler, 1985). Caro *et al.* (1976) found that carbofuran is readily absorbed by roots and is transported via plant fluids to areas of greatest transpiration, such as leaves. In corn, carbofuran concentrations were highest in the leaves. Lower levels were found in the stalks, with very small amounts detected in the ears. It was estimated that 0.14% of the applied carbofuran was taken up by the crop (Caro *et al.*, 1976).

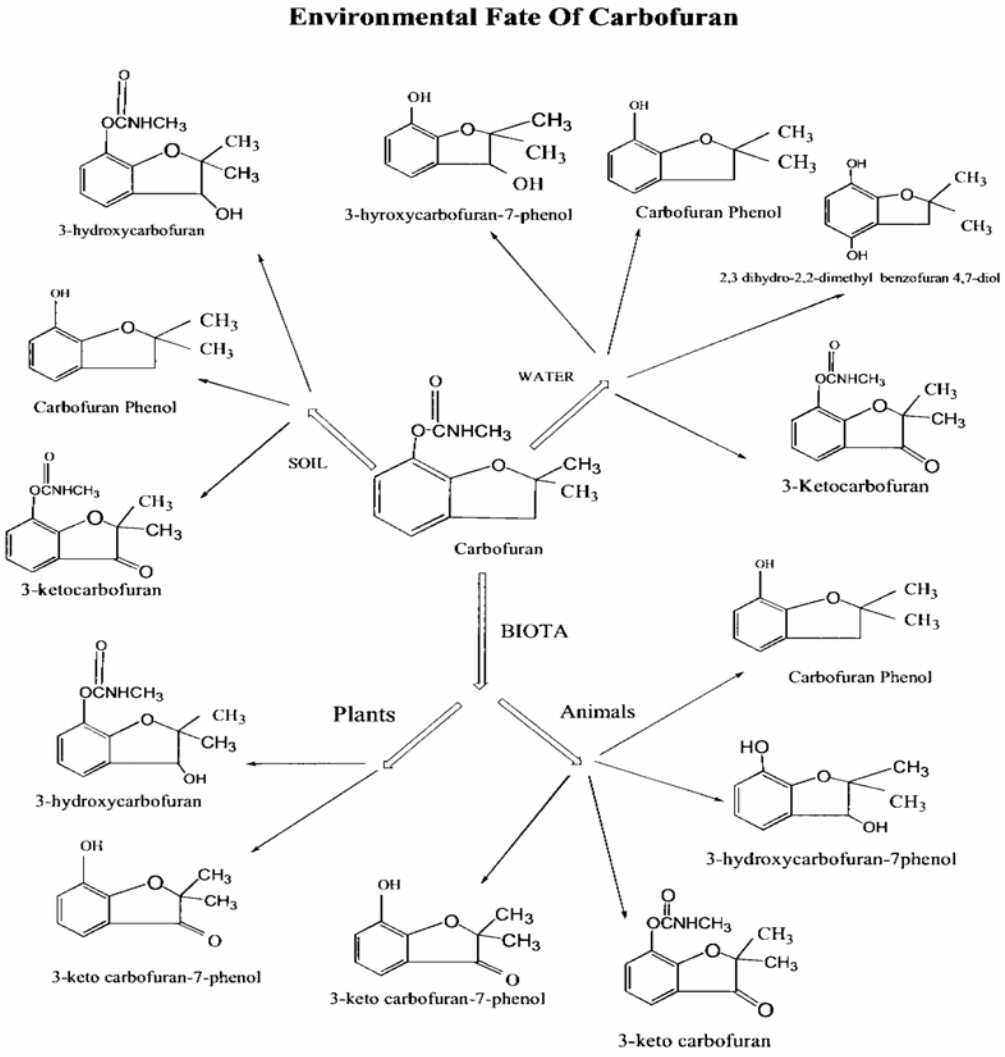
Because of its high water solubility, low K_{ow} and rapid degradation and biotransformation, carbofuran is not expected to bioaccumulate significantly (Eisler, 1985). Hydroxylation (oxidation) and hydrolysis reactions, along with the appropriate polar conjugations, comprise the major metabolic transformations of carbofuran in mammals, creating esters or ester cleavage products (see detailed discussion of pharmacokinetics below, section III.A.1).

Carbofuran does not accumulate significantly in aquatic systems. While disruptions to enzyme and lipid metabolism have been observed in fish, such effects appeared reversible with no observable permanent damage (Eisler, 1985). LC_{50} values ranged from 130 ppb to 1,420 ppb in tests of 72 to 96 hours, with yellow perch (*Perca flavescens*), green sunfish (*Lepomis cyanellus*)

and lake trout (*Salvelinus namaycush)* being among the most sensitive, and fathead minnow (*Pimephales promelas*) among the most resistant (Eisler, 1985). When compared with the toxicities of other aquatic species, marine worms seemed to be the most resistant to the pesticide, while fish were the most sensitive (NRCC, 1979).

Among terrestrial species, honeybees are extremely sensitive to carbofuran (LD_{50} is 0.16 mg/bee [Eisler, 1985]). Earthworms (*Lumbricus herculeus)* are also particularly susceptible, with an LC_{50} value in soil of 0.5 ppm at 5 hours. Earthworm exposure could result in secondary poisoning in many species (Eisler, 1985). There have been no confirmed detections of carbofuran in California's groundwater (DPR, 2002a). However, carbofuran was detected in surface water every year from 1991 through 1998, with a total of 279 detections out of 3007 samples taken as of December 2002 (DPR, 2002a). Most detections occurred in rice-growing regions of Northern California between April and June while rice applications were still permitted (DPR, 2002a).

Figure 1. The environmental fate of carbofuran



III. TOXICITY PROFILE

A. PHARMACOKINETICS

1. Overview

No FIFRA guideline pharmacokinetics or metabolism studies on carbofuran were submitted to DPR. However, a series of studies from the open literature were available which examined the handling and disposition of this insecticide in mammals after acute oral, intravenous, dermal, or inhalation exposure. As detailed in the following sections, hydroxylation (oxidation) and hydrolysis reactions, along with the appropriate polar conjugations, comprise the major metabolic transformations of carbofuran, creating esters or ester cleavage products (JMPR, 1996). Metabolism and excretion can be followed using carbofuran labeled in one of two sites on the molecule: 1. in the carbonyl carbon, which permits analysis of the fate of the carbarnate group after hydrolysis, or 2. in the benzofuranyl ring, which allows analysis of the fate of the ring moiety. In the rat, the data using carbonyl-^{14}C-carbofuran indicate rapid absorption by the oral route, followed by carbamate hydrolysis and excretion either through the lungs ($^{14}CO_2$) or through the urine and feces. The data using ring-^{14}C-carbofuran indicate rapid excretion, predominantly in urine. One bile cannulation study demonstrated carbofuran entry into the enterohepatic circulation. In this manner, appreciable cholinesterase inhibiting activity is maintained in the blood after the disappearance of the parent molecule. One study suggests that *N*-nitroso carbofuran, a mutagenic and cytotoxic derivative, might be formed in the stomach.

No systematic study of carbofuran pharmacokinetics after a series of daily exposures was submitted. Such a paradigm is also recommended under FIFRA guidelines (one such experiment in lactating goats [Tejada *et al.*, 1988] was not analyzed in sufficient detail to be useful). It is thus not known if recurrent exposure would change the pharmacokinetic profile.

2. Absorption (oral exposure)

Dorough (1968) analyzed carbofuran metabolism in the rat (strain and numbers of animals dosed were not stated) after single oral doses of carbonyl-^{14}C-carbofuran (0.4 mg/kg) or ring ^{14}C-carbofuran (4 mg/kg). Measurements of radioactivity in urine, feces and, for carbonyl-^{14}C-carbofuran, expired air (the hydrolysis of ring-^{14}C-carbofuran was not expected to generate $^{14}CO_2$) were carried out at designated times. Clinical signs were evident at the higher dose, which was near the LD_{50}.

By 24 hours post dose, 43.4% of the administered carbonyl-^{14}C-carbofuran dose had appeared as $^{14}CO_2$, suggesting that hydrolysis of the carbamate ester bond was relatively rapid. At 32 hours, this proportion was 44.6%, remaining stable at that level through 120 hours. Urine contained 36.8% and 38.4% of the dose at 24 and 32 hours, respectively, while 1.9% and 2.4% appeared in feces. Thus by 24 hours, 82.1% of the administered carbonyl-^{14}C-carbofuran had been excreted. By 32 hours excretion had risen to 85.6% and by 120 hours to 87.4%. The urinary and expired air data indicated that carbofuran was rapidly absorbed by the oral route. A similar conclusion was suggested by the ring-^{14}C-carbofuran data; 74.5% of the dose had been excreted by 24 hours (72.2% in the urine, 2.3% in the feces), 90.1 % by 32 hours (87.7% in the urine, 2.4% in the feces), and 94.9% by 120 hours (91.6% in the urine, 3.3% in the feces).

****

Ferguson *et al.* (1984) investigated the metabolism of carbofuran in male Sprague-Dawley rats following intravenous and oral exposure to 50 µg/kg carbonyl-^{14}C-carbofuran. At two minutes

post iv dose, RBC AChE was inhibited by 83%, returning to control levels by 3 hours. 37% inhibition was detected 15 minutes after the oral dose, indicating a very rapid absorption from the GI tract. AChE activities returned to control levels by 3 hours. Elimination of ^{14}C was unaffected by route of exposure. At 8 hours post iv or oral exposure, 41-47% of the radioligand had been excreted as CO_2, 14-15% appeared in the urine, <1% in feces and 30-31% in carcass, resulting in 86-92% of the total dose. Peak plasma levels after oral exposure were attained within 7 minutes.

****

Metcalf *et al.* (1968) briefly examined carbofuran metabolism in the white mouse (strain unidentified) after oral exposure to 2 mg/kg ring-labeled ^{3}H-carbofuran. Because of the low acute LD_{50}, these authors claimed that the most satisfactory results were obtained using ring labeled ^{3}H-carbofuran, which had a higher specific activity than the equivalent ^{14}C-labeled compound. Thirty seven percent and 67% of the label were eliminated in the urine by 24 hours in each of the two mice that were exposed. Further measurements were not attempted.

****

Ahdaya *et al.* (1981) studied the absorption and distribution of various radiolabeled carbamates (including ring-labeled carbofuran), organophosphates, chlorinated hydrocarbons and other insecticides. Fasted ICR mice were exposed by gavage to the radioligands. The half-time for absorption ($T_{0.5}$) from the gastrointestinal tract was estimated using a mathematical model from percentage absorption data taken at 1, 5, 15, 30 and 60 minutes. For carbofuran, this value was 10 minutes, similar to that for the other carbamates tested (propoxur = 8 minutes, carbaryl = 17 minutes), and lower than all of the organophosphates (diazinon = 23.5 minutes, malathion = 33.5 minutes, parathion = 33.3 minutes, chlorpyrifos = 78.1 minutes). Of the three chlorinated hydrocarbons tested, lindane had the lowest $T_{0.5}$, (14.2 minutes), with dieldrin and DDT somewhat higher (42.1 and 62.3 minutes, respectively). For the "miscellaneous" insecticides, nicotine showed a $T_{0.5}$, of 23.1 minutes, while the $T_{0.5}$ for permethrin was 177.6 minutes. By the final measurement at 60 minutes, 24% of the carbofuran dose had appeared in the urine, with 6% expired as CO_2. Fecal excretion was not studied due to the short times examined and the fasted status of the animals. Very prompt appearance of radiolabel was detected in the blood, liver and carcass, however.

****

Mostafa *et al.* (1992) examined the bioavailability and toxicity in rats of carbofuran residues that were bound to faba beans (*Vicia fava*). The beans were treated with ring-labeled or unlabeled carbofuran under conditions simulating farm storage. This was followed by washing in water:acetone (3:1) to remove surface residues. The quantity of bound residues was dose dependent, but did not exceed 3%. For characterization of bioavailability, a paste of ring-labeled carbofuran-bean extract and white cheese was fed to three male albino rats (strain not reported) that were individually housed in metabolism cages for collection of CO_2 and excretory products. After 2 days, 34.6% of the administered dose appeared in urine, 15.4% in feces, 11.5% in blood, 7.3% in liver, 4.6% in fat, 1.5% in kidney and 11.5% as CO_2. This was a far lower amount appearing in urine and higher amounts in feces than was expected from the earlier study of Dorough (1968; see above), which showed about 90% of the radioactivity in urine and <3% in feces by that time. Considering that ring-labeled ligand was used, it was unclear, nor did the

authors speculate, why radiolabel should have been found in CO_2. The two major metabolites in urine were carbofuran phenol (7-phenol) and 3-OH carbofuran, with additional quantities of these metabolites obtained after acid hydrolysis of conjugates.

For toxicity determination, 40 female Swiss mice were fed for 90 days with a diet mixed with non-labeled carbofuran bound residues to ensure a daily dose of 1.5 ppm insecticide. Twenty animals served as controls, receiving the same diet mixed with non-treated, extracted crushed beans. There were no significant effects on body weight gain. RBC cholinesterase was inhibited by 35-40%* (*$p<0.05$) at 30 and 60 days, though it had nearly regained control levels by 90 days. Plasma cholinesterase activities appeared unaffected. Statistically significant increases were noted in the following blood parameters: serum glutamic oxaloacetic transaminase (1.7-fold at 30 days, 1.2-fold at 60 days, 1.2-fold at 90 days), serum glutamic-pyruvic transaminase (3.1-fold at 30 days, 1.1-fold at 60 days, 2.1-fold at 90 days), blood urea nitrogen (2.2-fold at 30 days, 2.1-fold at 60 days, 1.9-fold at 90 days). There was no effect on alkaline phosphatase. These data were considered consistent with carbofuran-induced injury to liver and kidney.

This study demonstrates that food-bound carbofuran has access to bodily tissues, is metabolized, and has the potential to induce toxicity. It was not conducted according to FIFRA guidelines.

3. Distribution (oral exposure)

In the Dorough (1968) rat study, tissue analysis was conducted at 1, 2, 4, and 8 hours after exposure to 4 mg/kg ring-^{14}C-Furadan. At 1 hour, the highest proportions of radioligand were found in the liver (1.43 ppm/mg dry weight), followed by blood (0.47 ppm/mg), kidney (0.38 ppm/mg), brain (0.30 ppm/mg), leg muscle (0. 19 ppm/mg) and bone (0.08 ppm/mg). By 8 hours, noticeable declines had occurred. The liver still contained the greatest quantity of radioligand at that time (0.78 ppm/mg), followed by blood (0.30 ppm/mg), kidney (0. 14 ppm/mg), brain (0.09 ppm/mg), leg muscle (0.06 ppm/mg) and bone (0.06 ppm/mg).

****

Ferguson *et al.* (1984) showed that ^{14}C-carbonyl-carbofuran distributed evenly (~650 dpm/g) to well-perfused tissues following oral exposure.

4. Biotransformation (oral exposure)

Hydroxylation (oxidation) and hydrolysis reactions, along with the appropriate polar conjugations, comprise the major metabolic transformations of carbofuran. These reactions likely occur predominantly in the liver. For a discussion of the conjugation reactions, see the review of the study by Marshall and Dorough (1979) in section 6 below.

****

About 95% of the urinary metabolites in rats exposed to ring-^{14}C-Furadan by the oral route were water-soluble conjugates (Dorough, 1968). These metabolites resolved into 6 chemical entities after acid hydrolysis of the conjugate moieties: 3-OH-N-CH_2OH-Furadan (4.02%), 3-OH-Furadan (14.78%), Unknown III (0.04%), 3-OH-Furadan-phenol (1.43%), 3-keto-Furadan-phenol (50.54%), Furadan-phenol (21.12%), and unidentified water solubles (8.07%).

****

A diagram of the generally accepted metabolic pathways for carbofuran in mammals is presented in Figure 2.

5. Excretion (oral exposure)

Ingested carbofuran was excreted primarily through the urine and expired air, with much smaller amounts associated with feces. As delineated by Dorough (1968), the majority of the dose in the rat was excreted by 24 hours. Precise figures and times in the Dorough study are presented in section 1 above.

****

Ferguson *et al.* (1984) showed that after oral exposure in rats to ^{14}C-carbonyl-carbofuran (50 µg/kg), nonconjugated 3-OH-carbofuran was eliminated more slowly than carbofuran, with an elimination $t_{1/2}$ of 46 minutes from liver and 64 minutes for the remaining tissues. This longer elimination time, which may seem surprising in view of its polar (i.e., water soluble) nature, was described as due to "the formation of and increase in 3-OH-carbofuran over time within the GI tract and liver" (p. 20), and is thus impacted by the enterohepatic circulation (see below).

6. Special studies

a. Inhalation exposure

Ferguson *et al.* (1982) examined the disposition of carbofuran after inhalation exposure of rats to aerosols containing 4.1 µm (50-min exposure) or 1.5 µm (70-min exposure) AMAD (median aerodynamic diameter) monodispersed particles of ^{14}C-carbonyl-carbofuran (as indicated above, use of this ligand allows for measurement of CO_2 expiration). ^{14}C tissue distribution immediately after exposure was similar for the two particle sizes. For 4.1 µm AMAD particles (using pooled data for doses of 0.2 and 1.2 µg/L, n=10) and 1.5 µm particles (dose of 0.2 µg/L, n=4), the carcass contained 34-35% of the dose, head (minus brain, but including part of the nasopharyngeal system) 26-29%, GI tract 22-23%, and liver 6.5% (lower percentages were detected in other tissues). However, the proportions of carbofuran, 3-OH-carbofuran and conjugated 3-OH-carbofuran were impacted by the particle size. The head and GI tract contained 2.8-fold and 8.3-fold more carbofuran respectively with exposure to 4.1 µm particles than with exposure to 1.5 µm particles. Also, the liver contained 2.3-fold more 3-OH-carbofuran after exposure to the larger particles.

RBC AChE activities were inhibited only at the high dose (1.2 µg/L, 4.1 µm particles), registering 55% inhibition at 10 minutes post exposure. Normal AChE levels were reestablished by 60 minutes following exposure. Defecation also increased at 1.2 µg/L. There were no other toxic signs.

Carbofuran excretion measured at 8 hours was generally similar for 4.1 µrn particles (1.2 µg/L) and 1.5 µm particles (0.2 µg/L). These values were 38% (of the dose) and 31%, respectively, in expired air (as CO_2), 12% and 9% in urine, 5.3% and 2.5% in feces, and 44% and 58% in carcass. With both particle sizes, 3-OH-carbofuran, both conjugated and unconjugated, accounted for an appreciable proportion (14-18%) of the metabolites in urine. Levels of the parent compound were low or nonexistent. It should be noted, however, that the chemical nature of a high proportion of the urinary radioactivity was unknown. 3-OH-carbofuran was also present in feces of animals treated with either particle size (29-33% of the total fecal ^{14}C). Feces from animals treated with 4.1 µrn particles (1.2 µg/L) contained 11% unaltered carbofuran. Except for the GI tract, plasma and tissue carbofuran elimination were monoexponential. Interestingly, the time to total plasma ^{14}C elimination, 70 minutes, was similar to previous values obtained after oral and intravenous exposures. Elimination from the head and

lungs, $t_{1/2}$=60 minutes, was longer than elimination from nonexposure route tissues (kidney and liver, $t_{1/2}$=29 minutes). This was thought to reflect slower solubility and absorption in aerosol form than in solution.

b. Dermal penetration

Shah *et al.* (1981) determined comparative rates and amounts of dermal penetration for several radiolabeled insecticide types, including carbamates (of which ring-labeled carbofuran was one), organophosphates, botanicals and chlorinated hydrocarbons. These compounds were applied to female ICR mice over a 1-cm^2 area of shaved skin. The dose was 1 mg/kg, applied in 0.1 ml of acetone. Toxicosis was not evident for any of the insecticides. Carbofuran was among the most rapidly absorbed compounds, with a $T_{0.5}$ of 7.7 minutes. At 1, 5, 15, 60 and 480 minutes (8 hr), the percent of the carbofuran dose that was absorbed was 28.5, 32.6, 71.7, 76.1, and 94.7. At 5, 15, and 60 minutes, the following dose percentages were observed: blood - <0. 1, 1.7, 0.5; liver - 0. 1, 2.4, 0.6; fat - <0. 1, 0.2, <0. 1; urine / CO_2 / feces - <0.1, <0.1, 8.3; carcass - 32.4, 67.3, 66.4. By 8 hours, the vast majority of the applied dose was found in excretory products (72.8%; approximately 1/3 in urine, 2/3 in feces) and carcass (11.9%). Conversion to polar metabolites was evident in the marked decrease in the chloroform:water partition ratio in the carbofuran radiolabel extracted from various tissues after 8 hours. Thus, the control ratio was 32. In blood, fat, liver and urine/feces the ratios were 0.8, 1.8, 0.6 and 0.7, respectively.

****

Percutaneous penetration of ring-labeled carbofuran in young (33 days, representative of the prepubescent population) and adult (82 days) Fischer 344 rats was studied at 4 dose levels: 28, 285, 535 and 2680 nmol/cm^2 (Shah *et al.*, 1987). The test article was applied in 0.2 ml of acetone to approximately 2.3% of the body surface area. The test site was subsequently covered. (Note: There was an *in vitro* component to this study as well, but it will not be covered here.) Absorption at 285 nmol/cm^2, the only dose at which timed measurements were done, was 5.2% and 2.2% in young and adult animals, respectively, at 6 hours and 43.0% and 17.8% at 120 hr. In both age groups the bulk of the applied dose remained at the treatment site, even after 120 hr. The absorption $T_{O.5}$ was 128 hours for the young and 400 hours for the adult animals. In general, penetration in young animals was about 3-fold higher than that in adults. More than 75% of the absorbed dose had been excreted in the urine at 6 hours for both groups, a fraction which increased at the later time points. By 120 hours, 40.0% and 17.0% of the total applied dose was excreted in the urine in young and adults. Corresponding fecal excretion was 2.3% and 0.4%. Because of the rapid excretion, only very low amounts of radioligand were detected in tissues. The maximum tissue load was about 1% of the dose in the young and 0.4% in adults, measured at 6 and 24 hours. In general, kidneys had the highest levels among the tissues tested. Dose had a large effect on the fraction of carbofuran absorbed. Percent absorption in young animals at 72 hours was 24.5%, 36.3%, 9.2% and 3.7% at increasing doses. In adults absorption at 72 hr was 83.4%, 13.0%, 8.3% and 6.0%.

As a whole, the results of this study suggest that age may play a determining role in the amount of carbofuran that is absorbed through the skin. It should be noted, however, that absorption in the ICR mouse (Shah *et al.*, 1981; see above) appears to be far more rapid than what is presented here for the Fischer 344 rat. The adult $T_{0.5}$ in the mouse was shown to be 7.7 minutes, compared to the adult value for the rat of 400 hours. The reason for this is not apparent, though it seems unlikely that a species difference could be the sole source for such a large difference. The dose is also not likely to account for the difference because they were

similar in the two studies (1 mg/kg vs. ~1.4 mg/kg in the mouse and rat, respectively, or, expressed differently, 136 nmol/cm^2 vs. 285 nmol/cm^2).

Neither the mouse nor the rat dermal penetration studies were considered adequate to estimate dermal penetration for humans under occupational scenarios. For a summary of these inadequacies, see section IV.B.1 and DPR (2006). A default value of 50% was chosen to represent human dermal penetration in this assessment (DPR, 2006).

c. Enterohepatic circulation and conjugation

Marshall and Dorough (1979) examined the biliary excretion of carbofuran and a number of other carbarnate insecticides in male ARD-SD rats. Six hours after surgical installation of a bile cannula in each of two rats, 0.1 mg/kg ^{14}C-ring-carbofuran in vegetable oil was administered by gavage. Conjugate-hydrolyzing enzymes (P-glucuronidase, P-glucosidase and aryl sulfatase) were used to aid in the identification of conjugated metabolites in freeze-dried bile and urine. At 24 hours post treatment, 28.1 % of the dose had been excreted in the bile, 59.1 % in the urine. These values rose to 28.5% and 65.4% at 48 hours (<l% in feces). It was thus clear that absorption from the GI tract was efficient. In addition, it was evident that enterohepatic circulation was occurring; the 48-hour fecal excretion of carbofuran was only about 3%, meaning that the biliary conjugates were being reabsorbed. Inability to remove the radioligands from bile with ether suggested that these compounds were conjugated. Also supporting this view is the observation that the minimum molecular weight for bile excretion in the rat is assumed to be about 350 (Hirom, *et al.*, 1972), well above the molecular weight of 221 for carbofuran. Conjugation as a means of increasing the molecular weight was thus indicated.

Glucosidase and sulfatase treatments of the bile failed to convert the radioligand to free metabolites. In contrast, glucuronidase treatment effected a 78% conversion. The primary metabolite released by this treatment was 3-OH-carbofuran, which comprised 60% of the cleaved radioligand. Other biliary cleavage products included carbofuran phenol (3%), 3-OH-carbofuran phenol (1.1%), 3-keto carbofuran phenol (5.2%), and an unknown (8.7%).
In contrast to bile, both glucuronidase and sulfatase treatment of urine released free metabolites. 3-OH-carbofuran was the predominant glucuronidase-freed metabolite (15.2% of the total glucuronidase-released fraction), though 3-keto carbofuran phenol was also prominent (110. 1 %). The predominant metabolite released by sulfatase treatment was 3-keto carbofuran phenol, followed by 3-OH-carbofuran phenol (13.6%) and carbofuran phenol (10.0%).

These results indicate that the enterohepatic circulation has the potential to maintain appreciable carbofuran-based anticholinesterase activity after the disappearance of the parent molecule. As stated in the article (p. 62): "despite the fact that 3-OH-carbofuran glucuronide is the primary biliary product, it is clear that this metabolite is metabolized further by hydrolytic and oxidative mechanisms to yield hydroxylated intermediates which, in turn, are conjugated and voided in the urine. 3-OH-carbofuran possesses in vitro anticholinesterase activity within one order of magnitude of the parent compound... Carbofuran has an oral LD_{50} of 8 to 14 mg/kg in rats and, in our hands, the 3-OH-carbofuran is of similar toxicity. The precise contribution of the latter to the toxicity of carbofuran to mammals cannot be elucidated completely. Nonetheless, the present findings suggest that its contribution could be substantial and that enterohepatic circulation may be a key factor in maintaining anticholinesterase activity after the parent material no longer exists in the body."

d. Metabolism in lactating animals

The metabolic fate of carbofuran in lactating cows was investigated by Ivie and Dorough (1968). Because cows eat carbofuran -treated alfalfa, there was concern that the insecticide may enter the milk and thus expose human populations. One lactating Jersey cow was used in the study.

The animal exhibited nervous behavior for ~3 hours after a first exposure to 0.52 mg/kg carbonyl-^{14}C-carbofuran. A subsequent exposure 38 days later to 1 mg/kg ring-^{14}C-carbofuran generated poisoning symptoms (salivation, tearing, hyperactivity and diarrhea) within 50 minutes. The most severe symptoms occurred at 2 hours, with recovery manifested by 4 hours (though a slight loss of balance persisted for up to 3 more hours).

Radioactive residues appeared in the blood within 40 minutes of oral administration of 0.52 mg/kg carbonyl-^{14}C-carbofuran. The maximum blood concentration occurred at 2 hours, coincident with the greatest severity of signs, declining quickly thereafter. However, radioligand was still detectable at the final measurement, taken at 144 hours.

After treatment with 0.52 mg/kg carbonyl-^{14}C-carbofuran, the peak concentration of residues in milk (0.569 ppm) occurred at 12 hours, declining quickly thereafter. Residues were quantifiable for 132 hours. After treatment with 1 mg/kg ring-^{14}C-carbofuran, the peak residue concentration in milk (0.26 ppm) occurred at 8 hours. The higher residues after carbonyl ^{14}C-carbofuran treatment, unexpected in view of the use of a lower dose, were probably due to the incorporation of $^{14}CO_2$ residues into other milk components (this was also true for fecal residues). 3-OH-carbofuran, 3-keto-carbofuran phenol and carbofuran phenol were the major milk metabolites, comprising 70-80% of radioactive content of the samples. Over 75% of the radioactive milk components at 2 hours from both treatments were organosoluble, though this proportion declined noticeably between 2 and 8 hours. The decline rate was faster for carbonyl-^{14}C-carbofuran than for ring-^{14}C-carbofuran, suggesting that the carbonyl carbon was removed from the benzofuranyl moiety and independently eliminated.

Approximately 94% of the ring-^{14}C-carbofuran was excreted in the urine by 72 hours, with the vast majority of this having occurred by 8 hours. In contrast, ~21% of the carbonyl-^{14}C-carbofuran was excreted in the urine by 240 hours. This difference, 73%, represents the amount of carbofuran hydrolysis that occurred. It was concluded that "a small portion of the carbofuran-^{14}C was quickly converted into products which were no longer susceptible to hydrolytic attack and were slowly excreted from the body" (p. 853).

Table III-1 (Table VII in the original paper) provides a summary of the proportions of carbofuran metabolites in milk, urine and feces in this particular lactating cow after oral exposure to ring-^{14}C-carbofuran (hydrolytic products could not be accounted for when using carbonyl-^{14}C-carbofuran). The table does not indicate the proportion of each metabolite that was conjugated.

Table III-1. Nature of the total radioactivity eliminated from the body of a lactating cow fed ring-^{14}C-carbofuran. (Ivie and Dorough [1968])[1]

	% of administered dose appearing as indicated metabolites			
	Milk	**Urine**	**Feces**	**Total**
Carbofuran	0.001	0.000	0.000	0.001
3-OH-carbofuran	0.046	16.710	0.109	16.865
3-OH-N-CH$_2$OH-carbofuran	0.004	5.938	0.052	5.994
3-keto-carbofuran	0.002	0	0	0.002
Carbofuran phenol	0.016	23.803	0.031	23.850
3-OH-carbofuran phenol	0.001	10.994	0.023	10.968
3-keto-carbofuran phenol	0.071	14.179	0	14.250
Unknowns	0.016	22.339	0.468	22.823
Total	0.157	93.913	0.683	94.753

[1] The times required to establish this final-status picture were not explicitly stated in the paper. However, the paper did graphically delineate the last times in which each sample provided detectable residues: milk, ~24 hr; urine, ~72 hr; feces, ~40 hr.

****

Knaak *et al.* (1970) examined the metabolic fates of ring-^{14}C-carbofuran, carbonyl-^{14}C-carbofuran, carbonyl-^{14}C-3-OH-carbofuran and the ring-labeled and carbonyl-labeled carbofuran metabolites from alfalfa (these included glycosides of 3-OH-carbofuran, the 7-phenol, the 3,7-diol and the 3-keto-7-phenol forms), in a lactating Holstein cow. The latter compounds were administered in alfalfa, while carbofuran and 3-OH-carbofuran were administered in gelatin capsules. Carbofuran and 3-OH-carbofuran were efficiently absorbed; only about 3% of the label had appeared in the feces by 96 hours. On the other hand, 83%, 12% and 23.7% of the ring-"C-carbofuran, carbonyl-^{14}C-carbofuran, and carbonyl_^{14}C-3-OH-carbofuran residues appeared in urine by that time. This differential suggests that hydrolysis of the carbamate residue released the carbonyl-associated label to appear as $^{14}CO_2$ in expired air, or to be incorporated into other molecules as part of intermediary metabolism.

Interestingly, much larger percentages of the carbofuran metabolites from alfalfa (18-22% of the dose) appeared in the feces, suggesting non-absorption. The excretion pattern in the urine bore similar characteristics to that seen for carbofuran and 3-OH-carbofuran, *i.e.*, a high proportion (77%) thus excreted for the ring labeled metabolites and a much lower proportion (38%) for the carbonyl labeled metabolites.

Residues of up to 2.5% of the dose of ring-^{14}C-carbofuran, carbonyl-^{14}C-carbofuran, carbonyl-^{14}C-3-OH-carbofuran, and of carbonyl-labeled alfalfa metabolites appeared in the milk. The ring-labeled alfalfa metabolites and the carbonyl-^{14}C-3-OH-carbofuran were present in milk at up to 1% of the dose.

Ion-exchange and silica get chromatography were used to identify metabolites in urine and milk. The main metabolic presence in urine following carbofuran exposure were glucuronide and sulfate conjugates of the 7-phenol form, comprising 58% of the dose. Other components included the glucuronides and sulfates of the 3,7-diol and 3-keto-7-phenol forms and the glucuronide of 3-OH-carbofuran.

****

A study by Tejada *et al.* (1988) addressed the fate of ring-^{14}C-carbofuran in lactating goats, with special attention to the question of residues in meat and milk. There were five separate groups, each consisting of two lactating females. Group I: a single 0.03 mg/kg dose added to a piece of bread, sacrificed at 15 days. Group II: 7 consecutive daily doses on bread, 0.5 mg/kg/day, sacrificed at 22 days. Group III: 7 consecutive daily doses on bread, 1.0 mg/kg/day, sacrificed at 22 days. Group IV: 15 days receiving feed containing 5.0 ppm, sacrificed at 30 days. Group V: Untreated offspring of the Group IV mothers, sacrificed 7 days after the last dosing of their mothers. 93% of Group I dose was excreted in the urine within 12 hours. ~1 % of the total residues for the animals dosed on 7 consecutive days (Groups II and III) appeared in the feces. Low, but consistent, levels of carbofuran residues appeared in milk from Group II and III animals. Peak levels were 0.02 mg/kg for Group II and 0.03 mg/kg for Group III. Interestingly, these residues were present at the final measurement on day 22, 15 days after the final dose (though most of these were reported at the limit of detection of 0.01 mg/kg). Total elimination in milk was ~0.5%. Residue analysis revealed that only 3-OH-carbofuran, but not carbofuran or other metabolites assayed, was present in milk. The highest tissue levels of carbofuran residues were detected in the liver (0.55 and 0.69 for Groups II and III) and omental fat (0.84 and 1.42 for Groups II and III). Omental fat was the only tissue in which unaltered carbofuran was detected. Other metabolites and the tissues they were found in included carbofuran phenol (liver, kidney, urine), 3-OH-carbofuran phenol (urine) and 3-OH-carbofuran (milk). No tissues from Group V animals had residue levels exceeding the limit of detection of 0.01 mg/kg.

e. Enzymes involved in carbofuran metabolism

Bartow *et al.* (1994) determined the in vitro rate constants of carbofuran oxidation in rat liver microsomes. The K_m and V_{max} were 0.37±0.12 mM and 106.5±17.8 picomoles/min/mg microsomal protein, respectively. Diallyl sulfide (DAS), a cytochrome P-450 2E1 inhibitor, inhibited 3-OH-carbofuran formation in a dose-related fashion, suggesting that this cytochrome is involved in carbofuran metabolism. Rat lung microsomes were not capable of metabolizing carbofuran.

f. Formation of *N*-nitroso carbofuran

Rickard and Dorough (1984) investigated the possibility that the *N*-nitroso derivatives of carbamate pesticides could be formed under the acidic conditions of the stomach. In the *in vivo* experiments, female Sprague-Dawley rats and Hartley guinea pigs were treated by gavage with ^{14}C-carbofuran or ^{14}C-carbaryl and sodium nitrite (controls consisted of animals treated with carbamate alone). The stomach contents were removed from the animals, processed and analyzed by two-dimensional thin layer chromatography using nitrosocarbamate standards. *In vitro* experiments were conducted by incubating the sodium nitrite and radiolabeled carbamates with stomach contents.

Guinea pigs formed nitrosocarbamates more readily than rats: 1.54% of the carbaryl dose and 0.65% of the carbofuran dose were detected as the *N*-nitroso derivative in guinea pigs *vs.* 0.02% and 0.03% in the rat, respectively. When the incubations were carried out *in vitro* using isolated stomach contents, 37.4% of the carbaryl dose and 18.9% of the carbofuran dose were detected as the *N*-nitroso derivative in guinea pigs *vs.* 0.57% and 0.31% in the rat, respectively. This species difference was attributed to the lower pH of the guinea pig stomach (1.2-1.6) *vs.* the pH of the rat stomach (3-5), a conclusion which was supported by an experiment in which the incubation with carbaryl was performed after the pH of the rat stomach was artificially lowered with HCl or acetic acid. As the guinea pig stomach pH approximates that of the human, this supports the possibility that nitrosocarbamates may be formed readily in the human stomach. The low nitrosocarbamate *in vivo* yields in either species were considered to

reflect the instability of the derivatives, as well as the rapid absorption of both the parent compound and the derivative.

****

The structures of carbofuran, its major carbamate metabolites and their nitroso derivatives appear in Figure 3.

Figure 2. Metabolic pathways of carbofuran (from JMPR, 1996)

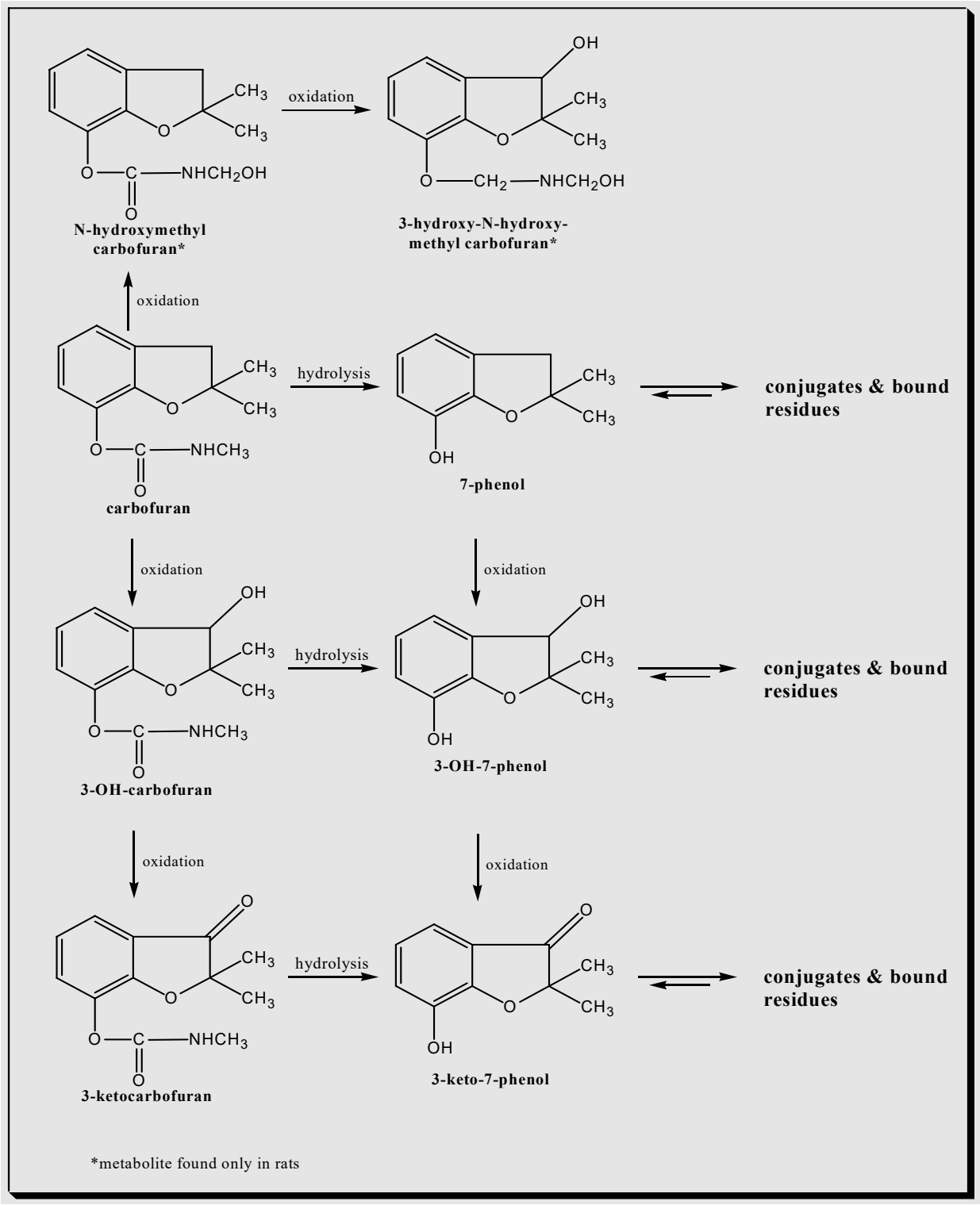
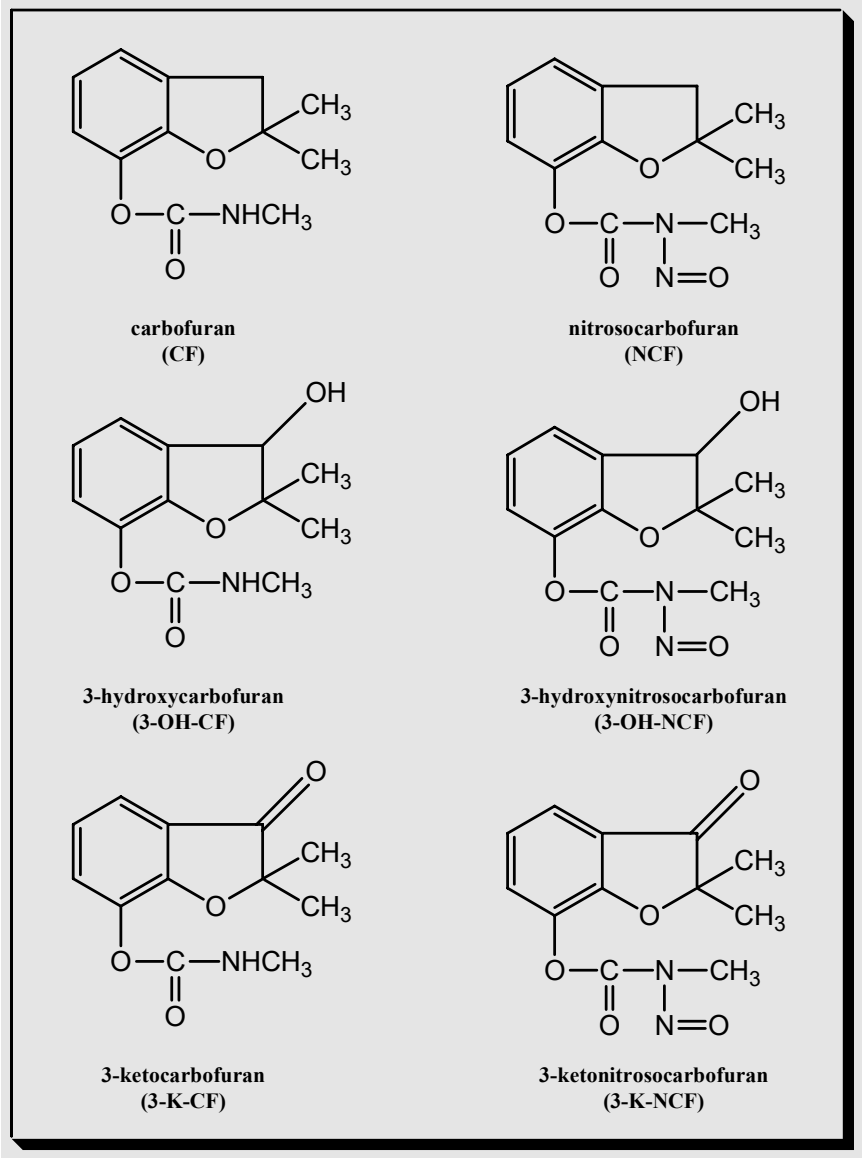


Figure 3. Chemical structures of carbofuran with its carbamate metabolites and nitroso derivatives (adapted from Nelson *et al.*, 1981)



B. ACUTE TOXICITY

1. Overview

The acute toxicity of carbofuran results from its ability to carbamylate, and thus inhibit, acetylcholinesterase (AChE) at synapses and neuromuscular junctions. Consequent local accumulations of acetylcholine (ACh) generate cholinergic signs and symptoms, including "nausea, vomiting, abdominal cramps, sweating, diarrhea, excessive salivation, weakness, imbalance, blurring of vision, breathing difficulty, increased blood pressure, and incontinence" (Extoxnet, 1996). Due to the reversibility of the carbamate-AChE bond, recovery is expected when exposures are low. However, higher levels of carbofuran exposure can lead to death by respiratory failure (Gupta, 1994). LD_{50} and LC_{50} data from the available studies appear in Tables III-4a (end product) and III-4b (formulations).

2. Human studies (controlled exposures)

Human oral exposure. Carbofuran technical was administered to two male test subjects at 0.05 or 0.10 mg/kg or to four subjects at 0.25 mg/kg (FMC, 1976). One test subject was given a placebo. Signs & symptoms were monitored for 24 hr. EKG's, vital signs, vestibular function, pupil size and eye accommodation were also monitored. Blood samples were collected pre-treatment and at 0.5, 1, 3, 6 and 24 hr post-treatment for determination of plasma and RBC ChE levels. No effects were observed at 0.05 & 0.1 mg/kg. At 0.25 mg/kg all subjects showed exposure-related symptoms: dry mouth, salivation, diaphoresis, abdominal pain, drowsiness, nausea and vomiting. Symptoms generally began 0.5 to 3 hours post dose and persisted up to 3 hours. EKGs, vital signs and vestibular function were unaffected by treatment. Miosis of 2 mm was observed within 2 hr of dosing at 0.25 mg/kg, lasting 24 hr. Plasma ChE results were apparently too variable, even in the placebo, to interpret (the data were not reported). RBC ChE measurements showed an apparent dose-response relationship. The maximum depressions were 10% (placebo), 16.5% (0.05 mg/kg), 33% (0.1 mg/kg) and 57.5% (0.25 mg/kg). However, the time points at which "maximum depression" occurred were not indicated for any of the data points.

The NOEL was set at 0.1 mg/kg, based on clear clinical signs noted at 0.25 mg/kg. The toxicologic significance of the possible suppression of RBC ChE was not clear.

****

Human dermal exposure. Two male subjects/dose were treated cutaneously with Furadan 4F at 0.5, 1, 2, or 4 mg active ingredient/kg or with FMC 35001 4 EC at 0.5, 1, 2, 4, 8 or 16 mg active ingredient/kg (Arnold, 1977). The carbofuran content of both test articles was 480 mg active ingredient per ml (48% purity). Test article was applied to the back of each subject at a concentration of 0.5 mg a.i./cm^2. The exposure time was 4 hr. From 1 hr pre-treatment until 4 hr post-administration (*i.e.*, at the end of the exposure period), subjects were kept in a controlled environment with the temperature between 33 and 36°C and relative humidity between 70 and 80%. Subjects alternated between 5 min of mild ergometer exercise and 15 min of rest during the exposure period. The subjects were healthy adult males, Caucasian or Negro, with a median age of 36 yr (23-53 yr), a median height of 176 cm (166-188 cm) and a median weight of 70 kg (51-86 kg). Data on smoking status were collected, but did not appear in the final report. The report also did not state if the test site was occluded. Plasma and RBC ChE activities were determined at 0.5, 1, 2, 4, 6 and 24 hr after test article administration using a modified acetylthiocholine / DTNP procedure. There was no indication that special precautions were taken to prevent carbamate dissociation from the ChE enzyme during the assay. The

subjects were questioned frequently to identify unusual signs or symptoms. Arterial blood pressure, heart rate and pupil size / eye accommodation were determined at 0, 0.5, 1, 2, 3, 4, 6, 8 and 24 hr post administration. Laboratory determinations and physical examinations were carried out 24 hr post administration.

Both subjects treated with 4 mg/kg of Furadan 4F complained of nausea, dizziness and weakness. One or the other of the subjects also experienced dry lips, swollen tongue, increased salivation, stomach cramps, vomiting and/or tremors. The onset of these signs / symptoms ranged from 2 to 3.5 hours, with some signs / symptoms persisting for up to 2 hours. Both high-dose subjects were treated with atropine (0.4-1.2 mg *iv*). One subject treated at 0.5 mg/kg carbofuran complained of an unsettled stomach (2 episodes), though none of the other 5 individuals treated at 0.5, 1 or 2 mg/kg exhibited symptoms.

The subjects treated with 16 mg a.i./kg of FMC 35001 4 EC demonstrated similar effects (nausea, weakness/unsteadiness, stomach cramps, and headache). Both subjects treated at 0.5 mg/kg reported headaches (at 4 and 5 hr after application, persisting for 1 and 12 hr, respectively), though none of the other 8 individuals treated at 1,2, 4 or 8 mg/kg had such a symptom. Other complaints were noted at the intermediate doses, but were also not clearly treatment-related. Except for nausea, which occurred after each exercise period starting at 1.25 hours, all of the other signs/symptoms were evident at 2.5-3 hours and persisted for up to 5.5 hours (headache).

Dose-dependent inhibition of RBC cholinesterase in response to Furadan 4F exposure was noted at 4 hr post administration, the time point of maximum inhibition for this test article (Table III-2). The mean levels of inhibition at that time (compared to pretreatment levels) were 15% (0.5 mg/kg), 25% (1 mg/kg), 41% (2 mg/kg) and 55% (4 mg/kg). Enzyme activities showed signs of recovery by 6 hr. By 24 hr, they had largely returned to pretreatment levels.

With FMC 35001 4 EC, maximum RBC ChE inhibition occurred at 1-6 hours. This test article appeared less potent than Furadan 4F, with mean percentage decreases in activity of 0% (0.5 mg/kg), 6% (1 mg/kg), 10% (2 mg/kg), 14% (4 mg/kg), 24% (8 mg/kg) and 35% (16 mg/kg). Thus with both test articles, RBC ChE inhibition was dose-dependent. Dose dependent inhibition of plasma ChE was not detected using either test article.

In conclusion, while both test articles produced clinical toxicity and a dose-related inhibition of RBC ChE, Furadan 4F appeared to be more potent than FMC 35001 4 EC. The authors postulated that this may have been due to greater dermal absorption of the former test article. As dermal morphology was not examined, it was not possible to conclude that the epidermal barrier was damaged by either test article. Based on the observation of dose-dependent RBC ChE inhibition starting at the low dose of 0.5 mg/kg, a LOEL of 0.5 mg/kg was established for this study. However, the low number of subjects, the lack of females, the lack of individuals outside the 23-53 yr age range, and the age of the study (which meant that it did not have sufficient institutional review), cast questions on the reliability of this value, making it unusable for regulatory purposes. Also, while carbofuran could not be ruled out as the cause of the episodes of unsettled stomach experienced by one low-dose volunteer, it was considered unlikely in view of the lack of dose response. Clear test article-related clinical signs were not detected below the Furadan 4F high dose of 4 mg/kg.

Because this was not a FIFRA guideline study, it was considered supplemental.

Table III-2. Time course of RBC cholinesterase inhibition in human males after dermal exposure to Furadan 4F (Arnold, 1977)

Subject	Dose (mg/kg)	Time (hr) 0	0.5	1	2	4	6	24	% decrease, 4 h [1]	mean % decrease, 4 h [1]
0007	0.5	357	377	448	379	278	299	315	22	15
0123		385	372	393	387	359	404	350	7	
0094	1.0	322	299	306	242	228	276	347	29	25
0201		430	459	415	379	338	368	414	21	
0020	2.0	390	381	386	446	225	258	391	42	41
0077		398	403	407	342	237	269	377	40	
0065	4.0	400	388	326	207	157	193	377	61	55
0106		391	402	407	258	200	305	389	49	

[1] 4 hours was the time of maximal inhibition

3. Human studies (poisoning incidents)

Two case reports describe suicide attempts. In one, a 33 year old male ingested 60 ml of Furadan (the carbofuran concentration was not indicated in the Report) (Baban *et al.*, 1998). Quoting from the study (pp. 103-104), "He was stuporous when the emergency rescue unit arrived, and became comatose before reaching the hospital. His blood pressure was 100/70 mm Hg, pulse rate 55/min, respiratory rate 10/min, and temperature 98.2°F. He manifested hyper-salivation, miosis, and facial fasciculations. His corneal reflexes were intact bilaterally, and his eye movements were spontaneous but roving. All four extremities were flaccid with fine fasciculations. He made no response to painful stimuli, but the deep tendon reflexes were unaffected and his plantar response was neutral. His total WBC count was elevated at 17,600/cu mm.... An oxygen concentration of 100% was required to maintain a Pa02 of 75 mm Hg, suggesting the presence of an intrapulmonary shunt. His pH was measured at 7.20, with a serum bicarbonate of 12 mEq/L, consistent with a metabolic acidosis. Liver function tests were normal on admission.... The RBC cholinesterase on admission was reduced to 8 U/gm of hemoglobin (normal 24 to 40). The patient was intubated and mechanical ventilation was initiated in order to protect his airway while gastric lavage with charcoal was instituted. Decontamination of his skin was performed. A second chest radiograph made for confirmation of ET-tube placement revealed bilateral fluffy infiltrates consistent with pulmonary edema. Correction of his hypoxemia with a safe F102 of 50% required the use of 12 cm PEEP. He received repeated doses of intravenous (IV) atropine to control cholinergic hyperactivity, for a total dose of 206 mg of atropine sulfate over the first 48 hours. Pralidoxime, a cholinesterase activator, was also administered IV as an adjunctive therapy to potentiate the effects of the atropine sulfate. He received 1 gm initially, followed by a continuous drip providing 300 mg/hr. He remained in a deep coma, with EEG activity consistent with metabolic encephalopathy and subacute periodic epileptiform discharges. CT of the head confirmed mild diffuse cerebral edema. His neurologic examination slowly improved, with return of the doll's eye sign, cough reflex, and improved pupillary light reflex. He remained comatose for a full week before he would respond to pain, spontaneously open his eyes, or turn his head to the side of voice stimulation. The patient developed toxic hepatitis with liver function tests that increased

gradually over two weeks to maximum values of aspartate aminotransferase at 469 U/L (normal 15 to 46), alanine aminotransferase 707 U/L (normal 7 to 56), lactate dehydrogenase 652 U/L (normal 100 to 190), and alkaline phosphatase 218 U/L (normal 38 to 126). After three weeks, the hepatitis resolved, with normalization of the liver function studies.... His RBC cholinesterase level gradually improved to the normal value of 29 U/gm of hemoglobin, he regained diaphragmatic strength, and was gradually weaned from the mechanical ventilator after two weeks. His extremities remained flaccid, however, and an EMG revealed diffuse axonal subacute motor polyneuropathy. Three weeks after ingestion of the carbarnate compound he regained his speech and could answer simple questions, and after one month he could move his extremities and grip on command. Early in the recovery period abnormal visual acuity was noted, but ophthalmologic evaluation revealed no evidence of structural ocular abnormalities, and he is believed to have sustained permanent partial cortical blindness. He has required continuous physiotherapy, speech therapy, psychiatric evaluation, and treatment for agitation and depression." CNS manifestations, including memory impairment, confusion, and irritability, are listed. Interestingly, a distal motor neuropathy developed two weeks after the poisoning. The investigators consider this similar to that induced by organophosphates ("organophosphate-induced delayed neurotoxicity" or OPIDN) caused by inhibition of neuropathy target esterase (NTE). The study concludes that respiratory and CNS effects are "the most dramatic and life-threatening." Permanent residual CNS effects may be expected. Adequate oxygenation must be addressed. Atropine is recommended to decrease morbidity and mortality from pulmonary effects.

****

Another case study dealt with a successful suicide attempt by a 26-year old male, found dead on a trail in Tennessee (Ferslew *et al.*, 1992). He had ingested up to 345 ml of Furadan 4F (44.9% carbofuran), equivalent to 1.6 g/kg-bw, evident by the partially emptied 1 -gallon plastic container found next to him. The blood carbofuran concentration was 29.3 pg/ml. Of the 155 grams of carbofuran ingested, 50.6 grams remained in the gastric contents. Cholinesterase activities from plasma serum, whole blood and erythrocytes were between 1 % and 7% of normal levels. These figures should not be understood as final, however, because the time since death, and consequently the degree of enzyme degradation, was not known. Cholinesterase inhibition in vitreous humor and bile were 13% and 26% of activities measured in control autopsy tissues. It is considered that the victim died of anoxia due to respiratory paralysis produced by cholinesterase inhibition.

4. Laboratory animal studies

a. Technical carbofuran

LD_{50}, LC_{50}, and primary irritation data for technical carbofuran are listed in Table III-4a. Carbofuran is a category I oral toxicant, with LD_{50}s as low as 2 mg/kg in the rat and mouse, 2.5 mg/kg in the cat, 9.5 mg/kg in the guinea pig and 15 mg/kg in the dog. Cholinergic signs, including salivation, cramps, trembling and sedation, were observed almost immediately after dosing and lasted up to three days. In addition to the LD_{50} data, Gupta (1994) cites evidence that 9 and 18 mg/kg are lethal in sheep and cattle, respectively. In one oral gavage study in rats, clinical signs were observed at a low dose of 0.5 mg/kg, along with inhibition of RBC cholinesterase activity (see next paragraph for summary). Further rat data indicate that carbofuran is a category II inhalation toxicant, with 4-hr LC_{50}s between 0.075 and 0.11 mg/L. Dermal toxicity studies were not entirely consistent; LD_{50}s in rat studies ranged between 120 mg/kg and >500 mg/kg and in rabbit studies between 885 and 4402 mg/kg. It is possible that

some of this disparity is related to variations in dermal penetration afforded by different solvents, which were not always reported. Studies done by IBT demonstrating an increase in dermal toxicity with organic, as opposed to aqueous, solvents, suggest that dermal penetration is enhanced under the former condition. Intraperitoneal exposure in rats resulted in LD_{50}s between 1.4 and 8.2 mg/kg. Two studies examining intraperitoneal exposure in mice led to disparate LD_{50}s (0.055 mg/kg in the study of Amer *et al.* (1997) *vs.* 2 mg/kg in the study of Chauhan *et al.* (2000). An explanation for this was not forthcoming, though it is noted that the lower value was obtained using pure dimethyl sulfoxide as a vehicle, while the higher value was associated with use of a 5% dimethyl sulfoxide vehicle. Finally, ocular exposure in rabbits was fatal at sufficiently high doses (Baron, 1991).

****

Clinical observations were made and RBC and plasma cholinesterase activities measured in a recent oral gavage study in CD rats (FMC, 2002). Groups of 8-9 rats/sex/dose were given a single dose of 0 (corn oil), 0.5 or 1 mg/kg carbofuran (98.6% purity). Dose selection was based on a preliminary test with doses of 0.5, 1, 2 or 4 mg/kg (3/sex/dose). In the preliminary test, 4 mg/kg was too high and cholinesterase inhibition was not evaluated. Note that in this preliminary test, where animals were sacrificed after 1 hour, there were no clinical signs at 0.5 and 1 mg/kg. For the definitive test, cannulae were inserted into the jugular vein to facilitate blood sampling over the 8-hour time period. Samples were taken predosing (baseline) and at 15, 30, 45, 60, 75 and 90 minutes and 2, 2.5, 3, 4, 6 and 8 hours. Plasma and RBC cholinesterase activities were determined and compared with control values and as a percent of baseline. The control cholinesterase activities also varied over the time course of the experiment. Plasma cholinesterase was not significantly inhibited at either 0.5 or 1 mg/kg. RBC cholinesterase, however, was significantly inhibited at both doses. The activity remained below baseline throughout the 8 hours in males, but returned to baseline values in females by 6 hours in both dose groups. RBC cholinesterase was also maximally inhibited by the time of the first measurement at 15 minutes.

Clinical signs, seen both at 0.5 mg/kg and, with slightly increased incidences, at 1 mg/kg, included teeth grinding and slight body tremors (Table III-3). Most of these signs resolved by 60 minutes. Teeth grinding was probably equivalent to the “abnormal chewing behavior”, a putative cholinergic sign noted as the most sensitive clinical effect in the WARF (1978a) rat acute gavage study. The latter study was used to establish the critical acute LED_{05} for carbofuran (see discussion of this study in sections III.G.2.a., IV.A.1.a. and V.A.1.a.). For comparative purposes, it was of interest to establish the LED_{05} for teeth grinding in the current study, particularly for females, who appeared to be slightly more sensitive than males with respect to this character (though the small number of animals dosed precluded a definitive statement on this matter). After comparing various benchmark dose algorithms, AIG analysis indicated that the multistage algorithm most closely represented the teeth grinding data in females (Table III-3; for details of the BMD analysis, see Attachment III). In this manner, an LED_{05} of 0.02 mg/kg (ED_{05} = 0.03 mg/kg) was established. This compared favorably to the LED_{05} of 0.01 mg/kg (ED_{05} = 0.02 mg/kg) generated for the same character in the WARF (1978a) study.

This study was considered to be supplemental with respect to FIFRA guidelines.

Table III-3. Dose dependence of two clinical signs in the acute oral gavage study of FMC (2002)

	Carbofuran, mg/kg		
	0	**0.5**	**1.0**
Teeth grinding [1]			
Males	0/8	3/9	4/9 [2]
Females	0/8	5/8*	7/9**
Body tremors [1]			
Males	0/8	0/9	4/9 [2]
Females	0/8	1/8	8/9**

*, **: p<0.05, 0.01 (Fisher exact statistics were executed by DPR.)
[1] Observations were limited to one occurrence per animal.
[2] p=0.053

****

Only summary information on the capacity for ocular and dermal irritation by technical carbofuran is available. No ocular irritation at 1-168 hours post dose was observed in rabbits upon conjunctival instillation of 5 mg of carbofuran in one summary study (FMC, 1971). Another reported only a pale red erythema after a 24-hr dermal contact period (FMC, undated). (*Note*: These FMC studies may have been done by IBT, though it's not always possible to discern.) Carbofuran was reported not to cause dermal sensitization in guinea pigs (JMPR, 1996).

****

A series of studies by Gupta, Goad and Kadel established biochemical changes accompanying acute subcutaneous injection into rats of 1.5 mg/kg carbofuran. This dose was sufficient to produce cholinergic effects. Hypercholinergic signs of both central and peripheral origin, including severe muscle fasciculations, convulsions, tracheobronchial secretions and diarrhea, developed within 7-30 minutes. These lasted for about 2 hours. Decreases in ATP and phosphocreatine were noted soon after treatment in hemidiaphragm muscle. It was speculated that these resulted from tremor-induced high energy phosphate utilization (Gupta *et al.*, 1991a). However, similar decreases were also noted in the liver, which cannot undergo muscular tremors (Gupta *et al.*, 1994b). Total creatine kinase (CK) activity in serum was increased concomitantly with depletion of certain CK isozymes in brain, heart and hemidiaphragm, suggesting leakage from damaged tissues. It was hypothesized that lower ATP and phosphocreatine levels in muscle led to increased membrane permeability and resultant leakiness (Gupta *et al.*, 1994b, 1994c). Increased ATP synthesis was indicated by initially reduced phosphocreatine levels and elevated levels of CK isozymes in muscle and brain. Serum LDH levels also increased due to carbofuran-induced leakage (Gupta *et al.*, 1991b). Organ-specific LDH isozyme profiles were altered in the hemidiaphragm, brain, heart, liver and kidney, suggesting a more generalized pattern of tissue damage. In some cases, particular LDH isozyme activities increased. This was arguably a response to alterations in metabolic demand. Perturbations of serum and liver lipids and lipoproteins were also observed (Gupta *et al.*, 1994c). It was not known whether these were direct or secondary effects.

b. Carbofuran formulations

Results of acute toxicity and primary irritation studies on carbofuran formulations are summarized in Table III-3.

One acute 6-hour inhalation toxicity study on Furadan 75 WP (NIA 10242 75 WP) attempted to establish a NOEL for cholinesterase inhibition in rhesus monkeys (FMC, 1967c). In study group #1, 2 males and 2 females were first exposed to 1.3 mg/m^3, and then, one day later, to 2.0 mg/m^3. Plasma AChE was suppressed 74-87% in males and 39-71% in females after the 6-hour exposure to 1.3 mg/m^3, and remained suppressed the following day. It was less clear that an effect occurred with the RBC AChE. Exposure to 2.0 mg/m^3 resulted in similar suppressions. It was clear that recovery was in process by 6 days post dose. In study group #11, 2 males and 2 females were exposed to 0.43 mg/m^3 on day 1, 0.56 mg/m^3 on day 3, 0.86 mg/m^3 on day 8 and 1.8 mg/m^3 on day 13. Exposure to 0.86 mg/m^3 resulted in a 19-27% inhibition of plasma AChE and 17-30% inhibition of RBC AChE. Inhibition was not evident at 0.56 or 0.43 mg/m^3 . For unknown reasons, inhibition of RBC AChE was more evident in study #11. A NOEL for AChE inhibition was established at 0.56 mg/m^3 (0.56 pg/L).

Table III-4a. The acute toxicity of technical grade (96-99%) carbofuran

Species	Toxicity Category	Dose / Score	Ref.
Oral LD_{50}		**mg/kg**	
Rat	I	*M*: 7.8-18; *F*: 5-13.8	1
Rat	I	*M*: 13.2-13.3; *F*: 5.3-5.6	2,3
Rat	I	11-15 (sex not reported)	4
Rat (corn oil vehicle)	I	*M*: 14.1 (6.82-29.3)	8
Rat (propylene glycol vehicle)	I	*M*: 14.1 (8.91-22.4)	8
Rat	I	*F*: 2-20	9
Rat	I	*M*: 10.5 (8.4-13.1); *F*: 8.0 (6.7-9.5)	12
Rat	I	*M*: 12.0 (10.0-14.2); *F*: 12.9 (11.2-14.9)	13
Rat	I	*M*: 5.2 (3.7-7.4); *F*: 5.8 (4.3-7.9)	14
Rat	I	*M*: 9.17 (7.37-11.40); *F*: 10.94 (8.75-13.69)	15
Rat (neonates)	I	*M/F*: 8.11	16
Rat (weanlings)	I	*M/F*: 7.30 (1.85-51.34)	16
Rat	n/a	LED_{05}=0.02 mg/kg (ED_{05}=0.03 mg/kg)	18
Mouse	I	14.4 (sex not reported)	1
Mouse	I	2 (sex not reported)	5
Mouse	I	9.5 (sex not reported)	11
Guinea pig	I	9.2 (sex not reported)	1
Cat	I	2.5-3.5 (sex not reported)	1
Dog	I	15-19 (sex not reported)	1
Dermal LD_{50}		**mg/kg**	
Rat	II	*M/F*: >500	1
Rat	I	120 (sex not reported)	5
Rabbit (abraded skin)	III	*M*: 2703 (2093-3489)	17
Rabbit (intact skin)	III	*M*: 4402 (2900-6685)	17
Rabbit	II	885 (sex not reported)	5
Rabbit	II / IV	*M/F*: >2000	1
Inhalation LC_{50}		**mg/L**	
Rat, 1-hr	n/a	*M*: 0.091-0.108; *F*: 0.080	1
Rat, 4-hr	II	*M*: 0.088; *F*: 0.075-0.11	1
Intraperitoneal LD_{50}		**mg/kg**	
Rat	n/a	*M*: 8.2; *F*: 2.8	1
Rat	n/a	*M/F*: 1.4	1
Rat	n/a	*M/F*: 2 (lethal dose)	5
Mouse (100% DMSO vehicle)	n/a	0.055 (sex not reported)	10
Mouse (5% DMSO vehicle)	n/a	2 (sex not reported)	11
Eye irritation			
Rabbit	n/a	non-irritating (sex not reported)	6
Dermal irritation			
Rabbit	n/a	slightly irritating (sex not reported)	7
Dermal sensitization			
Guinea pig	n/a	negative (sex not reported)	1

*NR, not reported

[1] JMPR, 1996; [2] FMC, 1983a; [3] FMC, 1983b; [4] Abdel-Aal & Helal, 1980; [5] Gupta, 1994; [6] FMC, 1971a; [7] FMC, undated; [8] FMC, 1964; [9] Jayatunga *et al.*, 1998; [10] Amer *et al.*, 1997; [11] Chauhan *et al.*, 2000; [12] CSE, 1979; [13] MB Res., 1979; [14] Stillmeadow, 1979; [15]FDRL, 1980a; [16]FDRL, 1980b; [17]Stillmeadow, 1981; [18] FMC, 2002

Table III-4b. The acute toxicity of carbofuran formulations

Species	Tox. Category	Dose / Score	Ref.
Furadan 5 Granules (5% granular formulation)			
Oral LD_{50}		mg/kg	
Rat	II	*M*: 119 (101-137); *F*: 212 (157-267)	3
Dermal LD_{50}		mg/kg	
Rabbit (Note: 1/10 rabbits died at this dose)	IV	>10.2 g/kg	3
Dermal irritation			
Rabbit	IV	no irritation	3
Furadan 10G (10% granular formulation)			
Oral LD_{50}		mg/kg	
Rat	II	*M*: 114 (83-157); *F*: 71 (52-97)	1
Rat	II	*M/F*: 131.2±13.3	3
Dermal LD_{50}		mg/kg	
Rabbit	III / IV	>2000 mg/kg	1
Rabbit	IV	>10.2 g/kg	3
Eye irritation			
Rabbit	IV	slight irritation	1
Dermal irritation			
Rabbit	III	slight to moderate irritation	1
Rabbit	III	slight irritation	3
Furadan 15G (15% granular formulation)			
Oral LD_{50}		mg/kg	
Rat	II	*M*: 102.5 (82.0-128.1); *F*: 69.9 (54.8-89.0)	4
Dermal LD_{50}		g/kg	
Rabbit (Note: 1/10 rabbits died at this dose; death not attributed to test article)	III / IV	>2 g/kg	4
Eye irritation			
Rabbit	IV	no irritation	4
Dermal irritation			
Rabbit	IV	slight irritation	4
Furadan 4 Flowable (40% flowable formulation)			
Oral LD_{50}		mg/kg	
Rat	I	*M*: 9.76 (6.03-15.79); *F*: 7.34 (5.62-9.59)	5
Dermal LD_{50}		g/kg	
Rabbit	IV	*M*: 10.29 (6.30-16.81); *F*: 6.78 (4.13-11.14)	5
Inhalation LC_{50}			
Rat	n/a	*M/F*: chamber concentration level not reported; 2 ♀ died	5
Furadan 4 Flowable (40% flowable formulation) (continued)			

Eye irritation			
Rabbit	n/a	slight to moderate irritation (Note: only 0.025 ml applied to each eye due to potential of systemic toxicity) (sex not reported)	5
Dermal irritation			
Rabbit	IV	slight irritation (sex not reported)	5
NIA 10242 50 WP (50% wettable powder formulation)			
Inhalation LC_{50}			
Guinea pig, 4 hr	I	*M/F*: >0.022 mg/L	2
NIA 10242 75 WP (75% wettable powder formulation)			
Inhalation LC_{50}		mg/L	
Guinea pig, 4 hr	I	*M/F*: >0.023	6
Guinea pig, 4 hr	II	*M*: 0.053 (0.047-0.60); *F*: 0.045 (0.028-0.072)	6

*NR, not reported
[1] FMC, 1979
[2] FMC, 1967a (IBT) and Ellison, 1980
[3] FMC, 1981a
[4] FMC, 1981b
[5] FMC, 1984
[6] FMC, 1967b (IBT)

C. SUBCHRONIC TOXICITY

1. Overview

In subchronic studies, cholinergic signs were evident at higher doses, though these may represent acute responses in some cases. Despite a lack of quantitative consistency across laboratories, lowered ChE activities were also noted in the plasma, RBC, and brain compartments. Decrements in body weight and food consumption were common observations, though it was not clear that the former were necessarily a consequence of the latter since demonstration of consumption decrements did not always parallel the weight gain decrements. NOEL/LOEL data from the subchronic studies reviewed for this document appear in Table III-10 at the end of section III.D.

2. Laboratory animal studies

a. Rat - dietary

Carbofuran technical (98.6%) was administered in the diet to 5 Sprague-Dawley rats/sex/dose at 0, 50, 200, 500, 1000, 3000, or 6000 ppm (FMC, 1993). Dosing time was 28 days. Two males in the 6000 ppm group died on days 6 and 7, respectively. No clinical signs were noted for either sex in the 50 ppm treatment group. Exophthalmos was the one sign observed for both sexes in the 200 ppm treatment group. Otherwise, tremors, staggered gait, abdominal staining, unkempt appearance and unthriftiness, splayed hindlimbs, chromorhinorrhea and chromodacryorrhea were noted for the animals in the higher dosing groups. The mean body weights for the males in the 200 ppm groups and above, and for the females in the 500 ppm groups and above, were less than that of the controls ($p<0.05$ or 0.01). No gross lesions were noted in the necropsy examination.

The NOEL for this rangefinding study was set at 50 ppm based on the appearance of clinical signs and lower mean body weights at 200 ppm. As food consumption was not monitored, the carbofuran consumption rate could not be determined.

b. Mouse - dietary

Carbofuran was administered in the diet to CD-1, COBS mice (20/sex/dose) at doses of 0, 50, 100, 500 and 1000 ppm (Bio/dynamics, 1982). Due to an absence of overt toxicity, the 50- and 100-ppm dose groups were elevated to 1500 and 2000 ppm, respectively, after 4 weeks of exposure. The survivors in these groups were sacrificed after one further month (*i.e.*, after 2 months total exposure). The remaining dose groups were terminated after 3 months of exposure. There was one spontaneous death at 50 pprn during week 2 and one accidental death at 500 ppm during week 4. These were not attributed to treatment. Observations of red / clear nasal discharge and yellow ano-genital staining were made at and above 500 ppm, though the frequency of occurrence was not provided in the Report. Weight losses of 8-10% were evident in the 50/1500-ppm and 100/2000-ppm groups in the week following the dose change, achieving statistical significance in weeks 7 and 8 (all animals in these dose groups were terminated at that time). A similar statistically significant loss in body weight occurred after 1 week among 1000-ppm females, though subsequent weight gains appeared similar to controls. Food consumption was lowered in the two dose groups after the dose change, achieving statistical significance in females. Consumption was also somewhat lower than controls in 500 and 1000-ppm females. Brain AChE activities were measured only at the 1-month interim sacrifice, before the dose change. The following activities, expressed in µM/ml/min, were obtained at increasing doses (% inhibition compared to controls appears in parentheses): males - 2.74, 2.05** (25%), 2.12** (23%), 1.15** (58%), and 1.19** (57%); females - 2.84, 2.28 (20%), 1.93** (32%), 1.37** (52%), and 1.47** (48%) (**p, 0.01). Thus statistically significant inhibition

was measured at as low as 50 pprn in males. However, greater inhibition was not noted at the next higher dose, casting some doubt on the toxicologic significance of the effect at the LOEL.

A LOEL based on inhibition of brain cholinesterase at 1 month was at 50 ppm, equivalent to a mean consumption of 7.9 mg/kg/day in males and 10.3 mg/kg/day in females. A NOEL was not estimated. The study was not FIFRA compliant. It was used by the Registrant as a dose justification for the later chronic mouse dietary study (IRDC, 1980a).

c. Rabbit - dermal

In a rangefinding study, carbofuran (96.9%) was administered to an occluded site on the shaved backs of rabbits for 7 days, -6 hr/day (FMC, 1985a). Four animals/sex/dose received 0, 100, 300 or 1000 mg/kg-bw/day of saline-moistened test material. Standard observations for clinical signs, mortality, skin irritation, body weights and food consumption were made. Blood and brain were collected for cholinesterase assays following the final exposure day. There were neither deaths nor clinical signs (systemic or local) of carbofuran-mediated toxicity. No clear effects on body weight or food consumption were observed. ChE activities in U/ml (RBC and plasma) or U/g (brain) at ascending doses were as follows: RBC, males - 2.20, 1.90 (14%), 2.03 (8%), 1.83 (17%); RBC, females - 2.53, 1.95 (23%), 2.35 (7%), 1.83 (28%); plasma, males - 0.90, 0.63 (30%), 0.63 (30%), 0.48** (47%) (**p<0.01); plasma, females - 0.70, 0.80 (-14%), 0.73 (-4%), 0.55 (21 %); brain, males - 13.20, 9.80 (26%), 6.78 (49%), 6.10 (54%); brain, females - 11.28, 10.05 (11%), 11.10 (2%), 12.37 (-10%). Statistically significant inhibition was noted only in high dose male plasma. The general lack of statistical significance may have been a function of the low number of animals tested. Necropsies did not reveal carbofuran-mediated effects.

A NOEL of 100 mg/kg/day was established based on non-statistically significant inhibition of brain cholinesterase at 300 mg/kg/day. An estimated NOEL was not calculated because this was a rangefinding test; as such, it was not designed to be a complete FIFRA compliant study.

In the definitive study, 6 rabbits/sex/dose were exposed by the dermal route to saline-moistened carbofuran (96.9% purity) for 21 consecutive days, ~6 hr/day (FMC, 1985b). Doses were 0, 10, 100, or 1000 mg/kg-bw/day. The test site was shaved and semi-occluded. Observations for overt toxicity and mortality were made twice per day prior to, and during, the exposure period. Observations for local skin irritation were made daily before dosing. Body weights were measured weekly, while food consumption was measured daily. Clinical laboratory determinations were made immediately following the final exposure period on day 21. These measurements included cholinesterase determinations (RBC, plasma and brain) and standard hematologic and clinical chemistry determinations. Brain ChE was measured in the right half of the brain and in a slice from the left half.

There were no deaths, clinical signs nor effects on body weight or food consumption that were clearly related to treatment. ChE activities may have been lower in male brains at 100 and 1000 mg/kg/day, though the lack of statistical significance at those doses combined with the apparent lack of any effect in brain slices or in female brains should temper the interpretation of this result (Table III-5). However, male brain cholinesterase inhibition was also seen in the rangefinding study (see preceding summary; FMC, 1985a), strengthening the case for a carbofuran-based etiology in the current study. The apparently greater inhibition in the rangefinding study could have been due to the fact that the tissues were assayed after only one week, compared to 3 weeks in the present study. No effects were seen on RBC or plasma cholinesterases. Clear test article effects were not seen with hematology, serum chemistry, organ weight determinations, necropsy, or histopathology.

The NOEL was set at 100 mg/kg/day based on apparent inhibition of male brain

cholinesterase activity at 1000 mg/kg/day. The apparent brain ChE inhibition at 100 mg/kg/day was not considered to be toxicologically significant in light of the similar level of non-statistically significant inhibition at 1000 mg/kg/day. This study was considered acceptable by FIFRA guidelines.

Table III-5. Mean ChE activities in rabbits after 21 consecutive days, 6 hr/day, of dermal exposure to carbofuran (FMC, 1985b)

			Carbofuran, mg/kg/day			
			Control	10	100	1000
Plasma	n					
Males	6	Day 21	0.88 [1]	1.03 (-17)	0.85 (3)	0.72 (8)
Females	6	Day 21	0.86	0.90 (-5)	0.92 (-7)	0.77 (11)
RBC						
Males	6	Day 21	1.95[1]	1.93 (1)	1.78 (9)	1.72 (13)
Females	6	Day 21	1.78	1.57 (12)	1.60 (10)	1.62 (9)
Brain halves						
Males	6	Day 21	15.13[1]	15.13 (0)	12.00 (21)	11.25 (26)
Females	6	Day 21	12.74	15.07 (-18)	12.58 (1)	13.25 (4)
Brain slice						
Males	6	Day 21	15.35[1]	15.33 (0)	16.82 (-10)	14.93 (3)
Females	6	Day 21	14.84	15.60 (-5)	13.72 (8)	15.92 (7)

Note: Numbers in parentheses represent the percent inhibition of enzyme activity compared to controls.
[1] Enzyme activities are expressed in units/ml for both plasma and RBC, and in units/g for brain.

d. Dog - dietary

Carbofuran (99.6% pure) was fed to beagles through the diet for 13 weeks at 0, 10, 70 and 500/250 ppm (the concentration was reduced at the high dose from day 6 onwards due to severe toxicity) (RCC, 1987a). These were equivalent to carbofuran doses of 0, 0.45, 3.11 and 10.85 mg/kg/day in males and 0, 0.41, 2.99 and 10.41 mg/kg/day in females. There were 4/sex/dose, plus an additional 2/sex were added to the control and high dose groups to study reversibility of any effects over an additional 4-week period.

One high dose female died on day 5. This death was considered treatment-related. Symptoms exhibited by this dog included muscle twitching, hyperemia of the oral mucus membranes, vomiting and salivation on day 1, and decreased motility, hyperemia of the oral mucus membranes and abdominal skin, vomiting and salivation on days 2-4. Invaginated jejunum, possibly a result of intestinal hypermotility, was observed at necropsy. Clinical signs at all doses included hyperemia of the ear pinnae (foci or larger areas), abdominal skin and oral mucus membranes and an increase in salivation. Only high dose dogs exhibited muscle spasms (twitching of the facial muscles, occasionally accompanied by tremors), ataxia, decreased motility, tachypnea, deep respiration and vomiting. Body weight measurements in the week between the pretest measurement and treatment day 2 (when the first treatment weight determinations were made) showed substantial mean losses at the high dose in both sexes (grams gained at ascending doses, males: 286, 273, 156, -467**; females: 206, 142, 168, -499**; **p<0.01). Weight gains between days 2 and 9 also showed statistically significant

effects at the high dose (males: 286, 277, 68, -39**; females: 262, 332, 188, 49*; *, **p < 0.05, 0.01). After this point, weight gain rates were not significantly different from controls at any dose. Decrements in food consumption may partially account for the decrements in body weight (food consumption in g/animal/day, days 1-7, males: 250, 267, 243, 109**; females: 251, 231, 202, 126**; p<0.01). Male food consumption remained statistically depressed at the high dose through day 56; female consumption was not significantly different from controls after day 7. In general, it appears that after the lowering of the dose on day 6, a period of weight gain and food consumption similar to the other dose groups ensued,

Hearing tests, ophthalmoscopic exams, electrocardiograms, hematology, clinical chemistry, and macroscopic and microscopic pathology failed to reveal treatment-related anomalies.

Dose dependent inhibition of plasma and RBC cholinesterases was noted at each time point (Table III-6). For plasma ChE, statistical significance was only noted at the mid and high doses; non-statistically significant inhibition at the low dose never rose above 27%. Similarly, for RBC ChE, statistical significance was only achieved at the mid and high doses; however, nonstatistically significant inhibition at the low dose was consistently above 20% in males and rose to 37% on test day 1 and 35% at 13 weeks. Brain ChE, measured only at completion of the study at 14 weeks, did not show inhibition. At the end of the recovery period, ChE activities in plasma, RBC, and brain were comparable to controls.

The LOEL for this study was set at 10 ppm (0.41 mg/kg-bw/day) based on nonstatistically significant inhibition of RBC ChE at that dose, particularly in males. The estimated NOEL (ENOEL), calculated using an uncertainty factor (UF) of 3, was 0.15 mg/kg-bw/day. A UF of 3 was chosen in recognition of the non-statistically significant nature of the inhibition, in addition to questions concerning the biological meaning of RBC ChE inhibition.

This study was considered acceptable by FIFRA guidelines.

Table III-6. Mean ChE activities in beagle dogs at various time intervals during daily gavage administration of carbofuran over a 13-week period (RCC, 1987a)

		Carbofuran, ppm [1]			
		Control	**10**	**70**	**500/250**
Plasma ChE					
Males	**Pretest**	6.65 [2]	7.83	7.13	7.83
	Day 1	5.83	5.47 (6)	1.93* (67)	0.93* (84)
	Day 3	6.11	6.17 (-1)	2.63* (57)	3.43* (44)
	Day 7	6.04	5.90 (2)	2.84* (53)	1.50* (75)
	Day 14	6.61	6.49 (2)	3.16* (52)	1.79* (73)
	Week 6	7.22	7.19 (0)	3.81* (47)	1.61* (78)
	Week 13	6.86	6.60 (4)	3.38* (51)	1.54* (78)
	Week 14	6.61	6.17 (7)	2.73* (59)	1.50* (77)
Females	**Pretest**	6.83	5.74	6.01	7.08
	Day 1	5.61	4.45 (21)	1.82* (68)	1.22* (78)
	Day 3	6.36	4.72 (26)	2.52* (60)	3.22 (49)
	Day 7	6.11	4.67 (24)	2.41* (61)	1.20* (80)
	Day 14	6.94	5.52 (20)	2.84* (59)	1.80* (74)
	Week 6	8.04	6.38 (21)	3.49* (57)	2.06* (74)
	Week 13	7.76	5.63 (27)	3.16* (59)	1.63* (79)
	Week 14	-----	-----	-----	-----
RBC ChE					
Males	**Pretest**	2.49 [2]	2.50	2.78	2.95
	Day 1	2.34	1.71 (37)	0.81* (65)	0.31* (87)
	Day 3	2.61	2.07 (21)	1.15* (56)	1.20* (54)
	Day 7	2.66	1.95 (27)	1.07* (60)	0.57* (79)
	Day 14	2.68	2.05 (24)	1.15* (57)	0.68* (75)
	Week 6	3.15	2.35 (25)	1.33* (58)	0.67* (79)
	Week 13	2.37	1.54 (35)	0.81* (66)	0.50* (79)
	Week 14	2.76	2.24 (19)	1.13* (59)	0.67* (76)
Females	**Pretest**	2.85	3.06	2.18	2.19
	Day 1	2.64	2.18 (17)	0.73* (72)	0.37* (86)
	Day 3	3.11	2.52 (19)	1.05* (66)	0.80* (74)
	Day 7	2.96	2.46 (17)	1.03* (65)	0.53* (82)
	Day 14	3.12	2.54 (19)	1.00* (68)	0.63* (80)
	Week 6	3.53	3.12 (12)	1.30* (63)	0.62* (82)
	Week 13	2.22	2.09 (6)	0.92* (59)	0.46* (79)
	Week 14	-----	-----	-----	-----
Brain ChE					
Males	**Week 14**	4.97 [3]	5.43 (-9)	5.45 (-10)	4.70 (5)
Females	**Week 14**	4.45	4.78 (-7)	4.41 (1)	5.26 (-18)

Note: Numbers in parentheses represent the percent inhibition of enzyme activity compared to controls. All control & high dose groups consisted of 6/sex/dose except for high dose ♀, days 7 & 14 and weeks 6 & 13, which had 5 due to the death of animal #38. All low and mid dose groups contained 4/sex/dose.
[1] Mean equivalent doses: 0, 0.45, 3.11 and 10.85 mg/kg/day (♂); 0, 0.41, 2.99 and 10.41 mg/kg/day (♀)
[2] µmol-SH/ml [3] µmol-SH/g *$p \leq 0.05$, Dunnett test

The accompanying study (RCC, 1987b) was designed "to establish a 'no effect level' with

respect to hyperemia, increased salivation, plasma and erythrocyte cholinesterase activity of carbofuran in Beagle dogs", all of which were demonstrated in the RCC (1987a) study. Carbofuran (99.6% pure) was administered in the diet to male beagles, 4/dose, for 4 weeks. Doses were 0 and 5 ppm (~0.22 mg/kg/day). There was a higher incidence in treated animals of vomiting (0/4 in controls, 2/4 at 5 ppm). However, this sign only occurred once over the entire 4-week period in each animal. Mucus in feces was detected in 2/4 controls and 4/4 dosed animals. In two of the dosed animals, this was observed only once or twice over the 4-week period. Food consumption was not convincingly impacted by treatment. Mean body weight gains were also not noticeably affected, though the 5-ppm group appeared to have some very low gainers in the first two weeks (for example, the mean and standard deviation in percent weight gain during the first week among controls was 5.23% ± 1.41%, while among treated animals was 3.50% ± 3.52%). Erythrocyte ChE was statistically lower than controls by 25-37% on days 1, 3, 7, 14 and 28 ($p<0.05$). However, as pretest values were also 21% lower than controls ($p<0.05$), it was difficult to confidently assign the effect to carbofuran.

The LOEL was set at 5 ppm (~0.22 mg/kg/day) based on (1) clinical signs (vomiting and mucus in feces), though the high incidence of these signs in controls and the low occurrence rate in the dosed animals placed this designation in some doubt, and (2) a decrease in RBC ChE activity at 5 ppm. The validity of the latter measurements is in question due to observation that the pretest mean body weight for the treatment group was also lower than the control value.

A NOEL was not established for this study, which was designed as a companion to the 13-week study (RCC, 1987a). It did not fulfill FIFRA requirements for a subchronic study.

D. CHRONIC TOXICITY AND ONCOGENICITY

1. Overview

As was true for the acute and subchronic toxicity tests, cholinergic responses to carbofuran exposure were apparent in the chronic tests, as were suppressions of plasma, RBC, and brain cholinesterases. Decrements in body weight gain and food consumption were also documented. Perhaps the most toxicologically interesting responses, observed in the 1-year dog study (as well as in some of the genotoxicity, reproductive toxicity, and developmental toxicity studies; see sections E, F, and G below), were testicular and spermatogenic disturbances. A mechanistic basis for such responses is not currently available. NOEL/LOEL data from these studies appear in Table III-9 at the end of this section (section III.D). No evidence for oncogenicity was forthcoming in the chronic toxicity studies reviewed for this document. However, epidemiologic evidence for an association between carbofuran exposure and lung cancer incidence was forthcoming in a recent study of pesticide applicators.

2. Human studies (epidemiology)

Bonner *et al.* (2005) examined data from the Agricultural Health Study, a prospective cohort study of restricted-use pesticide applicators and their spouses, in an attempt to define a relationship between carbofuran exposure and cancer incidence. Exposure of 49,877 licensed pesticide applicators from Iowa and North Carolina was documented based on responses to a self-administered questionnaire. The basic parameters used to classify the extent of exposure to 22 pesticides (including carbofuran) were: (1) years of use, (2) use frequency per average year, and (3) date that use began. Poisson regression was used to calculate rate ratios (RR) and 95% confidence intervals. Analyses were limited to tumor sites showing more than five cases per exposure category. These included all lymphatic-hematopoietic cancers (Hodgkin,

non-Hodgkin, multiple myeloma and leukemia), non-Hodgkin's lymphoma, and cancers of the colon, lung and prostate. Adjustments were made for age, gender, education, smoking, alcohol consumption, family history of cancer, year at enrollment in the study, state of residence and the five pesticides most highly correlated with carbofuran use (permethrin, *S*-ethyl dipropylthiocarbamate (EPTC), chlorpyrifos, fonofos and trichlorfon).

No association between carbofuran exposure and "all cancers" was identified. However, when cancer types were differentiated, lung cancer risk showed a positive association, with the RR increasing from 1.0 in those with 0-9 lifetime exposure days (LFD) to 1.61 (10-39 LFD), 2.54 (40-109 LFD) and 3.05 (>109 LFD). This was the case when the referent was the low-exposed population (*i.e.*, the 0-9 LFD category). On the other hand, no association was identified when the referent was the nonexposed population - the RR was 1.38 for the 40-109 LFD category. This apparent incongruity was unexplained, though confounding factors such as differences in exposure to other pesticides and differences with regard to corn production activities may have contributed. The authors speculated that the low-exposure group may be a more appropriate referent than the nonexposed group, though this remains unclear. The authors claim to have removed smoking as a confounder because pack-years of smoking was not correlated with LFD and use of "pack-years as a continuous variable or a combination of smoking status (never, former, current), number of cigarettes smoked per day and number of years smoked [were so used], the risk estimates were similar with each respective model". However, this point was not entirely clear, as the very low number of lung cancer cases in the non-smoker category precluded analysis, making it possible that "the risk of lung cancer is limited to smokers and former smokers".

The positive correlation between lung cancer incidence and extent of carbofuran exposure may suggest a causative role for carbofuran. However, the lack of correlation when the nonexposed group was used as the referent, the possibility that smoking is a confounder, and the paucity of corroborating studies either in animals or humans, suggest caution should be exercised in the interpretation of these data.

3. Laboratory animal studies

a. Rat - dietary

In a study of the effects of long-term carbofuran exposure, 90 Charles River CD rats/sex/dose were exposed to technical grade carbofuran (95.6% purity) in the diet for 2 years (IRDC, 1979a). Doses were 0, 10, 20 or 100 ppm, resulting in mean internal doses of 0, 0.38, 0.76, and 4.04 mg/kg/day in males, and of 0, 0.44, 0.86, and 4.93 mg/kg/day in females (calculated by the risk assessor from mean food consumption and body weight data provided on p, 10 of the study report). Interim sacrifices of 10/sex/dose were conducted at 6, 12 and 18 months. Hematologic and biochemical exams, including blood and brain AChE activity determinations, were carried out at those times, as well as at termination (24 months). In addition, general observations (appearance and behavior, mortality, body weights and food consumption), ophthalmologic exams, urinalyses and pathologic exams were performed.

Neither mortality nor clinical signs were observed. Ophthalmology, urinalysis and pathology were negative. Between weeks 13 and 104, statistically significant decrements in body weight between experimental and control animals were seen among 100-ppm males (7-14%). Smaller decrements (1-9%) were seen among 100-ppm females, achieving statistical significance only at week 39. Food consumption was unaffected by dose. Inhibition of plasma, RBC, and brain ChE was noted at the high dose at 6, 12, 18 and 24 months, achieving statistical significance on a number of occasions. Levels of inhibition in males reached 37%, 24% and 25% for plasma, RBC and brain AChE, respectively. The corresponding maximal

inhibition levels in females were 26%, 19% and 43%. These results are summarized in Table III-7. There was no evidence for tumorigenicity.

The NOEL for this study was established at 20 ppm, equivalent to a mean consumption level, calculated by the risk assessor, of 0.8 mg/kg/day in males and 0.9 mg/kg/day in females. The NOEL was based on statistically significant inhibition of brain, plasma, and RBC ChEs and reduction of body weight at 100 ppm (4.0 mg/kg/day in males and 4.9 mg/kg/day in females). This study was considered acceptable under FIFRA guidelines.

Table III-7. Mean ChE activities in rats at 6-month intervals during dietary administration of carbofuran over a 2-year period (IRDC, 1979a)

		Carbofuran, ppm [1]			
		Control	10	20	100
Plasma ChE					
Males	**Month 6**	2.2 [2]	2.0 (9)	2.3 (-5)	1.6** (27)
	Month 12	3.5	3.3 (6)	2.8 (20)	2.2** (37)
	Month 18	4.4	4.9 (-1)1	4.5 (-2)	3.3* (25)
	Month 24	6.0	5.2 (13)	5.4 (10)	4.2 (30)
Females	**Month 6**	7.1	6.4 (10)	7.5 (-6)	6.9 (3)
	Month 12	12.9	12.6 (2)	10.5 (19)	9.6* (26)
	Month 18	11.2	12.3 (-10)	11.2 (0)	9.5 (15)
	Month 24	11.9	13.5 (-13)	13.2 (-11)	10.7 (10)
RBC ChE					
Males	**Month 6**	11.9 [2]	12.1 (-2)	11.7 (2)	11.8 (1)
	Month 12	14.2	14.5 (-2)	13.4 (6)	11.7** (18)
	Month 18	22.5	21.3 (5)	20.0 (11)	17.1* (24)
	Month 24	16.1	15.7 (2)	15.1 (6)	13.1** (19)
Females	**Month 6**	13.9	13.1 (6)	12.4 (11)	12.1* (13)
	Month 12	14.6	14.0 (4)	13.7 (6)	13.0 (11)
	Month 18	20.6	20.0 (3)	20.6 (0)	18.1* (12)
	Month 24	17.7	17.7 (0)	17.0 (4)	14.3** (19)
Brain ChE					
Males	**Month 6**	10.6 [3]	12.2 (-15)	11.8 (-11)	10.6 (0)
	Month 12	10.5	10.4 (1)	10.4 (1)	9.3 (11)
	Month 18	13.9	14.4 (-4)	13.9 (0)	10.4** (25)
	Month 24	10.5	10.8 (-3)	10.4 (1)	8.3** (21)
Females	**Month 6**	17.1	16.1 (6)	15.1 (12)	13.3 (22)
	Month 12	11.4	10.6 (7)	11.2 (2)	9.4 (18)
	Month 18	15.4	15.7 (-2)	14.9 (3)	11.4** (26)
	Month 24	15.1	13.3 (12)	13.3 (12)	8.6** (43)

Note: ChE assays were performed on 10 rats/sex/dose for months 6, 12 & 18. Assays were performed on 20 rats/sex/dose for Month 24.

[1] Mean equivalent doses: 0, 0.38, 0.76, and 4.04 mg/kg/day in males, and 0, 0.44, 0.86, and 4.93 mg/kg-bw in females

[2] Units of activity (note: the report provides no normalizing volume; it is presumed that this is 10 ml)

[3] Units of activity/g

*$p \leq 0.05$, **$p \leq 0.01$ (analysis of variance, Bartlett's test, and Dunnett's test)

b. Mouse - dietary

One hundred CD-1 mice/sex/dose were exposed for 2 years to dietary carbofuran technical (95.6% purity) (IRDC, 1980a). Doses were 0, 20, 125, or 500 ppm, resulting in mean internal doses of 0, 3.0, 18.4, and 72.6 mg/kg/day in males, and of 0, 3.3, 20.8, and 78.6 mg/kg/day in females (calculated by the risk assessor from mean food consumption and bodyweight data

provided on p. 15 of the study report). Interim sacrifices were performed for purposes of hematologic, biochemical and urine analysis on 10/sex/dose at 6, 12, and 18 months. Terminal sacrifices were conducted at 24 months. Conventional observations for mortality, clinical signs, body weight / food consumption, organ weights, and necropsy / histopathology were also made.

No significant differences between treated and control animals were noted in mortality or hematologic, ophthalmoscopic, or urinary parameters. Clinical signs attributable to exposure were not observed. Consistent statistically significant decrements in body weight were noted in both sexes only at the high dose and only at weeks 13, 26, 39, 52, and 65, but never exceeded 6.2%. At the end of the study, no statistical differences in body weights were observed, though group means were slightly lower than controls at the high dose. Food consumption at the high dose was statistically lower than controls for both sexes during weeks 1-13 (4.8 vs. 5.6 g/mouse/day in males and 4.6 *vs.* 5.3 g/mouse/day in females) and weeks 79-91 (5.4 vs. 6.0 g/mouse/day in males and 5.2 *vs.* 6.1 g/mouse/day in females). It was also statistically lower for females during weeks 53-65 (4.3 *vs.* 4.6 g/mouse/day). Slight, but not statistically significant, decrements were often observed at the high dose during the other weeks of the study. The only clinical chemical parameter affected was brain ChE (neither plasma nor RBC ChE was measured). Levels of this enzyme were statistically inhibited up to 31 % in both sexes at 125 ppm and up to 52% in males and 55% in females at 500 ppm ($p<0.01$; Table III-8). Sporadic changes in organ weights were noted. However, as these were not associated with specific pathologic changes, they were not attributed to exposure.

The NOEL was set at 20 ppm, equivalent to a mean consumption, calculated by the risk assessor, of 3.0 mg/kg-bw/day in males and 3.3 mg/kg/day in females. This was based on statistically significant inhibition of brain ChE at 18.4 mg/kg/day in males and 20.8 mg/kg/day in females (125 ppm). The study was deemed acceptable by FIFRA standards.

Table III-8. Mean brain ChE activities in mice at 6-month intervals during dietary administration of carbofuran over a 2-year period (IRDC, 1980a)

		Carbofuran, ppm [1]			
		Control	**20**	**125**	**500**
Brain ChE [2]					
Males	**Month 6**	55.4	53.4 (3)	46.4 (16)	40.5** (27)
	Month 12	47.5	58.4 (-23)	39.8 (16)	26.1** (45)
	Month 18	49.0	49.5 (-1)	39.9* (19)	31.2** (36)
	Month 24	54.7	52.9 (3)	37.8** (31)	26.3** (52)
Females	**Month 6**	58.2	56.1 (4)	46.3** (20)	34.6** (41)
	Month 12	54.7	52.8 (3)	39.4** (28)	28.4** (48)
	Month 18	50.4	46.5 (8)	36.7** (27)	22.8** (55)
	Month 24	57.0	53.9 (5)	39.4** (31)	26.7** (53)

Note: ChE assays were performed on 10 rats/sex/dose for months 6, 12 & 18. Assays were performed on 20 rats/sex/dose for Month 24.

[1] Mean equivalent doses, ♂: 0, 3.0, 18.4, and 72.6 mg/kg/day; ♀: 0, 3.3, 20.8, and 78.6 mg/kg/day

[2] Units of activity/g *$p \leq 0.05$, **$p \leq 0.01$ (analysis of variance, Bartlett's test, and Dunnett's test)

c. Wild mouse - dietary

The toxicity of dietary carbofuran (purity not stated) was studied under acute and chronic exposure scenarios in wild-caught mice and first-generation laboratory offspring of the species *Peromyscus gossypinus* (the cotton mouse) and *Peromyscus polionotus* (the old-field mouse) (Wolfe and Esher, 1980). A range-finding 4-day feeding test was conducted to determine dosing

for a chronic study. Ten *P. polionotus*/sex/dose were exposed to diet containing 0.25, 0.5 or 1 mg carbofuran/g feed. By 96 hr, 20% of the low dose and 100% of the high dose mice had died. An unspecified number of single male/female pairings was exposed to 0.1 mg carbofuran/g feed for 8 months. Survival, reproduction and development of young were monitored. Behavioral testing consisting of electronic monitoring of activity in a maze was conducted on male survivors after the end of the exposure period, as well as on animals first exposed for 2 weeks.

While no significant difference from controls was detected for *P. gossypinus*, 44% mortality was recorded for *P. polionotus* ($p<0.01$). Most deaths apparently occurred late in the study, causing little effect on the reproductive assessment. The number and size of litters seemed unaffected by carbofuran in both species. Survival of the litters to 14 days in *P. polionotus* appeared to decrease in exposed mice (90% to 62%), though the investigators did not consider this to be due to treatment. Carbofuran exposure resulted in a weight decrement in neonates of -10% by day 21 in *P. gossypinus*. No such effect was observed in *P. polionotus*, nor were significant effects detected in either species on the time of appearance of various developmental characteristics. (While it was not explicitly stated in the report, it appears that the offspring were not maintained on treated diets.) Eight months of treatment may have lowered the physical activity of *P. polionotus*. Ethanol (vehicle)-treated controls entered into arms of a residential maze 739±440 times compared to 641±370 times in treated animals on day 1 of the test. On day 4 the comparable values were 500±107 in controls and 225±117 in treated animals. The authors of the study argue that these behavioral tests produced negative results, possibly because statistical significance was apparently not achieved.

The LOEL was set at 0.1 mg/g feed, based on a slight body weight gain decrement through post-parturn day 21 in neonates from exposed *P. gossypinus* and somewhat decreased activity in adults following 8 months of exposure in the same species. It was also based on mortality in *P. polionotus*. Assuming that food consumption was 15% of the body weight, the LOEL was estimated at 15 mg/kg-bw/day. This study was not FIFRA-compliant, nor were the results considered robust enough for risk characterization with respect to reproductive or teratologic effects. However, the evidence for mortality at the LOEL dose is considered toxicologically significant.

d. Dog - dietary

In a 14-day rangefinding study, carbofuran (96.1 % purity) was administered in the diet to Beagle dogs (1/sex/dose) (Toxigenics, 1982; the complete study, Toxigenics, 1983, is summarized below). Doses were 0, 18, 32, 56, 100 and 316 ppm. Between days 4 and 14, the dose was raised to 1000 ppm in the 18-ppm group to increase the possibility of demonstrating an effect on RBC ChE. Using the average food consumption during the treatment period, carbofuran consumption was calculated by the risk assessor to be 0, 0.7/28.8, 1.4, 2.4, 3.7 and 9.4 mg/kg/day for males. For females carbofuran consumption was 0, 0.6/26.0, 1.2, 2.0, 2.3 and 7.9 mg/kg/day. At the end of the 14-day treatment, dogs were retained on a maintenance diet for an additional 29 days. Clinical observations, mortality, body weight, food intake, and cholinesterase activities were monitored.

There were no mortalities. Decreased food consumption and body weight loss were noted at 1000 ppm. Decreases in these parameters may also have been present at 316 ppm. However, the low number of animals made it impossible to make a clear determination. Clinical signs were seen only at 1000 ppm, and included muscle tremors, emesis and salivation (male only). As noted in the report (p. 25), symptoms occurred "within approximately two hours after food was offered, were seen (intermittently) for approximately three to seven hours, but were no longer apparent prior to the next day's feeding period." Plasma cholinesterase was inhibited at all doses in a dose dependent manner, ranging from 26-91% inhibition in males (expressed as a

percentage of the pre-test value in each dog) and 16-92% inhibition in females (at 18 ppm, the absolute values measured between days 1 and 3, fell within the historical control range). RBC cholinesterase (AChE) appeared unaffected by dose.

A systemic NOEL was set at 100 ppm (2.3-3.7 mg/kg/day), based on possible decreases in body weight and food consumption at 316 ppm. A cholinesterase NOEL was not established because there was an insufficient number of animals/dose to make meaningful distinctions between dose groups. This study was considered "supplemental", as it was designed to set appropriate doses for more elaborate following studies.

In the subsequent definitive study, six young beagle dogs/sex/dose were exposed to dietary carbofuran (96.1 % purity) at 0, 10, 20 or 500 ppm for 1 year (Toxigenics, 1983). This dosing regime resulted in mean carbofuran intakes of 0.3, 0.6 and 16 mg/kg/day in males and 0.3, 0.6 and 15 mg/kg/day in females. The diets of the high dose animals were supplemented with untreated diet starting in the fifth month. This was done to avert total mortality among males and loss of this treatment level, deemed possible due to frequent emesis of the treated diet, body weight losses, steady physical deterioration and death of one individual. Body weights, food consumption, clinical signs, ophthalmology, hematology, serum chemistry, urinalysis, organ weights and gross and microscopic signs were recorded as normally done for a study of this type. Brain ChE activities were determined using the cerebellum of each dog.

As noted, one 500-ppm male died on study day 202 (week 29) from emaciation and dehydration, having lost 43% of its body weight by the time of death. All other animals survived to study termination. Over the course of the exposure period, high dose males and females sustained statistically significant 12% and 6% mean body weight losses, respectively ($p<0.01$ in both sexes). The other three groups showed body weight gains of 29-33% among males and 19-24% among females, with no statistically significant differences emerging. Food consumption among males was not consistently affected by dosing. High dose females showed generally lower consumption than controls. Emesis was more frequent among 500-ppm males than among their female counterparts, though it was noted in all dogs at that dose. This was considered to reflect "a stronger and/or more rapid toxic response to the ingested test article." Loose stools were observed in all high dose males and 5/6 high dose females, though again, this sign occurred more frequently among the affected males. Thus gastrointestinal toxicity was the likely cause of the emaciation and failure to thrive at the high dose. Other exposure-related symptoms at the high dose included muscle tremors (3/6 males, 2/6 females), salivation (3/6 males, 3/6 females), lethargy (3/6 males, 1/6 females) and prominently exposed nicitating membrane (2/6 females). One high and one intermediate dose female had single incidents of clonic convulsions in week 30 or 43. Due to a lack of dose response, it was difficult to attribute this effect definitively to carbofuran exposure, though such a role could not be excluded. No other clinical signs could be correlated with exposure at 10 or 20 ppm.

Statistically significant reductions in hematocrit, hemoglobin concentration, and total erythrocytes were noted in high dose males starting at 5 months, with a similar, but less marked, response seen in females. Brain ChE was inhibited by 24% (not statistically significant) in males after 1 year. In females, brain ChE was increased by 44%. Statistically significant depression of RBC ChE was seen only in males (months 5, 6 and 11), though not exceeding 27%. Plasma ChE was consistently depressed in a dose-dependent manner. Males appeared to be somewhat more sensitive than females, exhibiting statistically significant inhibition of 17-20% at the low dose of 10 ppm from the first observation at 3 days through 5 months. Statistically significant levels of inhibition at the mid dose ranged between 21% and 31% (6% inhibition at 3 months appeared anomalous). Cholinesterase results are summarized in Table III-9. Some changes were noted for other serum chemical parameters, but their biologic or toxicologic

significance was unknown.

Mean absolute heart and brain weights were reduced by 38% ($p<0.001$) and 15% ($p<0.05$), respectively, in high dose males. Although the report authors judged these changes to be test article related, statistical significance was not realized in females for either organ, nor were relative weights (organ weight / body weight) statistically different in either sex. Also, morphologic changes were not noted for either organ at any dose. Thus the absolute heart and brain weight changes could not be unambiguously tied to treatment. There was a possibly dose-related trend for testes weight reduction at the mid and high doses (15% and 35%, respectively), though statistical significance was not achieved, nor were the relative weights (organ weight / body weight) clearly affected.

Gross pathology revealed 2/5 males with "a remarkable loss of body fat", one of which showed severe alopecia over the entire body. One high dose male and female had bilateral ear abrasions. The skin lesions "were judged to be the result of the depressed condition and recumbency of these animals during the later stages of the study", and thus were considered an indirect effect of exposure. Gross pathology on the high dose decedent revealed emaciation and dehydration, also attributed to exposure. Histopathology revealed the following exposure-related findings: testicular degeneration (degeneration of the seminiferous tubules, giant cell formation or aspermia) in 4/5 high dose and 1/6 mid dose males and minimal-to-moderate lung inflammation in 0/12, 3/12, 1/12 and 7/11 dogs (attributed to carbofuran exposure at the high dose). Hepatocellular centrilobular cytoplasmic atypia suggestive of increased hepatocellular endoplasmic reticulum was noted in 2/12, 9/12, 7/12 and 6/11 dogs. This was also attributed to exposure, though "there were no indications of this compound related lesion progressing to cellular degeneration or necrosis". Such an effect may be indicative of increased enzyme synthesis in the endoplasmic reticulum. In any case, it was not clearly characterizable as an adverse effect. Hepatocellular cytoplasmic atypia (without a centrilobular designation) was also noted in 7/12, 3/12, 3/12 and 4/11 dogs. There was some indication that the severity of this lesion may have increased at the upper two doses.

The NOEL of 10 ppm (0.3 mg/kg-bw/day) was based on dose-dependent testicular degeneration in males, clonic convulsions in one mid- and one high-dose female, and consistent statistically significant reductions in plasma cholinesterase activity in males (21%-31%) at 20 ppm (0.6 mg/kg-bw/day). This study was acceptable by FIFRA standards.

Table III-9. Mean ChE activities in dogs at selected intervals during dietary administration of carbofuran over a 1 -year period (Toxigenics, 1983)

		Carbofuran, ppm [1]			
		Control	**10**	**20**	**500**
Plasma ChE [2]					
Males	**Day 3**	2.11	1.73* (18)	1.59** (25)	0.36** (83)
	Day 7	2.30	1.85* (20)	1.69** (27)	0.54** (77)
	Day 14	2.10	1.70* (19)	1.66** (21)	0.40** (81)
	Month 1	2.30	1.87* (19)	1.58** (31)	0.35** (85)
	Month 2	2.24	1.87* (17)	1.67** (25)	0.40** (82)
	Month 3	1.83	1.49* (19)	1.72 (6)	0.27** (85)
	Month 4	2.10	1.72* (18)	1.63** (22)	0.35** (83)
	Month 5	2.27	1.88* (17)	1.62** (29)	0.32** (86)
	Month 6	2.01	1.74 (13)	1.53** (24)	0.27** (87)
	Month 7	2.10	1.83 (13)	1.57** (25)	0.39** (81)
	Month 8	1.89	1.59 (6)	1.40** (26)	0.31** (84)
	Month 9	2.02	1.83 (9)	1.56* (23)	0.34** (83)
	Month 10	2.11	1.84 (13)	1.61* (24)	0.36** (83)
	Month 11	2.09	1.75 (16)	1.46** (30)	0.30** (86)
	Month 12	2.26	1.99 (12)	1.58** (30)	0.49** (78)
Females	**Day 3**	1.96	1.65 (16)	1.56 (20)	0.33** (83)
	Day 7	2.14	1.82 (15)	1.67 (22)	0.43** (88)
	Day 14	1.99	1.71 (14)	1.59 (20)	0.41** (79)
	Month 1	2.15	1.79 (17)	1.76 (18)	0.40** (81)
	Month 2	2.07	1.79 (14)	1.72 (17)	0.40** (81)
	Month 3	1.68	1.44 (14)	1.36 (19)	0.31** (82)
	Month 4	2.01	1.70 (15)	1.72 (14)	0.34** (83)
	Month 5	2.17	1.88 (13)	1.88 (13)	0.47** (78)
	Month 6	1.90	1.79 (6)	1.63 (14)	0.30** (84)
	Month 7	2.00	1.84 (8)	1.62 (19)	0.43** (79)
	Month 8	1.83	1.60 (8)	1.35* (26)	0.38** (79)
	Month 9	1.96	1.83 (7)	1.59 (19)	0.44** (78)
	Month 10	2.19	1.94 (11)	1.73 (21)	0.45** (80)
	Month 11	2.00	1.66 (17)	1.60 (20)	0.46** (77)
	Month 12	2.20	1.87 (15)	1.83 (17)	0.50** (77)

RBC ChE [2]					
Males	**Day 3**	1.49	1.30 (13)	1.42 (5)	1.49 (0)
	Day 7	1.46	1.38 (5)	1.45 (1)	1.51 (-3)
	Day 14	1.53	1.32 (14)	1.48 (3)	1.39 (9)
	Month 1	1.46	1.40 (4)	1.54 (-5)	1.33 (9)
	Month 2	1.57	1.69 (-8)	1.42 (10)	1.38 (12)
	Month 3	1.49	1.43 (4)	1.40 (6)	1.43 (4)
	Month 4	1.57	1.37 (13)	1.56 (1)	1.43 (9)
	Month 5	1.59	1.43 (10)	1.57 (1)	1.25** (21)
	Month 6	1.54	1.39 (10)	1.50 (3)	1.13** (27)
	Month 7	1.48	1.38 (7)	1.50 (-1)	1.32 (11)
	Month 8	1.50	1.40 (11)	1.59 (-6)	1.35 (15)
	Month 9	1.40	1.33 (5)	1.30 (7)	1.16 (17)
	Month 10	1.34	1.27 (5)	1.30 (3)	1.13 (16)
	Month 11	1.40	1.32 (6)	1.39 (1)	1.06** (24)
	Month 12	1.66	1.56 (6)	1.71 (-3)	1.35 (19)
Females	**Day 3**	1.43	1.54 (-8)	1.54 (-8))	1.54 (-8)
	Day 7	1.45	1.51 (-4)	1.52 (-5)	1.61 (-11)
	Day 14	1.48	1.55 (-5)	1.55 (-5)	1.58 (-7)
	Month 1	1.45	1.63 (-12)	1.51 (-4)	1.56 (-8)
	Month 2	1.79	1.56 (13)	1.56 (13)	1.62 (9)
	Month 3	1.54	1.49 (3)	1.48 (4)	1.46 (5)
	Month 4	1.57	1.60 (-2)	1.53 (3)	1.55 (1)
	Month 5	1.50	1.54 (-3)	1.45 (3)	1.50 (0)
	Month 6	1.49	1.40 (1)	1.38 (7)	1.30 (13)
	Month 7	1.47	1.44 (2)	1.46 (1)	1.50 (-2)
	Month 8	1.51	1.44 (5)	1.55 (-3)	1.50 (1)
	Month 9	1.28	1.38 (-8)	1.30 (-2)	1.27 (1)
	Month 10	1.25	1.31 (-5)	1.35 (-8)	1.34 (-7)
	Month 11	1.35	1.41 (-4)	1.31 (3)	1.40 (-4)
	Month 12	1.65	1.68 (-2)	1.58 (4	1.55 (6)
Brain ChE [3]					
Males	**Month 12**	0.49	0.48 (2)	0.55 (0)	0.37 (24)
Females	**Month 12**	0.32	0.37 (-16)	0.36 (-13)	0.46 (-44)

Note: The data in this table represent the mean ChE activities for 6 animals/sex/dose, with one exception: starting with month 7, only 5 high dose males were assayed due to the death of one animal at that dose (found dead on day 202).

[1] Mean equivalent doses: 0, 0.3, 0.6, and 16 mg/kg/day in males, and 0, 0.3, 0.6, and 15 mg/kg-bw in females

[2] Units of activity, IU/ml (note: the report provides no normalizing volume; it is presumed that this is 10 ml)

[3] Units of activity/g

*$p \leq 0.05$, **$p \leq 0.01$ (analysis of variance, Scheffe's [unequal population] test and/or Tukey's [equal population] test)

Table III-10. NOEL and LOEL values for studies on subchronic and chronic toxicity of carbofuran

Species, strain	Study type and exposure regimen	Effects at LOEL	NOEL, mg/kg/day	LOEL, mg/kg/day	Reference
Rat, SD	28-day subchronic, dietary	Clinical signs and lower mean body weights	50 ppm [1]	200 ppm [1]	FMC, 1993
Mouse, CD-1 COBS	13-wk subchronic, dietary	Inhibition of brain ChE	n/a	M: 7.9 F: 10.3 (50 ppm) [2]	Biodynamics, 1982
Dog, beagle	13-wk subchronic, dietary	Inhibition of RBC ChE	0.15 (ENOEL, UC factor=3)	0.43 (10 ppm) [2]	RCC, 1987a
Rabbit, NZW	21-day repeat dose dermal	Inhibition of brain ChE	100	1000	FMC, 1985b
Rat, SD	2-yr chronic/onco, dietary	Body weight decrement and inhibition of brain ChE	M: 0.8 F: 0.9 (20 ppm)	M: 4.0 F: 4.9 (100 ppm)	IRDC, 1979a
Mouse, CD-1	2-yr oncogenicity, dietary	Inhibition of brain ChE	M: 3.0 F: 3.3 (20 ppm)	M: 18.4 F: 20.8 (125 ppm)	IRDC, 1980a
Mouse, *Peromyscus polionotus* (wild)	8-month chronic/repro., dietary	⇑ Mortality	n/a	~15 (sex unspecified) [2]	Wolfe & Esher, 1980
Dog, beagle	1-yr chronic, dietary	Testicular degeneration and plasma ChE inhibition in males, clonic convulsions in females	M: 0.3 F: 0.3 (10 ppm)	M: 0.6 F: 0.6 (20 ppm)	Toxigenics, 1983

[1] Food consumption was not measured; hence, the carbofuran dose was not estimated.
[2] Lowest dose tested

E. GENOTOXICITY

1. Overview

Evidence from several of the *in vitro* and *in vivo* tests summarized in this section suggest that carbofuran is genotoxic. The *in vivo* tests were of particular concern in the context of a human risk evaluation. Such tests were positive for chromosome abnormalities and micronucleus formation in mice. In addition, sperm abnormalities were induced in mice upon intraperitoneal injection. The latter observation was consistent with similar observations in several species subjected to chronic, reproductive, and/or developmental toxicity tests. These are reviewed in other parts of this document. NOEL/LOEL data from these studies appear in Tables III-11, III-12 and III-13. In addition, data from four studies indicate that the *N*-nitroso derivative of carbofuran was genotoxic in several different test systems.

2. Gene mutation

Tests of various carbofuran lots in the Ames / *Salmonella* test showed them to be weakly mutagenic in the TA 1535 and TA 100 strains in the absence of an S9 rat microsomal activating system. Similar tests conducted by Hour *et al.* (1998) in strains TA98, TA100, and TA1535 were negative. The same investigators obtained positive responses in *Salmonella* strain JK947 using the lactam test, however. Positive responses were also detected both in the absence and presence of S9 in the mouse L5178Y TK+/- lymphoma cell system. Carbofuran did not show mutagenic activity in *Drosophila* at tolerated dose levels. However, despite the submission of two acceptable *Drosophila* studies, the value of these studies was undermined due to the toxicity of this compound to insects. Carbofuran dissolved in ground water tested positive in the “Mutatox” assay for mutation in a dark (non light-emitting) mutant of the luminescent bacterium Vibrio fischeri, strain M169. The gene mutation studies are summarized in Table III-11.

3. Chromosomal aberrations

In vitro studies on Chinese hamster ovary cells designed to determine the potential for induction by carbofuran of chromosomal aberrations were negative (Table III-12). However, *in vivo* studies in the Swiss mouse indicated a potential for induction of chromosomal abnormalities and micronuclei in bone marrow cells after acute and subacute exposures (Amer *et al.*, 1997; Chauhan *et al.*, 2000). The effect on chromosomal abnormalities was accompanied by a decrease in mitotic index, an indication of the cytotoxic potential of carbofuran. As stated by Chauhan *et al.* (p. 126), "Single oral exposure of carbofuran-induced chromosome-type aberrations (fragments and ring formation), chromatid-type aberrations (chromatid breaks and gaps) and occasionally pulverization [occurred] in mouse bone marrow cells. The frequency of CAs [was] comparatively higher in the mice exposed for 4 consecutive days than that of single dose exposure... The types of aberrations were common in both the groups except the occasional induction of ring chromosomes observed in mice exposed to 1.9 mg/kg for 4 consecutive days." In addition, this study showed a non-statistically significant increase in micronucleus formation. Interestingly, the incidence of sperm abnormalities, in particular those occurring in the sperm head region, also increased. When 10,000 sperm from 5 animals were evaluated, a single intraperitoneal injection of 0, 1 or 2 mg/kg resulted in 190, 207 or 604 abnormal sperm, respectively. Treatment with 0.5 mg/kg/day for 5 consecutive days resulted in 584 abnormal sperm (Chauhan *et al.*, 2000).

****

De Saint-Georges-Gridelet *et al.* (1982) also demonstrated induction of micronuclei in mice

(C571311 strain) following oral exposure to carbofuran. However, for unknown reasons, they claim that the inducing dose, 150 mg/kg, was roughly equivalent to the LD_{50}. This is far above the reported LD_{50}s for mice (<14.4 mg/kg; Table III-4a). Either de Saint-Georges-Gridelet *et al.* had a highly impure carbofuran preparation or the particular mouse strain was resistant to its effects.

****

Twenty four hours after a single oral administration of carbofuran to white mice (neither strain nor numbers treated were reported) at 0, 0.1 and 1 mg/kg carbofuran, bone marrow cells were harvested and examined for chromosomal aberrations (Pilinskaya and Stepanova, 1984). 700 metaphases per dose were examined. No convincing effects were noted, though a positive control was not performed.

In the same publication, carbofuran and three metabolites were examined for their ability to induce chromosome aberrations in human lymphocyte cultures. The parent compound induced aberrations at 100 and 300 pg/ml. Two metabolites, 3-OH carbofuran and 3-keto carbofuran, also induced aberrations at 100 pg/ml. 3-keto-7-phenol did not induce aberrations at these concentrations.

The chromosomal aberration studies are shown in Table III-12.

4. DNA damage

Studies in bacterial, mammalian cell, and yeast cultures yielded no evidence for DNA damaging effects of carbofuran (Table III-13).

5. Genotoxicity and cytotoxicity of *N*-nitrosocarbofuran

Blevins *et al.* (1977) examined the ability of six carbamate insecticides - aldicarb, baygon, BUX-TEN, carbofuran, landrin and methomyl - and their *N*-nitroso derivatives to induce DNA strand breaks in cultured human skin fibroblasts. After pre-labeling the DNA by exposing the cells for 2 hours to ^{3}H-thymidine or $^{32}PO_4$, they were then incubated with 10^{-5} M test article for 1 hour, followed by analysis of the cellular DNA on alkaline sucrose gradients. While none of the parent carbamates had a notable effect on the gradient profiles, all of the *N*-nitroso derivatives induced numerous single strand breaks as evidenced by “a profound reduction in sedimentation rate of the DNA measured immediately, at 2 h and 20 h following treatment” (p. 3-4). For carbofuran, the “weight-average molecular weights” of the isolated DNA was 289±24 kD (untreated control, 300±29 kD) at zero time, 276±16 kD at 2 hr and 276±20 kD at 20 hr. For *N*-nitroso carbofuran, the parallel values were 60±5 kD, 38±4 kD and 40±3 kD, respectively. Thus the damage inflicted on the DNA was not amenable to repair within at least the 20-hr time period encompassed in the study. The authors speculated that numerous, relatively stable alkali-sensitive bonds (*i.e.*, bonds subject to disruption by the alkaline sucrose gradient process) were induced by these compounds.

****

Nelson *et al.* (1981) examined the activity of several *N*-nitroso derivatives of carbofuran in the Ames *S. typhimurium* mutagenicity assay and in chromosome aberration and sister chromatid exchange assays in Chinese hamster ovary (CHO) cells. The derivatives, including nitrosocarbofuran (NCF), 3-hydroxynitrosocarbofuran (3-OH-NCF) and 3-ketonitrosocarbofuran (3-K-NCF) (Figure 3, section III.A.6.f.), were synthesized in the laboratory and confirmed by

nuclear magnetic resonance and mass spectoscopy. All three nitroso compounds showed mutagenic activity in the Ames assay with tester strain TA100, though not with TA98. Linear dose responsiveness occurred at 1-5 µg/plate, peaking at 5 µg/plate for 3-OH-NCF and at 10 µg/plate for NCF and 3-K-NCF. Addition of S9 microsomes reduced this activity. 3-OH-NCF proved more toxic than the other two derivatives in the Ames system as gauged by background thinning and presence of microcolonies. The greater toxicity of 3-OH-NCF was probably due to its greater stability under the conditions of the assay.

All three compounds induced chromosome aberrations in CHO cells, though 3-OH-NCF and NCF seemed to be effective at lower doses (as low as $5x10^{-8}$ M) than 3-K-NCF ($5x10^{-6}$ M). Mitotic index and aberration frequency (*i.e.*, percent of metaphases with aberrations and number of aberrations per cell) were inversely related, suggesting that cytotoxicity and clastogenesis occurred at similar concentrations. Both NCF and 3-OH-NCF also induced dose-dependent sister chromatid exchanges between $5x10^{-9}$ and $5x10^{-5}$ M (3-K-NCF was not tested for SCE induction). While the degree of cytotoxicity was not clear at the lower doses, no metaphases were detected at 10^{-4} M.

****

Wang *et al.* (1998) examined the cytotoxicity, mutagenicity and ability to inhibit gap junctional intercellular communication (GJIC) of three *N*-methylcarbamate pesticides - carbofuran, methomyl and aldicarb - along with their *N*-nitroso derivatives in Chinese hamster V79 cells. Cytotoxicity was expressed as percent colony survival after treatment at low cell density. Three-day treatments with the parent compounds showed carbofuran to be the most cytotoxic with a cellular "LD_{50}" of 75 µg/ml, followed by methomyl at 950 µg/ml and aldicarb, which was not toxic. On the other hand, a 2-hour treatment with *NO*-methomyl (*i.e.*, nitrosomethomyl) generated a cellular LD_{50} of 3.6 µg/ml, followed by *NO*-carbofuran at 26.1 µg/ml and *NO*-aldicarb at 39.4 µg/ml. Low concentrations of the nitrosated derivatives apparently stimulated cell growth, though these data were not presented.

Mutation frequency at the *hprt* locus, expressed as the number of 6-thioguanine resistant colonies per 10^6 surviving cells, ranged between 1 and 7 for methomyl and aldicarb at a concentration range of 0-500 µg/ml, while it reached 11 for carbofuran at 50 µg/ml. Mutation frequencies rose substantially with the nitrosated derivatives. *NO*-aldicarb proved the most mutagenic in this study, inducing an average of >2000 resistant colonies per 10^6 surviving cells at 50 µg/ml (55% colony survival), followed by 1500 for *NO*-methomyl at 4 µg/ml (58% survival) and 1000 for *NO*-carbofuran at 25 µg/ml (63% survival).

GJIC was expressed in terms of the recovery rate of 6-thioguanine resistant cells in the presence of an overwhelming majority of 6-thioguanine sensitive cells (*i.e.*, the higher the survival rate, the more inhibited the gap junctional intercellular communication). All three parent compound inhibited GJIC at non-cytotoxic doses (aldicarb: 100, 200 and 400 µg/ml; carbofuran: 25 µg/ml; methomyl: 100 and 200 µg/ml). The nitroso derivatives were not tested for GJIC.

****

The ability of carbofuran and its gastric metabolite, *N*-nitrosocarbofuran (NOCF), to induce genotoxic and cytotoxic effects in Chinese hamster lung (CHL) cells was studied by Yoon *et al.* (2001). Carbofuran was negative in all of the assays performed in the study, but NOCF showed genotoxicity in a number of cases: (1) Ames - *S. typhimurium* test: NOCF was mutagenic in a dose dependent fashion through a concentration of 20 µg/plate in the absence, but not in the presence, of a metabolic activating system. (2) CHL cell proliferation test: NOCF showed

inhibitory activity, registering an IC_{50} of 12.8 μM. (3) DNA fragmentation test: incubation of CHL cells for 48 hr in the presence of 10-30 μM NOCF induced an "oligosomal DNA ladder" on agarose gel electrophoresis of genomic DNA. The presence of lower molecular weight DNA species was considered evidence for xenobiotic-induced fragmentation. (4) Morphologic analysis: The report claims that paraformaldehyde fixation followed by propidium iodide staining showed that a 48-hr treatment with 30 μM NOCF induced "substantial nuclear condensation, shrinkage and a loss of internal nuclear structure", as well as staining of apoptotic nuclear buds and fragments. However, none of this was clear in the photomicrograph supplied in the paper. (5) TUNEL staining (terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling, done with a Boehringer *in situ* "death detection" kit) showed an intense fluorescence in NOCF-treated cells, considered evidence for apoptosis. (6) Flow cytometry: NOCF treatment (48 hr at 10-50 μM) "resulted in the progressive generation of cells with hypodiploid DNA content, resulting in a dose-dependent increase in apoptotic cells. NOCF thus induced an increase in cell cycle arrest at the G_2 / M phase and a decrease of cells in the G_1 phase. (7) Caspase-3 activity: Treatment with NOCF (10-50 μM) resulted in a dose-dependent increase in caspase-3 activity, considered a late apoptotic signal in mammalian cells.

The authors postulated that NOCF induced a GC-to-AT mutation resulting from O^6MeG adduct formation which led to the effects recorded in this study. O^6MeG is the major mutagenic base derivative formed in the presence of DNA methylators. They further claimed that, in later work, they have measured O^6MeG formation when treating calf thymus DNA with NOCF.

Table III-11. Genotoxic effects of carbofuran: gene mutation

Test type / system	Species / strain	Dose	S9	Result	Comments / Reference
Ames test, *S. typhimurium*	TA 1535, 1537, 1538, 98, 100	0, 100, 500, 2500, 5000, 10,000 µg/plate	±	Weak positive -S9, TA 1535 only	Unacceptable (no purity given) / Microbiological Associates, 1983a
Ames test, *S. typhimurium*	TA 1535, 1537, 1538, 98, 100	0, 100, 500, 2500, 5000, 10,000 µg/plate	±	Weak positive -S9, TA 1535 only	Unacceptable (no purity given, single trial) / Microbiological Associates, 1983b
Ames test, *S. typhimurium*	TA 1535, 1537, 1538, 98, 100	0, 100, 500, 2500, 5000, 10,000 µg/plate	±	Weak positive -S9, TA 1535 only	Unacceptable (no purity given, single trial) / Microbiological Associates, 1983c
Ames test, *S. typhimurium*	TA 1535, 1537, 1538, 98, 100	0, 100, 500, 2500, 5000, 10,000 µg/plate	±	Weak positive -S9, TA 1535 only	Unacceptable (no purity given, single trial) / Microbiological Associates, 1983d
Ames test, *S. typhimurium*	TA 1535, 1537, 1538, 98, 100	0, 100, 500, 2500, 5000, 10,000 µg/plate	±	Weak positive -S9, TA 1535 only	Unacceptable (no purity given, single trial) / Microbiological Associates, 1983e
Ames test, *S. typhimurium*	TA 1535, 1537, 1538, 98, 100	0, 100, 500, 2500, 5000, 10,000 µg/plate	±	Weak positive -S9, TA 1535 only	Unacceptable (no purity given, single trial) / Microbiological Associates, 1983f
Ames test, *S. typhimurium*	TA 1535, 1537, 1538, 98, 100	0, 100, 500, 2500, 5000, 10,000 µg/plate	±	Weak positive -S9, TA 1535 only	Unacceptable (no purity given, single trial) / Microbiological Associates, 1983g
Ames test, *S. typhimurium*	TA 1535, 1537, 1538, 98, 100	0, 1, 10, 100, 500, 1000, 2500, 5000, 10,000 µg/plate	±	Negative	Unacceptable (single trial) / Litton Bionetics, 1983a
Ames test, *S. typhimurium*	TA 1535, 1537, 1538, 98, 100	0, 100, 500, 2500, 5000, 10,000 µg/plate	±	Weak positive -S9, TA 1535 & TA 100	Unacceptable (no purity given, single trial) / Microbiological Associates, 1983h
Ames test, *S. typhimurium*	TA 1535, 98, 100	0, 0.1, 1, 10, 100 µg/plate	?	Negative	Open literature study, Hour *et al.,* 1998
Lactam test, *S. typhimurium*	JK947	0, 0.1, 1, 10, 100 µg/plate	n/a	Positive	Open literature study, Hour *et al.,* 1998
Mutatox test, *Vibrio fischeri*	Strain M169	175 µg/plate	±	Positive	Open literature study, Canna-Michaelidou & Nicolaou, 1996
Mouse lymphoma cell mutagenesis	L5178Y TK+/- cells	0-211 µg/ml (-S9) 0-2373 µg/ml (+S9)	±	Positive -S9 Weak positive +S9	Acceptable, Micorbiological Associates, 1983i
Mouse lymphoma cell mutagenesis	L5178Y TK+/- cells	0-316 µg/ml (-S9) 0-1780 µg/ml (+S9)	±	Positive -S9 Weak positive +S9	Unacceptable (no purity given, single trial) / Microbiological Associates, 1983j
***Drosophila* sex-linked recessive lethal test**	*Drosophila*, dietary	0 & 7.5 ppm	n/a	Negative[2]	Acceptable / University of Wisconsin, 1983
***Drosophila* sex-linked recessive lethal test**	*Drosophila*, dietary	0 & 10 ppm	n/a	Negative[2]	Unacceptable (missing data) / WARF, 1981
***Drosophila* sex-linked recessive lethal test**	*Drosophila*, dietary	0, 5 & 10 ppm	n/a	Negative[2]	Acceptable / Litton Bionetics, 1983b

[1] This is the “lowest detectable concentration” (LDC) that induced mutation in this system. The full range of concentrations tested was not provided.
[2] Limitations on test interpretation based on toxicity of carbofuran to intact insects are acknowledged.

Table III-12. Genotoxic effects of carbofuran: chromosomal aberrations

Test type / system	Species / strain	Dose	S9	Result	Comments / Reference
***In vitro* chrom. aberrations**	CHO[1] cells, CHO-K1	-S9: 0-100 µg/ml +S9: 0-2500 µg/ml (16-19 hr)	±	Negative	Unacceptable (needs historical range, etc.); Microbiological Associates, 1983k
***In vitro* chrom. aberrations**	CHO[1] cells, CHO-K1	-S9: 0-1000 µg/ml (14 hr) +S9: 0-2500 µg/ml (2 hr)	±	Negative	Unacceptable (needs historical range, etc.); Microbiological Associates, 1983l
***In vitro* chrom. aberrations**	CHO[1] cells, lot 3-3-83	-S9: 0-200 µg/ml (24 hr) +S9: 0-2500 µg/ml (2 hr)	±	Negative	Acceptable; Microbiological Associates, 1983m
***In vitro* chrom. aberrations**	CHO[1] cells, lot 3-3-83	-S9: 0-200 µg/ml (24 hr) +S9: 0-2500 µg/ml (2 hr)	±	Negative	Acceptable; Microbiological Associates, 1983n
***In vitro* chrom. aberrations[2]**	Human lymphocyte cultures	0, 1, 10, 100, 300 µg/ml (28 hr)	n/a	Positive (5-fold increase at 300 µg/ml)	Non-guideline open lit. study; Pilinskaya and Stepanova, 1984
***In vitro* chrom. aberrations**	White mouse (strain not identified)	0, 0.1, 1 mg/kg (24 hr)	n/a	Negative	Non-guideline open lit. study; Pilinskaya and Stepanova, 1984
***In vitro* chrom. aberrations**	Swiss mouse	1.9-5.7 mg/kg acutely or 1.9 mg/kg for 4 days, by oral gavage	n/a	Positive (2-6 fold increase)	Non-guideline open lit. study; Chauhan *et al.*, 2000
***In vivo* induction of micronuclei**	Swiss mouse	0.025 mg/kg, by oral gavage and by ip exposure	n/a	Positive (3-6 fold increase)	Non-guideline open lit. study; Amer *et al.*, 1997
***In vivo* induction of micronuclei**	Swiss mouse	5.7 mg/kg acutely or 1.9 mg/kg for 4 days, by oral gavage	n/a	Positive (~3-fold increase)	Non-guideline open lit. study; Chauhan *et al.*, 2000
***In vivo* induction of micronuclei**	C57B1 mouse	150 mg/kg by oral gavage[3]	n/a	Positive (~4-8-fold increase)	Non-guideline open lit. study; de Saint-Georges-Gridelet *et al.*, 1982
***In vivo* chom. aberrations**	Sprague-Dawley rat	0-6 mg/kg/day by oral gavage, 5 consecutive days, bone marrow cells	n/a	Negative	Unacceptable (males only, single acrifice time); Microbiological Associates, 1983o
***In vivo* chom. aberrations**	Sprague-Dawley rat	1-10 mg/kg/day by oral gavage, 5 consecutive days, bone marrow cells	n/a	Negative	Unacceptable (males only, single acrifice time); Microbiological Associates, 1983p
Dominant-lethal mutagenicity	Charles River albino mice (male)	0-0.5 mg/kg, single ip injection	n/a	Negative	Acceptability not determined (only summary submitted); FMC, 1971b

[1] Chinese hamster ovary cells.

[2] This study also examined the clastogenicity of three metabolites: 3-OH carbofuran, 3-keto carbofuran, and 3-keto-7-phenol. The former two compounds were clastogenic at 100 µg/ml, the highest dose tested.

[3] The inducing dose of carbofuran is inexplicably high (see discussion).

Table III-13. Genotoxic effects of carbofuran: DNA damage

Test type / system	Species / strain	Dose	S9	Result	Comments / Reference
DNA damage & repair	*E. coli* W3110 & p3478 and *B. subtilis* H17 & M45	0-5 mg/6-mm disk (16 hr)	-	Negative	Unacceptable (no activation, inadequate concentration range, no cytotoxicity); SRI, 1979
Unscheduled DNA synthesis	Primary rat hepatocytes	0-100 µg/ml (18 hr)	n/a	Negative	Acceptable; Microbiological Associates, 1983q
Unscheduled DNA synthesis	WI-38 human fibroblastic cell line	0-1000 µg/ml (-S9: 3 hr, +S9: 1 hr)	±	Negative	Unacceptable (no purity given, no cytotoxicity, no WI-38 passage number); SRI, 1979
Mitotic recombination	*S. cerevisiae* D3	0-5% w/v or v/v (4 hr)	±	Negative	Unacceptable (missing data); SRI, 1979

F. REPRODUCTIVE TOXICITY

1. Overview

No clear effects on fertility were seen in the single FIFRA guideline Sprague-Dawley rat reproduction study submitted, though decrements in pup weight were evident. This was in contrast to the open literature Wistar rat study discussed in the next section, as well as to other Sprague-Dawley rat developmental toxicity studies. Testicular toxicity was observed in Druckrey rats and New Zealand White rabbits. NOEL/LOEL data from these studies appear in Table III-18 at the end of section III.G.

2. Laboratory animal studies

a. Rat - dietary

The potential for carbofuran-induced reproductive toxicity was examined in a 3-generation study in CD rats (IRDC, 1979b). Carbofuran (95.6% purity) was added to the diet at doses of 0, 20 or 100 ppm (mean compound intakes, males: 0, 1.2 & 6.1 mg/kg/day; females: 0, 1.9 & 9.9 mg/kg/day). 10 males / 20 females were mated in the first two generations and 12 males / 24 females in the third generation. Two separate matings produced 2 litters in each generation.

With the exception of dehydration in some F_{3a} and F_{3b} litters, no treatment-related clinical signs were noted. Body weights in high dose male parental rats were about 13% less than controls at termination. Female high dose parental animals appeared somewhat less affected, with terminal body weights reduced 3-7% from controls. However, weight gain in the 8 weeks prior to mating was 17% less in high dose females than in controls for the F_O parentals. Body weights of high dose offspring were reduced below control at birth for all 6 litters (mean decrement = 6.3%, range = 1.6-11.1 %), with the decrement widening as the pups approached weaning (mean decrement = 15%, range = 8.3-23.2%). No trend for increase or decrease of this effect was noted in successive generations. Mean food consumption was curtailed by 4-9% in 100 ppm parental males of all 3 generations, as well as in F_O 100 ppm females. Male and female fertility and length of gestation were unaffected by exposure. Survival of pups between days 0 and 4 in all 3 generations was slightly lower at the high dose (percent survival = 89-97%) than in control animals (percent survival = 98-100%). Neither gross pathology nor histopathology on parents and offspring revealed carbofuran-related lesions. Various statistically significant changes in organ weights occurred in treated F_2 parental rats and F_{3b} offspring. However, these were not accorded toxicologic significance because parallel histopathologic changes were not seen.

The NOEL was set at 20 ppm (males: 1.2 mg/kg/day; females: 1.9 mg/kg/day), based on reduced body weights in parental animals and offspring at 100 ppm. This study was considered to be FIFRA compliant.

b. Rat - gavage

Male Druckrey rats were dosed with carbofuran (97.2% purity) by gavage at 0, 0.1, 0.2, 0.4 or 0.8 mg/kg/day (10/group), 5 days/week, for 60 days (Pant *et al.*, 1995). At sacrifice, reproductive organs were weighed, testes were taken for histopathology and testicular enzyme assays, and epididymal sperm were evaluated for motility, count and abnormalities.

Seven of 10 high dose rats died (time of death was not noted); survivors at that dose showed lethargy and imbalance. Overt toxicity was not evident at the other doses. Progressive body weight decrements occurred at 0.2 mg/kg/day and above (Table III-14). Absolute testes weights did not change at any dose. However, testes-to-body weights were significantly increased at 0.4 and 0.8 mg/kgbw/day. Absolute and relative weights of epididymides, seminal vesicles, ventral prostate and coagulating gland were significantly reduced at and above 0.2

mg/kg/day. Epididymal sperm motility and counts were significantly reduced in a dose-dependent manner at and above 0.2 mg/kg/day. Morphologic sperm abnormalities, including curved or bent neck, or curved, bent, round, loop or signet tail, were induced by carbofuran. When expressed as "percent total abnormalities" (the sum of the individual percent abnormalities), statistical significance and dose dependence were evident ≥ 0.2 mg/kg/day. Testicular enzyme levels were altered at 0.2 mg/kg-bw/day and above (Table III-14). Reduced glucose-6-phosphate dehydrogenase and sorbitol dehydrogenase were considered to reflect disturbed germ cell maturation, whereas elevated δ-glutamyl dehydrogenase and lactate dehydrogenase levels were interpreted as indicating alterations in Sertoli cells and germinal epithelium, respectively. Moderate congestion and edema, predominantly in the peripheral region, were noted upon histopathologic examination of the testes ≥0.2 mg/kg/day. The same doses caused moderate vacuolization of the Sertoli cells and germinal cells including spermatids, though no changes in Leydig cell morphology were observed. Progressively higher dose levels led to tubular atrophy, disturbed spermatogenesis and, in some cases, atrophy of affected cell types. The authors speculate that the spermatogenic changes could be due to the mutagenic properties of carbofuran, though direct measurements of mutagenesis were not performed.

The NOEL was set at 0.1 mg/kg-bw/day, based on testicular toxicity and body weight gain suppression at 0.2 mg/kg-bw/day. This study, which was from the open literature, was not carried out according to FIFRA guidelines, nor was there mention of adherence to GLP standards. Nonetheless, the results were considered to be toxicologically significant, particularly in view of similar testicular effects in other studies (see section IV.A.1.b).

Table III-14. Testicular and body weight effects resulting from gavage exposure to carbofuran in Druckrey rats (Pant *et al.*, 1995)

	Carbofuran, mg/kg/day				
	0 (n=10)	**0.1 (n=10)**	**0.2 (n=10)**	**0.4 (n=10)**	**0.8 (n=3)** [6]
Body wt. @ 60 days (g) [1]	216	210	188	156	146
Organ weights					
Testes					
Absolute (g)	2.50	2.50	2.40	2.40	2.36
Relative[2]	1.15	1.20	1.20	1.48*	1.60*
Epididimydes					
Absolute (g)	0.81	0.78	0.50*	0.49*	0.43*
Relative [2]	0.38	0.37	0.30*	0.32*	0.27*
Seminal vesicles					
Absolute (g)	0.18	0.17	0.09*	0.08*	0.05*
Relative [2]	0.08	0.08	0.05*	0.05*	0.03*
Ventral prostate					
Absolute (g)	0.11	0.11	0.09*	0.05*	0.03*
Relative [2]	0.05	0.05	0.04*	0.03*	0.01*
Coagulating gland					
Absolute (g)	0.05	0.05	0.02*	0.02*	0.01*
Relative [2]	0.02	0.02	0.01*	0.01*	0.01*
Sperm motility (%)	85.0	83.7	63.7*	51.2*	36.6*
Sperm count (x10^7)	9.0	8.0	5.0*	4.0*	3.0*
Total sperm abnormalities (%) [3]	10.48	10.80	22.25*	33.80*	54.60*
Testicular enzyme levels [4]					
G6PDG [5]	15.0	14.7	8.5*	6.5*	4.2*
δ-GT	28.9	30.5	60.0*	65.5*	72.0*
SDH	5.2	5.4	3.2*	3.2*	2.3*
LDH	365.0	372.0	501.0*	501.0*	703.0*

*p<0.05

[1] Body weights were estimated by the reviewer from inspection of a bar graph in the study report. Statistical analysis was not performed.

[2] Relative to body weights.

[3] The values for abnormal sperm expressed in this table are the sums of percentages of various individual abnormal morphotypes. Morphotypes that were statistically significantly increased included detached head, curved neck, bent neck, curved tail, bent tail, round tail, looped tail, and signet tail.

[4] Enzyme units were not provided in the text. However, units were expressed as nmol/min/mg for LDH and δ-GT in the follow-up paper (Pant *et al.*, 1997 - summarized in section III.G. below). Since similar activities were obtained for these enzymes, it is assumed that nmol/min/mg applies in this case as well.

[5] G6PDH, glucose-6-phosphate dehydrogenase; SDH, sorbitol dehydrogenase; δ-GT, δ-glutamyl dehydrogenase; LDH, lactate dehydrogenase.

[6] Only 3, as opposed to 10, rats were examined at the high dose due to the 70% mortality at that dose.

c. Rabbit - gavage

Mature male New Zealand White rabbits, 4/dose, were subjected to daily oral exposure to carbofuran in gelatin capsules for 6 weeks (Yousef *et al.*, 1995). Doses were not designated specifically, but were only expressed relative to an unnamed LD_{50}. The animals received 0, 1 /100 LD_{50}, and 1 /10 LD_{50}. The study was mapped out in three 6-week periods: pretreatment, treatment and recovery. Body weights were determined and semen collected on a weekly basis.

Carbofuran exposure caused weight decreases at both doses during the treatment period. Mean body weights were lower than controls by statistically significant margins at both doses during the treatment period (10% lower at the low dose, 11 % at the high dose) and at the high dose during the recovery period (14% lower). The authors suggest that the body weight effect "may be due to direct cytotoxic effects of the pesticides on somatic cells, and/or indirectly through the central nervous system which controls feed and water intake and regulates the endocrine functions" (p. 519). Semen characteristics were impacted at both doses, in some cases maintaining differences during the recovery period, indicating the potential for long-term damage. The following statistically significant effects were noted during the treatment period (the asterisk indicates that effects were noted by the time of the first measurement at 1 wk): semen volume (↓*), sperm concentration (↓), abnormal sperm (the most common sperm abnormalities were coiled tail, tapering head, small head and double tail) (↑*), dead sperm (↑), methylene blue reduction time (a measure of sperm metabolic activity) (↓*), initial semen fructose (a measure of the contribution of seminal vesicle secretion to the total composition of ejaculate and of serum testosterone) (↓) and semen osmolality (a measure of the fertilizing capacity of sperm) (↓).

It was not possible to assign a NOEL or LOEL to this study because the precise doses were not stated. While this was not a FIFRA guideline study, the results directly confirmed the data of Pant *et al.* (1995, 1997) in Druckrey rats regarding the toxicity of carbofuran to the male reproductive tract.

In a follow-up study, Yousef *et al.* (1996) examined the effects of carbofuran on human and rabbit sperm motility in vitro. (Glyphosate was tested as well, but those results will not be reviewed here.) The percentage of motile sperm as well as the motility grade were evaluated under phase-contrast microscopy and combined to yield a sperm motility index (SMI). The following parameters were evaluated to generate the motility grade: grade 0 - no movement; grade 1 - twitching, but no forward progressive movement (fpm); grade 2 - slow fpm; grade 3 - good fpm; grade 4 - fast fpm. Spermatozoa were separated from seminal plasma by dilution in medium and centrifugation, followed by enumeration in a Burker chamber. Evaluations were performed at sperm concentrations of $1x10^5$/ml, 20 µl/well at 0, 15, 30, 45, 60, 240, 360 and 480 minutes of exposure. Rabbit sperm were tested at carbofuran concentrations between 50 µM and 5 mM. Human sperm were tested at concentrations between 10 pM and 1 mM.

Marked, dose-related curtailment of the SMI were noted for both preparations. Addition of bovine serum albumin (BSA) to the rabbit sperm cultures or human serum albumin (HSA) to the human sperm cultures modulated this effect to some degree. Thus in the absence of BSA, rabbit sperm SMI was completely and immediately inhibited at 2.5 and 5 mM. In its presence, some motility was noted for as long as 60 minutes at 2.5 mM. Addition of HSA to human sperm resulted in significant motility even at the high dose of 1 mM. In protein-free medium, the IC_{50} was 116 pM and 321 pM for rabbit and human sperm, respectively. In protein-containing medium these values were 910 and 920 pM.

While this was not a FIFRA guideline study, these data show that direct exposure of rabbit and human sperm to carbofuran *in vitro* can adversely affect sperm motility.

d. Rat - dietary

Shain *et al.* (1977) examined the effects of dietary exposure to carbofuran and other insecticides on the quantity and distribution of androgen receptors in the ventral prostate of the Sprague-Dawley rat. The exposure time was 90 days. The carbofuran dose was 30 ppm.

At the completion of exposure, the authors found that the number of cytoplasmic androgen receptors per cell was similar in carbofuran-treated and control animals, but the number of nuclear receptors was markedly higher (34,400 vs. 7560 in controls). Among the other compounds tested, a similar pattern was seen for chlordane and, to some extent, diazinon. Heptachlor, methoxychlor and parathion tended to elevate cytoplasmic receptor levels. Interestingly, the number of prostatic cytoplasmic sites in animals exposed to any of these compounds (chlordane was an exception) was reduced if they were orchidectornized 24 hours prior to sacrifice. These effects were not related to an ability to inhibit the binding of 5α-dihydrotestosterone to prostatic receptors. Carbofuran also lowered the RNA and DNA content of the prostate. The other compounds had similar or opposite effects. These data were consistent with an effect of pesticides on the homeostasis of androgen receptors in the prostate. Insofar as these effects are shared among compounds of various chemical classes, they suggest a non-specific mechanism of action, perhaps mediated through effects on the general metabolism of the cells and tissues.

These data support the studies of Pant *et al.* (1995, 1997) and Yousef *et al.* (1995, 1996), which suggest that carbofuran may be a male reproductive toxin. This was not a FIFRA-guideline study.

e. Mouse - gavage

Baligar and Kalwal (2003) exposed virgin female Swiss albino mice (10/group) by daily gavage to carbofuran (1.3 mg/kg/day) for 5, 10, 20 or 30 days. Estrous cycle status was determined by examination of vaginal smears. The animals were sacrificed on day 31. The ovaries were weighed. Five animals/group with ovaries of representative weight were selected for histologic analysis. The numbers of follicles in various stages of size and development were determined in serial sections.

Treatment for 30 days resulted in statistically significant ($p<0.05$) decreases relative to controls in the numbers of estrous cycles (⇓27%), in the duration of proestrus (⇓60%), estrus (⇓29%) and metestrus (⇓44%), and in the comcomitant incresase in diestrus (⇑61%). Similarly, the number of healthy follicles decreased by 9% ($p<0.05$), while the number of atretic follicles increased by 91% ($p<0.05$). Mean body weight gains were markedly reduced in the 30-day animals (from 2.3 g in controls to 1.0 g in treated animals, $p<0.05$). Relative ovary weight gains were also reduced by 35% ($p<0.05$). Shorter treatments were without statistically significant effect on any of these parameters, though there was some suggestion of an effect at 20 days.

The authors speculate that the ovarian effects could be mediated by a carbofuran-induced inhibition of neural dopamine-β-hydroxylase activity. Such an effect would inhibit the conversion of dopamine to norepeinephrine. The latter compound is required in the release of gonadotropin releasing hormone (GnRH), which, in turn, enables follicular development. However, the report did not provide data to support this proposed mechanism. It was also suggested that a nutritional deficiency, which may have underlaid the decreased body weight gain, may have contributed to the ovarian toxicity.

It was not possible to assign a NOEL in this non-FIFRA guideline study, as only one dose was examined. However, the possible reproductive dysfunction observed in this study supported other reports of female reproductive toxicity (see discussion of Jayatunga *et al.*, 1998a, in section G below).

G. DEVELOPMENTAL TOXICITY

1. Overview

This section presents evidence that low doses of carbofuran during the first few days of pregnancy were embryotoxic in Wistar rats. Whether this was due to cholinergic effects, to endocrine toxicity, or to some other mechanism, was not clear, though accompanying maternal clinical signs were seen at comparably low doses. Supporting evidence for an embryotoxic effect in Sprague-Dawley rats was also forthcoming, though early gestational exposure had no effect on fertility in the reproductive toxicity study described in the previous section. Testicular toxicity was again documented in Druckrey rats. Maternal brain cholinesterase inhibition was noted at extremely low doses in one open literature study. NOEL/LOEL data from these studies appear in Table III-18 at the end of this section (section III.G).

2. Human studies (poisoning incidents)

In one case study, a 17-year old woman, 18 weeks pregnant, ingested carbofuran with the intent of committing suicide (Klys *et al.*, 1989). Two hours later she was admitted to a local hospital. At the time, she was unconscious, exhibiting symptoms of pulmonary edema. Symptomatic treatment was instituted. Nineteen hours after admission, acetylcholinesterase (presumably RBC-derived) activity was 1700 IU (normal, 35008000 IU). Serum cholinesterase (presumably butyryl cholinesterase) was 15 IU (normal, 25-55 IU). Neither fetal pulse nor movement was detectable when examined on the second day. The uterine fundus was found to extend to the umbilicus, with the fetus demonstrating longitudinal pelvic presentation. The dead fetus was delivered after day 7. Postmortem exam "revealed a macerated, intrauterine-dead female fetus, of the age four to five lunar months, body length 29 cm, weight 250 g, with no congenital defects." Carbofuran assays were performed on maternal blood, sampled 9 hours after ingestion, and fetal kidney, brain and liver nine days after ingestion. The following levels were detected: maternal blood, 2.6 pg/g; fetal kidney, 1.4 pg/g; fetal liver, 2.5 pg/g; fetal brain, 0.3 pg/g. These data are interpreted by the study authors as providing evidence that carbofuran passed the placental barrier into the fetus. They further claim that "the level of poison in the blood of the poisoned mother was comparable to that in the fetus." The latter claim was not well supported, however. First, the sampling times were vastly different. Second, different tissues were sampled in the fetus and mother. And third, the fetus had probably been dead for over a week before sampling. Nonetheless, this study provides strong evidence that maternal ingestion of carbofuran leads to exposure of the fetus, with grave consequences.

Another report summarized two cases of acute carbofuran ingestion in pregnant women (Sancewicz-Pach *et al.*, 1997). The first case was exactly the one recounted in the above paragraph (Klys *et al.*, 1989). In the second case, (the following is quoted from page 742 of the article) "A 20-year old woman, 12 weeks pregnant, took carbofuran, probably to provoke abortion. Approximately 5 hours after the poison ingestion the patient was referred to the local hospital. On admission the patient was unconscious with the pulmonary oedema and respiratory insufficiency. Intensive symptomatic treatment was instituted and carbon gastric lavage with water was performed. After 12 h the patient was transferred to the Department of Clinical Toxicology. On admission to the Department the patient had considerably intensified muscarinic, nicotinic and OUN symptoms (VI grade of Glasgow scale) with movement excitation, tachycardia (1 60/min), pinpoint pupils and cyanosis. Tracheal intubation (110 hours), artificial ventilation (60 hours), fluid infusion/physiological salt solution, glucose and multielectrolytic fluid solution, atropine drip in doses of 10 to 15 mg in a 24 h period (106 mg), diuretic agents and antibiotics were administered. AChE activity was 500 IU, SChE - 120 U/L.

Because of dramatic course of poisoning gynecological examination and ultrasonography of the abdomen were carried out on the 10th day of hospitalisation. The pregnancy (12 weeks) was confirmed. Fetal pulse was audible with normal heart rate. The patient recovered and was discharged from the Clinic after 17 days of hospitalisation still pregnant. After 27 days which followed the poisoning a spontaneous abortion was stated. The patient was treated in local gynecological hospital." Carbofuran assays of maternal serum revealed levels of 1.26 pg/g 12 hours after poisoning, 9.71 pg/g 24 hours after poisoning, and 3.9 pg/g 48 hours after poisoning. Assays on fetal tissues were not performed. The spontaneous abortion was attributed to carbofuran exposure.

3. Laboratory animal studies

a. Rat - gavage

This rangefinding study (WARF, 1978a) provided adequate dose justification for the following complete teratology study in the rat. Carbofuran (95.6% pure) was administered by gavage in a 0.25% methylcellulose vehicle to pregnant Sprague-Dawley CD rats, 24/dose, at 0, 0.1, 0.3 and 1 mg/kg-bw/day on gestation days 6-15. Clinical effects and body weights were monitored during gestation. Dams were sacrificed on gestation day 20. Fetuses were examined after laparotomy.

One high dose female died on gestation day 9. The following clinical signs were noted: lethargy (incidence at ascending doses: 0, 0, 5*, 2), lacrimation (0, 0, 0, 2), pale eyes (0, 0, 0, 4), increased salivation (0, 0, 0, 5*), rough coat (3, 0, 4, 6), trembling (0, 0, 0, 14**), convulsions (0, 0, 0, 9*), and chewing motions (0, 5*, 12**, 16**) (*$p \leq 0.05$; **$p \leq 0.001$). Except for the chewing behavior, which was described as occurring “for a short period of time immediately following dosing each day”, the time of appearance of these signs was not noted. Consequently, it was not known if a single dose was sufficient to induce these effects or if several doses were needed. The chewing behavior, which exhibited a dose-related increase in incidence, was likely to be a neurotoxic response to exposure.

There were no significant body weight effects in the dams after treatment. Necropsies did not reveal treatment-related effects in the dams. Neither the number of litters nor the rates of pregnancy were affected. The incidence of fetal abnormalities in soft or skeletal tissues was not influenced by carbofuran exposure.

The maternal LOEL was set at 0.1 mg/kg-bw/day, based on chewing behavior observed at that dose (with an increasing incidence at higher doses). This behavior was considered to be an acute response to treatment. An exhaustive benchmark dose analysis revealed that the log-logistic algorithm (slope parameter restricted as slope >1) approximated the dose-response data better than any other algorithm (see Hazard Identification, section IV.A.1). The log logistic curve generated an ED_{05} (*i.e.*, the 5% benchmark dose response) of 0.02 mg/kg and a LED_{05} (*i.e.*, the lower bound on the 5% benchmark dose response) of 0.01 mg/kg. The latter value was used to evaluate acute risk. As no developmental signs were seen even at the high dose, the developmental NOEL was determined to be $\geq$1 mg/kg-bw/day.

In the subsequent definitive study, carbofuran (95.6% purity) was delivered daily between gestation days 6 through 15 by oral gavage in a corn oil vehicle to 25 pregnant CD rats/dose (IRDC, 1980b). Dosages were 0, 0.25, 0.5 and 1.2 mg/kg-bw/day. Pups were delivered by Cesarean section on gestation day 20.

There were neither deaths nor treatment-related clinical signs in the dams. Postmortem examination of the mothers did not reveal treatment-related clinical signs. No differences were observed among the dose groups in maternal weight gain for any gestational interval. Uterine weights at the high dose at Cesarean section (64, 60, 67 and 74 grams at ascending doses)

were actually higher at 1.2 mg/kg/day than among controls. No effect of treatment on fetal growth or development was discerned.

The maternal and developmental NOELs were set at ≥1.2 mg/kg/day. It was not clear why clinical signs were apparent in the preliminary study (see preceding summary, WARF [1978a]), while not apparent in this study at similar doses. It is noted, however, that the two studies were conducted by different laboratories and employed different vehicles. This study was considered to be consistent with FIFRA guidelines.

b. Rat - dietary

In a pilot teratology study designed as a rangefinder for a subsequent, more detailed study, "groups of ten pregnant [Charles River COBS CD] rats were fed with carbofuran by dietary inclusion at dose levels of [0,] 20, 60, 120, 160 and 200 ppm on gestation days 6 through 19" (IRDC, 1980c). [This description is quoted from the FIVIC summary available to DPR].

"Survival in all carbofuran treated groups was 100% and no significant and persistent clinical symptoms or uterine anomalies other than a body weight effect were observed. In all the endpoints measured, rats in the 20 ppm group are essentially the same as the control rats. An apparent dose-related weight loss was observed during the first 2 days of treatment in the 60, 120, 160 and 200 ppm groups. Lower maternal body weight gains were also noted in the 120, 160 and 200 ppm groups. Mean food consumption was decreased in the 120, 160 and 200 ppm groups. Based on the results, 20, 60 and 160 ppm were chosen as the dose levels for the definitive teratology study. It was reasoned that the clear-cut body weight effect at the 160 ppm level (21 % decrease in weight gain compared to control) would give a surely toxic effect with only a minimal decrease in mean food consumption, whereas the 20 ppm dose would serve as the no effect level." According to the JMPR review of this study (JMPR, 1996), a dose-related decrease in food consumption occurred at and above 60 ppm at the beginning of treatment. No effect on reproductive parameters was noted. Also according to JMPR, 1996, carbofuran consumption rates were equivalent to 0, 1.5, 4, 8, 11 and 13 mg/kg-bw/day.

A maternal NOEL was set at 20 ppm (1.5 mg/kg-bw/day) based on weight gain decrements at 60 ppm (4 mg/kg/day). A developmental NOEL was not determined.

In the definitive study, 40 pregnant Charles River COBS CD rats/dose were exposed through the diet to 0, 20, 60 and 160 ppm carbofuran (95.6% purity) on gestation days 6-19 (IRDC, 1981a). Mean compound intakes were 0, 1.48, 4.36 and 10.97 mg/kg/day. Cesarean sections were performed on at least 20 females/dose on gestation day 20. The remaining dams were allowed to deliver; necropsies were performed on those dams and their litters on lactation day 21.

Matting of the ventral haircoat was observed in a few rats at the mid and high doses. Soft stool occurred with similar frequency in all groups, including the controls, during treatment, though the duration of the condition tended to be longer among treated animals. Weight loss at the outset of the exposure period was observed at the top two doses. Thus between gestation days 6 and 8, mean weight gain at ascending doses was 7, 4, -4 and -16 grams. This situation tended to resolve as the exposure continued and the mid and high dose animals began to gain weight. Weight gain was 119, 109, 98 and 89 grams for gestation days 6-20. Maternal food consumption at the top 2 doses was reduced at the beginning of treatment (gestation days 6-7: 21, 20, 15 and 9 g/rat/day; gestation days 8-9: 22, 23, 21 and 13 g/rat/day). For the remainder of treatment, consumption values were comparable at all doses. Maternal weight gain during the first week of lactation, 20, 15, 5 and 3 grams, was compromised at the mid and high doses. Weight gains during the second week of lactation were greater at those doses.

Other than body weight and food consumption changes, there were no unusual findings

either in the dams subjected to Cesarean section or in the pups thus delivered. No malformations or developmental variations were associated with exposure. For those dams allowed to proceed to term, gestation length was comparable in all groups, as were mean body weight values during lactation, mean live litter size, and postnatal survival. Mean body weights of the high dose pups was significantly reduced (6.5, 6.4, 6.3 and 5.9** grams; **$p \leq 0.01$) at birth and remained depressed through termination on postnatal day 21 (40.9, 39.9, 39.7 and 35.6* grams; *$p \leq 0.05$).

The maternal NOEL was set at 20 ppm (1.48 mg/kg-bw/day) based on weight gain decrements at 60 ppm. The developmental NOEL was set at 60 ppm (4.36 mg/kg/day) based on reduced peri/postnatal pup weights at 160 ppm (10.97 mg/kg/day). This study was acceptable under FIFRA guidelines.

c. Rat - gavage

A detailed toxicologic and mechanistic study of the effects of oral carbofuran exposure during early pregnancy in the Wistar rat was undertaken (Jayatunga *et al.*, 1998a). The carbofuran used in the study was supplied in the "unformulated" state, which is interpreted as meaning it was the technical product.

In the first phase of the study, 6 pregnant females/dose received carbofuran by gavage at 0, 0.2, 0.4 or 0.8 mg/kg-bw/day, gestation days 1-5 inclusive. Besides normative observations for clinical signs, weight changes, etc., which were recorded throughout gestation, maternal blood pressure, rectal temperature, locomotive activity and muscle strength were determined on day 5, the final dosing day. On day 14, the rats were laparotornized and the number of uterine implants and corpora lutea determined. Also at that time, the cranio-cervical diameter of the implants and the intraimplantation distance between the first and second implant were recorded. The animals were sewn back up under aseptic conditions and the pregnancies were allowed to proceed to term. After birth, the number and condition of the pups was determined, including, on day 5 post-partum, the determination of cranial and cervicosacral length. The health of the pups was monitored until day 20-22.

There were no deaths among treated animals. Cholinergic signs exhibiting dose dependence, including salivation, lacrimation, pupillary constriction, convulsions, loose stools and frequent urination, were evident within 2-3 hours of treatment, lasting 7-8 hours. Mild-to-moderate piloerection was evident at all doses. Further dose dependent signs included lethargy and locomotive impairment, the latter at 5 days following treatment. (Unfortunately, incidence rates for clinical signs were not provided in the report, which made them difficult to evaluate in terms of their toxicologic significance.)

Statistically significant reductions in body weight gain were noted at the top two doses on day 5 (control *vs.* 0.4 *vs.* 0.8 mg/kg-bw/day: 11.5 *vs.* -1.4* vs. 4.44* g; $p<0.05$) and day 14 (26.2 *vs.* 2.42* *vs.* 7.23* g). Water intake was significantly suppressed ($p<0.05$) at all doses (at ascending doses: 2.28, 1.22*, 0.97*, 1.19 ml/hr; $p<0.05$). Food consumption was significantly suppressed at the high dose by day 5 (control vs. 0.8 mg/kg-bw/day: 914.28 vs. 494.99* mg/h; $p<0.05$). A comparable suppressive effect at the mid dose may also have been observed, though a typographic error in the text made this unclear.

Statistically significant bradycardia was evident on day 5 at all doses (at ascending doses: 432, 389*, 393*, 391* beats/min; *$p<0.05$). RBCs and WBCs were significantly reduced at the mid and high doses. Mean corpuscular hemoglobin was significantly increased at the high dose. Muscle strength and righting reflex time in the dams were not affected. Statistical reductions were obtained at all doses for number of rears (% inhibition compared to controls: 35%*, 44%*, 60%*) and locomotive activity (% inhibition compared to controls: 35%*, 34%*, 55%*), both examined on gestation day 5 as part of the "rat hole-board" technique. The number

of head dips was also reduced at all doses, though significance was achieved only at the low dose.

One hundred percent inhibition of quantal pregnancy (for definitions, see footnote to Table III-14), number of uterine implants, implantation index, and gestation index were observed at the high dose. Pre-implantation loss was also 100% at that dose. Statistically significant effects on reproductive parameters were seen at the mid-dose. Fetal and pup developmental parameters, including gestation length, cranial and pup body length, pup body weight gain, and time taken for fur to appear and to open eyes, were also affected at that dose. It appears that pups exposed to 0.4 mg/kg grew faster and achieved developmental endpoints earlier than those exposed to 0.2 mg/kg or control pups. This is not commented upon in the study, though it could be a function of the estrogenicity of carbofuran (see next paragraph) or of greater access to maternal care and milk resulting from lesser numbers of live pups/litter. The degree to which these latter effects should be considered adverse is not clear at this time. Female reproductive and pup post-natal parameters are shown in Table III-15.

In the second phase of the study, the possibility of carbofuran-mediated estrogenic activity was evaluated. Sixteen immature females were ovariectornized under anesthesia. Carbofuran was administered orally at 0 or 0.4 mg/kg-bw/day (8 animals /treatment) for 5 consecutive days starting 7 days after the operation. The rats were sacrificed 24 hours after the last dose. Daily vaginal smears were taken for determination of the numbers of cornified cells, leukocytes and rounded nucleated epithelial cells. Statistically significant ($p<0.05$) increases over controls were detected in wet uterine weight (control vs. 0.4 mg/kg, 480 *vs.* 740 mg/1 00 g bw), length of the uterine horn (control *vs.* 0.4 mg/kg, 2.5 *vs.* 3.25 cm on the right, 2.2 *vs.* 2.7 cm on the left), and percentage of cornified cells (control *vs.* 0.4 mg/kg, 3.8% *vs*. 15.3% on day 3, continuing in like manner until day 5, 4.5% *vs.* 40.3%). While data were not shown, there was an apparent concomitant decrease in the percentage of leukocytes and an increase in epithelial cells with rounded nuclei. This estrogenic effect of carbofuran is proposed as a possible mechanism for the implantation failures noted above, either through vaginal cornification or through increased oviduct motility leading to enhanced embryonic transport and loss. It was noted that other estrogenic compounds, notably DDT, dieldrin and aldrin, cause similar reproductive disruptions. Maternal stress, the sedative qualities of carbofuran (evidenced by decreased motor behavior), and interruptions in uterine blood flow (evidenced by bradycardia) are also considered possible sources of implantation failure.

In the third phase of the study, the possibility of antiestrogenic activity was evaluated. Again, 16 immature females were ovariectornized under anesthesia and treated for 5 consecutive days with 0 or 0.4 mg/kg-bw/day carbofuran commencing 7 days after the operation. Within 5 minutes of each treatment, the rats were dosed subcutaneously with 0.1 mg of estradiol. Similar assays were performed as for the estrogenic assay in the second phase. However, this experimental design did not allow for the detection of antiestrogenic activity because no non-estrogen controls were run. The reported data indicated that non-carbofuran (+ estradiol) controls showed mean uterine wet weights of 490±40 mg/1 00 g body weight, while cafbofuran-treated rats (+ estradiol) had uterine wet weights of 480 mg/1 00 g body weight. Since no non-estrogen controls were run, no conclusion could be made about whether estradiol itself had an estrogenic effect (the proximity to the non-estrogen controls in the second phase of the study suggested that no such effect was present). It remained possible that estradiol had an anti-carbofuran effect since the -50% increase in uterine wet weight caused by 0.4 mg/kg carbofuran observed in phase 2 (see above) did not occur when estradiol was present. Nonetheless, this experiment was inconclusive regarding the possibility of an anti-estrogenic effect of carbofuran.

In the fourth phase of the study, anti-progesterone activity was assessed by comparing 6

pregnant females dosed orally on gestation days 1-5 with 0.4 mg/kg carbofuran with 6 pregnant females dosed with carbofuran and subcutaneous progesterone, 2.5 mg. These rats were laparotornized on gestation day 10 and the number of uterine implants determined. Carbofuran failed to significantly alter the number of uterine implants. The value of this aspect of the study is questionable, however, because of the lack of a positive control (*i.e.*, animals that were treated with progesterone, but not with carbofuran).

Finally, an attempt was made to determine the oral LD_{50} in rats for carbofuran. While it is not explicitly stated, it is assumed that this test was performed with female rats only. No rats died at 2 mg/kg. 100% mortality was observed at 20 mg/kg. The LD_{50} for female Wistar rats was thus between 2 and 20 mg/kg.

An overall maternal LOEL of 0.2 mg/kg-bw/day was established in this study based on cholinergic signs, depressed food and water intake, bradycardia, reductions in locomotive activity, rearing behavior, and head dip behavior at that dose. Estrogenic activity was noted at 0.4 mg/kg/day which, perhaps in combination with the cholinergic effect, may have been the cause of the implantation failure noted at that dose (with more certain data reported at 0.8 mg/kg/day). A maternal NOEL was not established. A developmental NOEL of 0.2 mg/kg-bw/day was established based on statistically significant decreases in pup cranial and body length, pup body weight gain, and fetal survival ratio, and increases in the time to appearance of fur and to open eyes at 0.4 mg/kg/day). This open literature study was not conducted according to FIFRA guidelines.

Table III-15. Effects of carbofuran administration during gestation days 1-5 on female rat reproductive parameters at post-natal pup development (Jayatunga *et al.*, 1998a)

	Carbofuran, mg/kg/day			
	0	**0.2**	**0.4**	**0.8**
Quantal pregnancy (%) [1]	100	100	50	0
# implants	9.0	10.6	5.0	0.0*
Implantation index (%)	900	1060	500*	0*
Gestation index (%)	883.3	1020	1000	0*
Pre-implantation loss (%)	12.4	17.0	58.3*	100*
Post-implantation loss (%)	1.5	4.0	0.0	-----
Live birth index (%)	93.1	100.0	55.6*	-----
Fetal survival ratio (%)	61.6	84.0	26.7*	-----
Litter index (%)	66.8	84.0	40.0	-----
Viability index (%)	100	100	100	-----
Gestation length (days)	22.7	22.2	24.0*	-----
# pups born	5.8	9.0	4.0	-----
Day 5 pup cranial length (cm)	2.1	1.9*	1.9*	-----
Day 5 pup body length (cm)	3.8	3.9	4.1**	-----
Pup body wt. gain, days 0-5 (g)	2.3	2.6	4.2*	-----
Time taken for fur to appear (days)	5.5	5.3	3.7*	-----
Time taken to open eyes (days)	15.8	16.5	14.5*	-----

*p<0.05 **p<0.01

[1] *Definitions*: Quantal pregnancy: #pregnant/# mated x 100. Implantation index: # implants/# mated x 100. Gestation index: # live litters/# pregnant x 100. Pre-implantation loss: # corpora lutea/# implantations x 100. Post-implantation loss: # implantations/# viable implatnations x 100. Live birth index: # surviving pups/# littered pups x 100. Fetal survival ratio: # surviving pups/# implantations x 100. Litter index: # littered pups/# implantations x 100. Viability index: # day 1 surviving animals/live pups per dam x 100.

d. Rat - gavage

A detailed toxicologic and mechanistic study of the effects of oral carbofuran exposure during mid pregnancy in the Wistar rat was undertaken (Jayatunga *et al.*, 1998b). This study was a follow-up to an earlier study by the same authors, which examined the effects of carbofuran exposure early in gestation (Jayatunga *et al.*, 1998a; see above). As before, the carbofuran used in this study was supplied in the "unformulated" state, which is interpreted as meaning the technical product. Gavage dosing at 0, 0.2, 0.4, and 0.8 mg/kg occurred on gestation days 8-12.

Overt but transient signs of cholinergic toxicity (excess salivation, lacrimation, pupil constriction, soft feces, near colorless urine) were noted at and above 0.2 mg/kg. Mild to moderate piloerection without exophthalmia, considered evidence for adrenergic toxicity, was also observed. Mild vaginal bleeding occurred in 3/6 rats at 0.4 mg/kg on gestation day 11 (day 4 of treatment), lasting for 2 days. It is unclear why there was no such occurrence at 0.8 mg/kg/day. Interestingly, the mid dose group also seemed more adversely affected than the high dose group in various reproductive and developmental parameters (number of viable

implants, post-implantation loss, fetal survival ratio, litter index, gestation period, and cranio-cervical embryo diameter). Because of the apparent lack of dose response for these characters, their toxicologic significance remains unclear. However, there was a significant linear correlation between the doses of carbofuran tested and the inhibition in locomotor activity (r^2= -0.47; $p<0.05$) and number of head dips (r^2= -0.64; $p<0.01$). These were considered sedative actions.

As in the previous study (Jayatunga *et al.*, 1998a), a maternal LOEL of 0.2 mg/kg-bw/day was established in this study based on cholinergic and adrenergic signs at that dose, as well as possible sedative actions at 0.4 mg/kg-bw/day. A maternal NOEL was not set. A developmental NOEL of 0.4 mg/kg-bw/day was set based on significant decreases in pup cranial and cervico-sacral length and increased times to fur appearance and eye opening at 0.8 mg/kg-bw/day. Because this was a non-FIFRA guideline study, it was considered supplemental.

****

Between 8 and 32 fasted pregnant Sprague-Dawley rats/dose were treated with carbofuran (99% purity) by gavage on the morning of gestation day 18 (Cambon *et al.*, 1979). Doses were 0, 0.05, 0.25 or 2.5 mg/kg-bw. Animals were sacrificed 0.5, 1, 5 or 24 hours after dosing, though not all times were employed for each dose group. Cholinesterase activities were determined on hemolyzed whole blood, and on maternal and fetal liver and brain. Toxic signs, including tremors, salivation, miosis, dyspnea and piloerection, were noted very soon after dosing, with severity dependent on dose. Apparently such signs were observed in all dose groups, though detailed descriptions at each dose were not provided. Suppressions of AChE were evident in all tissues at the high dose, with a general reestablishment of enzymatic activity evident by 24 hours. The most profound level of cholinesterase suppression was realized in the high dose maternal brain at 0.5 hours with inhibition compared to controls reaching 73%. At the low dose, some inhibition was present in maternal and fetal blood and maternal brain and liver, though not in fetal brain and liver. A summary of the effects on AChE is shown in Table III-16.

A maternal acute LOEL of 0.05 mg/kg was established for this study, based on the non-statistically significant 16% inhibition of maternal brain ChE at that dose. According to the DPR interim policy, brain ChE inhibition greater than 10% is considered toxicologically significant, even in the absence of statistical significance (DPR, 2002b). However, the reliability of this result is in serious question for the following reasons: (1) The tissue samples were stored overnight at 4°C, which likely compromised both the stability of the enzyme and the inhibitor-enzyme complex. (2) The additional precautions now known to be necessary to prevent carbamate-enzyme dissociation (*eg.*, preventing over-dilution of the tissue sample) were not taken. (3) The lack of dose responsiveness in other tissues, even when the inhibition achieved statistical significance compared to controls, argued against according toxicologic significance to the inhibition observed at the low dose in maternal brain. (4) The poor characterization of clinical signs, including incidence rates, individual data and descriptions of the signs, made it difficult to connect overt toxicity with alleged enzyme inhibition.

This open literature study was not conducted under FIFRA guidelines.

Table III-16. ChE activities in maternal and fetal tissues from pregnant rats after acute gavage exposure to carbofuran (Cambon *et al.*, 1979)

		Controls		Carbofuran, mg/kg		
		Day 18 [4]	Day 19 [4]	0.05	0.25	2.5
	Time (hr)					
Maternal blood [1]	0 (controls)	22.9	23.7	n/a	n/a	n/a
	0.5			-----	-----	-----
	1			19.6 (14)**[3]	19.3 (16)**	18.3 (20)***
	5			-----	22.2 (3)	21.0 (8)*
	24			-----	23.6 (0)	24.3 (-3)
Fetal blood [1]	0 (controls)	24.0	17.7	n/a	n/a	n/a
	0.5			-----	-----	14.7 (39)***
	1			16.4 (32)***	17.5 (27)***	14.9 (38)***
	5			-----	19.7 (18)*	19.2 (20)*
	24			-----	18.7 (-6)	15.8 (11)
Maternal brain [2]	0 (controls)	9.41	9.30	n/a	n/a	n/a
	0.5			-----	-----	2.54 (73)***
	1			7.93 (16)	6.46 (31)**	4.11 (56)**
	5			-----	8.16 (13)	6.49 (31)*
	24			-----	7.42 (20)	8.44 (9)
Maternal liver [2]	0 (controls)	5.89	3.70	n/a	n/a	n/a
	0.5			-----	-----	-----
	1			4.08 (31)***	5.43 (8)	4.66 (21)*
	5			-----	4.60 (22)*	4.06 (31)***
	24			-----	4.84 (-31)	4.56 (-23)
Fetal brain [2]	0 (controls)	1.45	1.39	n/a	n/a	n/a
	0.5			-----	-----	1.17 (19)***
	1			1.42 (2)	1.45 (0)	1.24 (14)***
	5			-----	1.57 (-8)	1.27 (12)
	24			-----	1.55 (-12)	1.77 (-27)
Fetal liver [2]	0 (controls)	1.75	1.35	n/a	n/a	n/a
	0.5			-----	-----	1.07 (39)***
	1			1.81 (-3)	1.44 (18)**	1.08 (38)***
	5			-----	1.37 (22)***	1.37 (22)**
	24			-----	1.38 (-2)	1.47 (-9)

*p<0.05; **p<0.01; ***p<0.001

[1] ChE units of activity per gram protein

[2] ChE units of activity per gram of organ

[3] Parenthetical values represent the percent inhibition compared to controls

[4] Samples taken at 0.5, 1, and 5 hr were compared to Day 18 controls. Samples taken at 24 hr were compared to Day 19 controls.

****

In an examination of the potential for testicular or spermatogenic effects in fetal or neonatal animals, pregnant female Druckrey rats of proven fertility were dosed with carbofuran (97.2% purity) by gavage (Pant *et al.*, 1997). This study was a follow-up to that of Pant *et al.*, 1995, summarized above in section III.F., which evidenced testicular damage in male Druckrey rats exposed to 0.2 mg/kg/day carbofuran by daily gavage for 60 days. Dose groups for the current study were as follows: 6/group were dosed with either 0 or 0.4 mg/kg-bw/day daily throughout pregnancy, or 4/group were dosed with 0, 0.2 or 0.4 mg/kg-bw/day daily during lactation days 0-21. In all instances, pups were weaned on day 21. Examinations of 5/litter were conducted at 90 days of age for epididymal sperm appearance and motility, activities of key testicular enzymes, sperm motility, sperm count and sperm abnormalities.

At 0.4 mg/kg-bw/day in both the gestation and lactation treatment groups, there were statistically significant changes in testicular enzymes. Sorbitol dehydrogenase was reduced, and lactate dehydrogenase and δ-glutamyl dehydrogenase were increased after both *in utero* and lactational exposures (Table III-17). The latter effect may reflect changes in Sertoli cells (see below). Little or no effect on testicular enzymes was observed in animals exposed during lactation to 0.2 mg/kg-bw/day. Statistically significant decreases in sperm motility and sperm count were observed at 0.4 mg/kg-bw/day. The percent abnormal sperm increased in a statistically significant manner both in rats that had been exposed to 0.4 mg/kg-bw/day *in utero* and during lactation (Table III-17). Testicular histopathologic effects were also noted at that concentration, as indicated in the following quote (p. 270): "Rats given *in utero* exposure (0.4 mg carbofuran/kg) showed a few shrunken semeniferous tubules resulting in wide interstitial spaces where atrophied tubules demonstrated loss of spermatogenesis and depletion of a variety of cell types. Further, degenerative changes in Sertoli cell were characterized by vacuolation... At 90 days age testis of rat given lactational exposure (0.2 mg carbofuran/kg) showed almost normal appearance of successive stages of spermatogenic cells in the seminiferous tubule as well as interstitial tissue with prominent Leydig cells. With higher dose of lactational treatment (0.4 mg carbofuran/kg) testis of rat showed moderate intertubular oedema and at places, degenerative changes in Sertoli cells were also evident in a few tubules..." It is of interest to note that these biochemical, functional and morphologic changes were observed long after the discontinuance of exposure: 90 days in the case of *in utero* exposures, 69 days in the case of lactational exposures. In addition, this study provides ample evidence both for fetal exposure, presumably across the placenta, and for neonatal exposure through the milk.

The maternal NOEL was $\geq$0.4 mg/kg-bw/day, including both *in utero* and lactational exposures. The developmental NOEL was 0.2 mg/kg-bw/day based on degenerative testicular changes in the offspring of treated animals at 0.4 mg/kg/day.

This study was not conducted according to FIFRA guidelines. Nonetheless, the data were considered to be toxicologically significant with regard to the induction of testicular damage, particularly as similar results were seen in other studies (see section IV.A.1.b.)

Table III-17. Effects of maternal exposure to carbofuran by gavage during pregnancy or lactation on testicular enzymes and sperm characteristics in male rat offspring (Pant *et al.*, 1997)

	Carbofuran, mg/kg/day				
	In utero exposure [1]		Lactational exposure [2]		
	0	0.4	0	0.2	0.4
Sorbitol dehydrogenase (nmol/min/mg)	5.10±0.03	4.00±0.02* (-22%)	5.01±0.003	5.03±0.05 (0%)	3.40±0.02* (-32%)
Lactate dehydrogenase (nmol/min/mg)	306.20±3.50	360.34±6.10* (+18%)	310.02±4.04	317.63±5.62 (+2%)	465.30±6.27* (+50%)
δ-glutamyl dehydrogenase (nmol/min/mg)	27.61±1.11	47.20±2.90* (+71%)	23.02±1.22	24.31±1.00 (+6%)	32.41±0.68* (+41%)
Sperm motility (%)	89.2±0.4	72.0±1.2* (-19%)	87.0±1.2	86.0±1.0 (-1%)	72.0±1.0* (-17%)
Sperm count (per epididymisx10^7)	8.5±1.01	6.0±0.12* (-29%)	8.2±1.00	8.0±0.38 (-2%)	6.8±0.12* (-17%)
Abnormal sperm[3] (%)	9.4±0.40	21.6±1.43* (+130%)	9.4±0.40	10.0±1.6 (+6%)	17.0±0.89* (+81%)

[1] Exposure occurred throughout gestation.
[2] Exposure occurred between lactation days 0-21.
[3] The values for abnormal sperm expressed in this table are the sums of percentages of various individual abnormal morphotypes. Morphotypes that were statistically significantly increased included absent acrosome, banana head, detached head, amorphous head, curved neck, bent neck, round tail, looped tail, signet tail, and folded tail.
*p<0.05

e. Rat and mouse - gavage

Carbofuran (95.6% purity) was administered daily by gastric intubation to pregnant CD rats on gestation days 7 through 19. Doses were 0, 0.05, 0.1, 0.5, 1, 3 or 5 mg/kg (Courtney et al., 1985). The number of pregnant rats per dose was, at ascending doses, 10, 9, 10, 10, 12, 6 and 3 (though not explicitly stated, these appear to be the number of surviving pregnant rats). The total number of treated rats per dose was not provided. The rats were sacrificed on gestation day 20. Maternal mortality was 0%, 18.2%, 0%, 0%, 40%, 55% and 50%. No significant differences were discerned in maternal weight gain (though only gains for the entire treatment period were provided), liver-to-body-weight ratios or fetal body weight. However, the number of implantation sites/dam was statistically suppressed at 5 mg/kg, with an apparent, non-statistically significant effect at 3 mg/kg as well (# of sites at ascending doses: 11.8, 10.7, 10,8, 10.2, 11.1, 6.8 and 5.3*; *$p<0.05$). The number of fetuses per litter was similarly suppressed at the top two doses (11.2, 10.1, 10,8, 9.8, 10.8, 6.5 and 4.7*; *$p<0.05$). Percent fetal mortality also increased in a non-statistically significant manner at the top two doses (5.9%, 5.5%, 0%, 4.3%, 3.8%, 18.1% 20.8%; note, however that this parameter was not defined in the study). The number of fetal malformations did not show a dose-related increase. Examination of rib profiles did not reveal an effect. It appears, therefore, that carbofuran was not embryotoxic at dose levels lower than those inducing toxicity in the mothers.

The maternal NOEL for the rat study was set at 0.5 mg/kg-bw/day, based on mortality at 1 mg/kg-bw/day (0% at 0.5 mg/kg, 40% at 1 mg/kg/day). The developmental NOEL for the rat was set at 1 mg/kg/day, based on embryotoxicity at 3 mg/kg/day (decreased implantation sites/dam and decreased fetuses/litter). This observation supported the data of Jayatunga *et al.* (1998a), who documented embryo loss in Wistar rats following exposure of the dams to carbofuran at doses less than 1 mg/kg/day during gestation days 1-5 (see above).

As part of the same study, carbofuran was administered daily by gastric intubation to pregnant CD-1 mice on gestation days 6-16. Doses were 0, 0. 1, 1, 5, 10 or 20 mg/kg-bw/day. The mortality rate (as a fraction of the total number of treated mice) was 0/14, 0/14, 0/15, 0/18, 9/17 and 7/12. The number of pregnant mice at ascending doses was 11, 10, 13, 11, 5 and 3 (similarly to the rat part of the study, it appears that this represents the number of pregnant *surviving* mice, though it is not explicitly stated in the report). Survivors were sacrificed on gestation day 17. All dosed animals exhibited some degree of suppression of maternal weight gain, though at no dose did this achieve statistical significance. Significant reductions in the liver-to-body-weight ratio were noted at all doses except 10 mg/kg, with the greatest reduction, -21 %, occurring at 20 mg/kg. The role of carbofuran in both of these parameters was not clear. The numbers of implantations per litter and live fetuses per litter did not differ significantly from control values. Fetal body weights were significantly suppressed (14-15%) at the top two doses compared to controls. Malformations were unaffected by exposure. The percentage of fetuses with 13 ribs decreased significantly at the high dose (92.4%, 86.0%, 81.8%, 89.1%, 84.4%, 30.6%*; *$p<0.05$). These were compensated by an increase in fetuses with 14 ribs. The number of calcified centers in the fetal forepaws and hindpaws appeared slightly reduced at the high dose.

The maternal NOEL for the mouse was set at 5 mg/kg-bw/day, based on mortality at 10 mg/kg-bw/day. The developmental NOEL for the mouse was also set at 5 mg/kg/day, based on suppression of fetal body weights at 10 mg/kg-bw/day.

Neither the rat nor the mouse data in this published study were considered compliant with FIFRA guidelines.

f. Rabbit - gavage

This rangefinding study (WARF, 1978b) provided adequate dose justification for the following definitive teratology study in the rabbit (see next entry below). Carbofuran (95.6% pure) was administered by gavage in aqueous 0.25% methyl cellulose to pregnant New Zealand White rabbits, 17/dose, at 0, 0.2, 0.6 and 2 mg/kg-bw/day on gestation days 6-18. Clinical effects and body weights were monitored during gestation. Does were sacrificed on gestation day 30. Fetuses were examined after laparotomy. There were 2 deaths each at the low and mid doses and one death at the high dose that were not attributed to treatment. However, five deaths at the high dose were treatment-related. Three extra females were added to the high dose group; one of these also died. Pharmacotoxic signs of stress were noted repeatedly after treatment in nearly all animals in the high dose group. The following signs were noted: trembling (at ascending doses, 0, 0, 1, 6), no food or water intake (4, 3, 0, 5), loss of muscle control (0, 0, 0, 7), salivation (0, 0, 0, 3), sneezing (0, 3, 0, 4) and chewing motions (0, 0, 0, 7). There was no statistically significant body weight effect in does, nor were morphologic effects revealed upon necropsy. Neither the number of litters nor the rates of pregnancy appeared to be affected. Average fetal body weights, crown-rump lengths, and placental were not affected by carbofuran exposure, nor was the incidence of fetal abnormalities in soft or skeletal tissues.

The maternal NOEL was set at 0.6 mg/kg-bw/day, based on death and on cholinergic and other clinical signs at 2 mg/kg-bw/day. The developmental NOEL was $\geq$2 mg/kg-bw/day.

In the definitive study, groups of 20 artificially inseminated New Zealand white rabbits were treated with carbofuran (95.6% purity) by daily gavage in aqueous 0.5% methyl cellulose between gestation days 6-18 (IRDC, 1981b). Doses were 0, 0.12, 0.5 or 2 mg/kg-bw/day. Cesarean sections were performed on gestation day 29 on all surviving does. One high dose animal died on gestation day 11 of unknown cause. While matting and/or anogenital haircoat staining was observed in all dose groups, these signs increased in duration in the high dose group. Necropsies on the does did not reveal treatment-related abnormalities. Mean maternal weight gain on gestation days 6-12 was suppressed at the high dose (weight gain at ascending doses: 95, 137, 101 and 45 grams), though gain totals afterwards did not indicate clear differences between treated animals and controls. Over the entire treatment period, high dose weight gain was 20% less than controls. Observations made upon Cesarean section (numbers of corpora lutea, total implantations, early or late resorptions, postimplantation loss, viable fetuses, and fetal sex distribution crown rump length and weight) did not indicate an effect of exposure. Teratogenic responses were not observed.

The maternal and developmental NOELs were set at $\geq$2 mg/kg-bw/day. While it might be argued that a MTD was not achieved in this study (no clinical signs were observed, though high dose does gained less weight than controls during the first half of the dosing period), the dosing was justified in the preliminary dosing study. Therefore, this study was considered in compliance with FIFRA guidelines. Nonetheless, it was not clear why cholinergic signs observed in the preliminary study (done by WARF) were not observed in the complete study (done by IRDC). Both studies used comparably-sized animals, both administered the test article by gavage at a dose volume of 1 ml/kg, and both used methyl cellulose as a vehicle (WARF used a 0.25% aqueous solution, IRDC used a 0.5% aqueous solution). Possible differences in laboratory technique could explain the disparity.

Table III-18. NOEL and LOEL values for studies on reproductive and developmental toxicity of carbofuran

Species, strain	Study type & exposure regimen	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
Rat, SD	3-gen. repro, dietary	Parental: ↓ body wt. Repro.: reduced pup wt.	1.2/1.9 (M/F) 1.2/1.9 (M/F)	6.1/9.9 (M/F) 6.1/9.9 (M/F)	IRDC, 1979b
Rat (M), Druckrey	60-day exposure, effects on male repro. tissues	Testicular toxicity, ↓ body wt. gain	0.1	0.2	Pant *et al.*, 1995
Rat, SD	Teratology (rangefinding), GD[1] 6-15	Maternal: chewing behavior Develop.: n/a	0.01 (LED_{05}) >1	0.1 >1	WARF, 1978a
Rat, SD	Teratology (complete), GD 6-15	Maternal: n/a Develop.: n/a	>1.2 >1.2	>1.2 >1.2	IRDC, 1980b
Rat, SD	Dietary teratology (rangefinding), GD 6-19	Maternal: body wt. decrements Develop.: ND	1.5 ND	4 ND	IRDC, 1980c; JMPR, 1996
Rat, SD	Dietary teratology (complete), GD 6-19	Maternal: body wt. decrements Develop. ↓ pup wts.	1.48 4.36	4.36 10.97	IRDC, 1981a
Rat, Wistar	Teratology, GD 1-5	Maternal: cholinergic signs, ↓ food/water intake, bradycardia, locomotive behavior, ↓ head dips & rearing behavior Develop.: ↓ pup cranial & body length, ↓ fetal survival ratio, ↑ time to fur appearance & eye opening	0.01 (LED_{05}[2]) 0.2	0.2 0.4	Jayatunga *et al.*, 1998a
Rat, Wistar	Teratology, GD 8-12	Maternal: cholinergic & adrenergic signs, possible sedative actions Develop.: ↓ pup cranial & cervico-sacral length, ↑ time to fur appearance & eye opening	<0.2 0.4	<0.2 0.8	Jayatunga *et al.*, 1998b
Rat, SD	Teratology (acute), GD 18 only	Maternal: cholinergic signs, brain ChE depression Develop.: n/a (only ChE assessed)	ND ND	<0.05 ND	Cambon *et al.*, 1979
Rat, SD	Teratology, GD 7-19	Maternal: mortality Develop.: embryotoxicity	0.5 1	1 3	Courtney *et al.*, 1985
Rat, Druckrey	Teratology in male pups, GD 1-21 or LD 0-21	Maternal: n/a (no signs) Develop.: degenerative testicular changes	>0.4 0.2	>0.4 0.4	Pant *et al.*, 1997
Rabbit, NZW	Teratology (rangefinding), GD 6-18	Maternal: cholinergic signs & death Develop.: n/a	0.6 >2	2 >2	WARF, 1978b
Rabbit, NZW	Teratology (complete), GD 6-18	Maternal: n/a Develop.: n/a	>2 >2	>2 >2	IRDC, 1981b
Mouse, CD-1	Teratology, GD 6-16	Maternal: ↑ mortality Develop.: ↓fetal body wt.	5 5	10 10	Courtney *et al.*, 1985

[1] GD, gestation day; LD, lactation day; ND, not determined; LED_{05}, lower bound on the 5% benchmark dose response
[2] The LED_{05} in Jayatunga *et al.* (1996a) was modeled using the decrease rears/7.5 minutes data.

H. NEUROTOXICITY

1. Overview

A rat 13-week neurotoxicity study provided evidence for gait impairments and reduced limb grip strength after dietary exposure to carbofuran. A detailed rat developmental neurotoxicity study evidenced some higher order (possibly CNS-related) neural disruptions in pups exposed during gestation, though the doses were higher than those eliciting frank cholinergic signs or ChE inhibition in other studies, and they appeared to be reversible. The latter study also showed the embryotoxic potential of carbofuran. NOEL/LOEL data from these studies appear in Table III-19 at the end of this section.

2. Human studies (poisoning incidents)

A case report from Taiwan described what appeared to be delayed neuropathy in the aftermath of a suicide attempt by a 23-year old male (Yang *et al.*, 2000). This individual ingested 100 ml of carbofuran (the concentration was not stated). As stated in the report, "After recovering from acute cholinergic toxicity, he had notable paresthesia in his lower limbs and difficulty walking. Electrophysiological findings revealed sensorimotor neuropathy. Recovery began at 1 week and continued for 4 months. [In this case], after recovering from acute cholinergic toxicity, acute leg weakness was accompanied by electrophysiological findings [*i.e.*, reduced compound muscle action potential amplitude] consistent with axonal neuropathy." The authors state that it is unknown if carbarnate insecticides bind to neurotoxic esterase, the enzyme implicated in organophosphate-induced delayed neuropathy. They suggest that, in any case, the current symptoms were consistent with a predominantly axonal neuropathy.

3. Laboratory animal studies

a. Rat - dietary

Carbofuran technical (99.5%) was fed in the diet to Sprague-Dawley CD rats, 10/sex/dose, at 0, 50, 500 and 1000 ppm for 13 weeks (FMC, 1994). The equivalent internal doses for males at increasing doses were 2.4-4.7 mg/kg/day, 27.3-46.1 mg/kg/day and 55.3-92.2 mg/kg/day. For females they were 3.1-4.8, 35.3-50.7 and 64.4-100 mg/kg/day. Functional observational batteries and motor activity testing were done pretest and after treatment weeks 4, 8 and 13. Food consumption in both sexes was intermittently decreased at 1000 ppm. Gait impairment was the primary effect at $\geq$500 ppm in both sexes. This was expressed as staggered gait, splayed hindlimbs, ataxia and exaggerated hindlimb flexion. Reduced hindlimb grip strength was also observed. Females at $\geq$500 ppm had exophthalmos and, at 1000 ppm, an increased number of urine pools. Females at 1000 ppm showed decreased motor activity following the 4th and 8th weeks of treatment.

The systemic NOEL was set at 50 ppm (2.4 mg/kg/day in males, 3.1 mg/kg/day in females), based on gait impairments and reduced hindlimb grip strength in both sexes and exophthalmos in females at 500 ppm. The neurohistopathology NOEL was $\geq$1000 ppm, reflecting the fact that no neuropathologic effects were noted at any dose.

b. Rat (developmental neurotoxicity) - dietary

The potential for functional and/or morphological hazards to the neonatal rat nervous system following exposure of the pregnant mothers to dietary carbofuran (99.1 % purity) was examined in this study (Pharmaco LSR, 1994). Twenty four CD females/group received doses of 0, 20, 75, or 300 pprn from gestation day 6 through lactation day 10. Carbofuran intakes during gestation were 0, 1.70-1.73, 4.95-6.91, and 8.57-31.38 mg/kg/day. The wider ranges in test article consumption at the top two doses were due to fluctuations in food consumption during gestation. Dams were examined for physical signs, body weight and food consumption. The number of live pups per litter was recorded at selected intervals during lactation. Pinna detachment, incisor eruption, eye opening, vaginal patency, and preputial separation were evaluated in surviving pups. Motor activity, auditory startle response and swimming, learning, and memory evaluations were performed on one male and one female pup per litter. Brain

weights were determined for selected pups on postnatal days 11 and 60. Six pups/sex/group were subjected to neuropathological examinations, also on postnatal days 11 and 60.

There were no maternal deaths during the study. Other than elevated frequencies of general alopecia during gestation at 75 and 300 ppm, no physical signs were associated with exposure among the dams. Mean body weight gains at ascending doses during gestation days 6-10 were 14, 12, 1** and -27** grams (**$p \leq 0.01$). Statistically significant decreases in food consumption at the top two doses compared to controls were also noted during this time period. Recovery was evident in both of these parameters.

Pregnancy rates were unaffected by treatment. The number of pups per litter that were dead at birth appeared to increase at the high dose (increasing doses: 0.3, 0.1, 0.4, 1.2; not statistically significant).

Viability indices (ratios of the number of pups alive on day 4 vs. the number of pups born alive) were markedly reduced at the top two doses (98.5%, 94.7%, 83.4%**, 33.8%**; **$p \leq 0.01$). Much of the decline at the high dose was due to total litter loss; 14 dams lost their entire litter by day 21, with 13 of these having occurred by day 4. Subsequent pup losses were minor in all groups. The ratios of the number of litters on day 21 with at least one live pup *vs.* the number of "live" litters on day 0 were 23/23, 23/23, 21/24, 9/23** (**$p \leq 0.01$). The cause of the pup mortality was unclear. However, problems in fetal development, inability of dams to lactate, or lack of nurturing by the dams were considered possibilities.

Substantial pup weight decrements were evident at the two top doses throughout lactation, even though treatment ended on lactation day 10 (pup weight (g) on day 0: 6.2, 6.0, 5.8**, 5.2**; day 11: 24.7, 23.3, 18.6**, 15.2**; day 21: 51.1, 48.7, 40.9**, 35.6**; **$p \leq 0.01$). These reductions in body weight persisted throughout the postweaning period.

Vaginal patency and preputial separation were delayed from 1-3 days at 75 ppm and for 3-4 days at 300 ppm. Other markers of neonatal development (pinna detachment, lower incisor eruption, and eye opening) may also have been delayed, though clear evidence of dose responsiveness was lacking.

Evaluation of the auditory startle response in day 22 pups suggested the possibility of an effect at the top two doses, though statistical significance was not attained. By day 60, the startle evaluations were unremarkable. Motor activity evaluations indicated a possible effect in high dose females at day 13. However, in light of the stunted growth exhibited by these animals at that time, it was difficult to attribute this decrease to a direct nervous system effect. In any case, by the next measurement on day 17, the effect had largely disappeared.

Swimming development evaluations indicated reduced angle (*i.e.*, ability to keep head above the water line) at the mid and high doses between days 6 and 14, occasionally attaining statistical significance. Water maze time trials indicated a clear, also occasionally statistically significant, effect in high dose male "acquisition" (ability to learn to negotiate a maze). The effect in females on days 24-30 was so pronounced that they appeared unable to learn to negotiate the maze at all. Statistically significant deficits were also observed in 75-ppm females. Data were unremarkable for the day 60-65 test series.

Absolute brain weights were significantly reduced in the two higher dose groups at day 11. However, due to the marked body weight decreases at those doses, the relative brain weights (brain weight ÷ body weight) actually increased. By day 60, statistically significant reductions in brain weight were still evident among males (but not females) at the top two doses. Relative weights were statistically indistinguishable in both sexes on day 60. These data were consistent with a conclusion that there was no direct effect of carbofuran on brain weight. Necropsy and neuropathology exams did not reveal treatment-related abnormalities.

The maternal NOEL for this study was set at 20 ppm (~1.70 mg/kg/day), based on reductions in maternal body weight and food consumption at 75 ppm (4.95-6.91 mg/kg/day) and 300 ppm (8.57-31.38 mg/kg/day). The developmental NOEL was also set at 20 ppm (~1.70 mg/kg/day), based on reductions in pup survival and body weight gain, delays in pup developmental landmarks (in particular, vaginal patency and preputial separation), and possible indicators of slowed behavioral development at 75 ppm (4.95-6.91 mg/kg/day) and 300 ppm (8.57-31.38 mg/kg/day).

This study was in compliance with FIFRA guidelines.

Table III–19. NOEL and LOEL values for neurotoxicity studies on carbofuran

Species, strain	Study type & exposure regimen	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
Rat, SD	Neurotoxicity	gait impairments and reduced hindlimb grip strength in both sexes and exophthalmos in females	2.4/3.1 (M/F) (50 ppm)	27.3/35.3 (M/F) (500 ppm)	FMC, 1994
Rat, SD (F)	Developmental neurotoxicity, GD[1] 6 - LD[1] 10	Maternal: body wt. decrements, ↓ food consumption Develop.: ↓ pup survival, ↓ wt. gain, delayed development	1.7 1.7	4.95 4.95	Pharmaco LSR, 1994

[1]GD, gestation day; LD, lactation day

I. MISCELLANEOUS STUDIES

Sheep - dietary (endocrine function). Rawlings *et al.* (1998) studied the effects of dietary exposure to one of several pesticides on endocrine function in 1-4-year old polypay ewes. The compounds examined were carbofuran, dimethoate, chlorpyrifos, 2,4-D, trifluralin, triallate, lindane, and pentachlorophenol. Doses were designed to be at least 10-fold lower than the acute NOEL, determined both from the literature and from preliminary tests. This was done "to avoid any acute toxicity and yet keep doses high enough to see effects of chronic exposure to pesticides on the endocrine system" (p. 24). Carbofuran was administered *via* gelatin capsule to 6 ewes, three times weekly, for 43 days (for chemicals that were deemed capable of accumulating within the body, dosing was performed twice weekly). The dose was 0.3 mg/kg-bw. Blood samples were taken twice weekly, except that after 36 days, "ewes were bled every 12 minutes (4 ml) for 6 hours from a jugular catheter fitted 1 day previously.... This intensive bleeding was necessary to accurately assess serum concentrations of some hormones that are secreted in a pulsatile manner. This blood sampling was done when ewes were at days 8-10 of an estrous cycle to ensure that serum concentrations of reproductive hormones did not vary due to the stage of estrous cycle. To ensure all ewes were at this stage of the cycle, estrus was synchronized by a 12-day treatment with intravaginal sponges containing 60 mg medroxy progesterone acetate..." (p. 25). Assays were done for luteinizing hormone, follicle stimulating hormone, progesterone, estradiol, thyroxine (T_4), cortisol, and insulin.

There was no overt toxicity, nor were there body weight effects, in response to any of the compounds administered. This was consistent with the intent of the dosing regime. Pentachlorophenol and triallate treatment led to intraepithelial cysts, the only treatment-associated histopathologic effect noted. Carbofuran exposure caused a statistically significant increase (~10%, from -84 nmol/L to -92 nmol/L) in the level of blood T4 at the 36-day bleed. Except for trifluralin, which had no effect, all of the other compounds tested depressed T_4 levels. The authors speculated that the carbofuran effect was due to inhibition of liver metabolism. This was based on previously published evidence that carbofuran inhibited hepatic corticosteroid metabolism. While various other hormonal effects were noted, carbofuran action was restricted to the effect on T_4.

This was a non-guideline study. The consequences of the increased T_4 levels are not known. For this reason, it was not considered advisable to designate this as an adverse effect. However, these data provide evidence that carbofuran may have endocrine-disruptive effects.

Mice - dietary (immunotoxicity). Barnett *et al.* (1980) examined serum immunoglobulin concentrations over the lifespan of mice exposed *in utero* to carbofuran or diazinon. Drug-naive F_2 dihybrid mice (offspring of crosses involving C57BL/6, A/JAX, C34/He and BALB/c mice) were mated. The resultant pregnant females were exposed daily throughout gestation to measured amounts of homogenized peanuts containing sufficient pesticide to deliver doses of 0, 0.01 or 0.5 mg/kg carbofuran or 0, 0.18 or 9 mg/kg diazinon. There were 43 control dams, 23 and 18 low and high dose carbofuran dams, and 21 and 19 low and high dose diazinon dams. Dosing was based on pilot studies in which a minimum lethal dose (MLD) to F_3 neonates was determined. As stated in the report, "the higher dose was 1% of the lowest level which caused an increase in terata, morbid or moribund pups on gestational day 18; the lower dose was 2% of the higher dose" (p. 55). Litters were culled to 4/sex within 6 hours of birth. Weaning was carried out at 28 days of age. The serum levels of five classes of immunoglobulin, IgG_1, IgG_{2a}, IgG_{2b}, IgM and IgA, were determined on days 101, 400 or 800. The results were expressed as the mean of 10 animals per dose group or 7-10 vehicle controls.

While dams from all pesticide groups produced similar numbers of viable offspring, the high dose diazinon neonates were more susceptible to lethal respiratory infection resulting from acute bronchitis. After weaning at 28 days, there was no difference in average lifespan. High dose carbofuran pups weighed significantly less than controls at birth (actual body weights were not provided in the report). Pups from both high dose pesticide groups weighed less than controls through day 28, but these differences disappeared thereafter.

No effects of treatment were seen on IgG_{2b} or IgM levels. Non-dose-related changes were seen in IgA levels. These were not further discussed. IgG_1 levels were significantly elevated over controls in carbofuran high dose males at 101 and 400 days. IgG_1 levels for carbofuran low dose females were significantly lower than controls throughout the experiment (101, 400 and 800 days). IgG_{2a} levels for carbofuran low dose females were significantly lower at 101 days, but approximated controls for the remainder of the experiment. Interestingly, no effects on IgG_1 or IgG_{2a} were seen in female carbofuran high dose animals.

High dose diazinon males exhibited elevated levels of IgG_1 throughout the study, though statistical significance was achieved only at 400 days. Low dose diazinon males had statistically elevated IgG, levels only at 101 days. IgG_{2a} levels were statistically elevated in high dose males at 400 days. IgG_1 levels for diazinon high dose females were significantly lower than controls only at 101 days.

In light of this data, it is apparent that gender could be a mediating factor in determining the IgG_1 and IgG_{2a} status subsequent to prenatal pesticide exposure. However, the quantitative extent of the effects - generally, the difference between control and experimental groups, resulted in differences of less than 2-fold; the only exception was the nearly 3-fold suppression of IgG_{2a} in carbofuran low dose females - combined with the unclear role of pesticide dose, make it evident that further study is necessary to solidify any conclusions.

J. TOXICITY OF CARBOFURAN METABOLITES

1. Overview

Both environmental degradation and metabolism of carbofuran result in intermediates with potential mammalian toxicity. Of particular concern is the production of 3-OH-carbofuran, a product of furanyl ring hydroxylation. 3-OH-carbofuran is produced in plants and in soil, as well as being a mammalian metabolite. Its potential toxicologic importance was reinforced by the fact that tolerances for carbofuran also include 3-OH-carbofuran. 3-keto-carbofuran, another degradation product / metabolite, is produced in plants, soil and water, as well as in mammals, though tolerances are not currently established for this compound. The decarbamylated carbofuran metabolites (*i.e.*, the carbofuran phenols) appear to have lower acute toxicity, thus posing a lower level of health concern. Tolerances are not established for the latter compounds. Another group of metabolites, the nitroso derivatives, have also received attention. These compounds may be formed in the presence of nitrates under the acid conditions prevailing in the human stomach. They are mutagenic and cytotoxic (see sections III.A.6.f. and III.E.5. for details), though *in vivo* toxicity studies do not appear to have been done. It is also not clear if the nitroso derivatives would be absorbed as such from the gastrointestinal tract.

Only scant data were available on the toxicity of carbofuran metabolites. A series of summaries of acute and subchronic studies has been provided by FMC. One study on the acute toxicity of 3-OH-carbofuran and 3-keto-carbofuran was available from the published literature. The order of acute toxicities for these metabolites, as indicated by their relative LD_{50}s in rats after gavage dosing, was (from greater to lesser toxicity): 3-OH-carbofuran (LD_{50}=17.9 mg/kg), 3-keto carbofuran (LD_{50}=69.0 mg/kg), 3-keto-7-phenol (LD_{50}=295 mg/kg), 3-OH-7-phenol (LD_{50}=1350 mg/kg), and 7-phenol (LD_{50}=1800-2200 mg/kg). For purposes of comparison, the oral LD_{50} of carbofuran fell between 2 and 20 mg/kg (see section III.B.2. above).

The following section provides the results of these studies.

2. 3-OH-carbofuran (2,3-dihydro-2,2-dimethyl-3-hydroxy-7-benzofuranyl N-methylcarbamate)

"The acute oral toxicity of '3-hydroxy carbofuran' was determined in the Sprague-Dawley strain of rat. The material was administered as a 0. 1 % (w/v) corn oil suspension and two male and two female rats were used at each dose level evaluated. The acute oral LD_{50} was found to be 17.9±4.3 mg/kg." (quoted from FIVIC, undated, DPR record #23164)

****

"Four groups, each consisting of 15 male and 15 female Sprague-Dawley rats, were used to evaluate the subacute oral toxicity of '3-hydroxy carbofuran." The compound was incorporated into the diet at concentrations corresponding to 0, 10, 30, and 100 ppm and fed to the animals for a period of 90 days.

No adverse effects attributable to the ingestion of '3-hydroxy carbofuran' were noted. Parameters evaluated were growth, food consumption, reactions, mortality, hematology, clinical blood chemistry, urine analysis, organ weights and ratios, and gross and microscopic pathology." (quoted from FMC, undated, DPR record #23163)

****

The acute toxicity of carbofuran and its two major metabolites, 3-OH-carbofuran and 3-keto-carbofuran, were examined using the "Microtox" method (Kross *et al.*, 1992). In this assay, a photomultiplier tube was used to measure light from the bioluminescent bacterium, *Photobacterium phosphoreum*. This bacterium produces light in response to respiration-induced ATP production. Toxicity was thus proportional to the degree of inhibition of light production. The "EC_{50}", which was the concentration at which light production was halved, was very similar for carbofuran and 3-keto-carbofuran. The EC_{50} for carbofuran was at or below 50 mg/L, while

that for 3-keto-carbofuran was at or above 50 mg/L. 3-OH-carbofuran appeared to be much less toxic, exhibiting an EC_{50} at or above 600 mg/L.

The reason for the lower toxicity of 3-OH-carbofuran than 3-keto-carbofuran was not apparent, especially in light of the FMC observation that 3-OH-carbofuran is more acutely toxic than 3-keto carbofuran (see #1 and #2 in this section). It should be noted, however, that Microtox is a measure of *in vitro* toxicity. A possible relationship to the probable major mechanism of toxicity *in vivo*, *i.e.*, AChE inhibition, seems doubtful.

3. 3-keto carbofuran (2,3-dihydro-2,2-dimethyl-3-keto-7-benzofuranyl N-methylcarbamate)

"The acute oral toxicity of '3-keto carbofuran'was determined in the Sprague-Dawley strain of rat. The material was administered as a 1.0% (w/v) corn oil suspension and two male and two female rats were used at each dose level evaluated. The acute oral LD_{50} was found to be 69.0±14.7 mg/kg." (quoted from FMC, undated, DPR record #23162)

4. 7-phenol (2,3-dihydro-2,2-dimethyl-7-benzofuranol)

"The acute oral toxicity of 7-phenol' was determined in the Sprague-Dawley strain of rat. The material was evaluated undiluted, as a 25% (w/v) corn oil solution and as a 75% (w/v) propylene glycol solution. In each study two male and two female rats were used at each dose level. The acute oral LD_{50} for undiluted '7-phenol' was found to be 2200±500 mg/kg. The LD_{50} values for the corn oil and propylene glycol solutions were 1800±400 mg/kg and 1800±300 mg/kg, respectively." (quoted from FIVIC, undated, DPR record #23161)

****

"Three groups, each consisting of 15 male and 15 female Sprague-Dawley rats, were used to evaluate the subacute oral toxicity of ‘7-phenol.' The compound was incorporated into the diet at concentrations corresponding to 0, 300, 1000, and 3000 ppm and fed to the animals for a period of 90 days.

No adverse effects attributable to the ingestion of ‘7-phenol' were noted. Parameters evaluated were growth, food consumption, reactions, mortality, hematology, clinical blood chemistry, urine analysis, organ weights and ratios and gross and microscopic pathology." (quoted from FMC, undated, DPR record #23160)

5. 3-OH-7-phenol (2,3-dihydro-2,2-dimethyl-3,7-benzofurandiol)

"The acute oral toxicity of '3-hydroxy-7-phenol' was determined in the Sprague-Dawley strain of rat. The material was administered as a 5.0% (w/v) corn oil suspension and two male and two female rats were used at each dose level. The acute oral LD_{50} was found to be 1350±158 mg/kg." (quoted from FMC, undated, DPR record #23159)

6. 3-keto-7-phenol (2,3-dihydro-2,2-dimethyl-3-oxo-7-benzofurandiol)

"The acute oral toxicity of '3-keto-7-phenol' was determined in the Sprague-Dawley strain of rat. The material was administered as a 5.0% (w/v) corn oil suspension and two male and two female rats were used at each dose level evaluated. The acute oral LD_{50} was found to be 295±30 mg/kg." (quoted from FIVIC, undated, DPR record #23158)

****

"A one-generation reproduction study was conducted on '3-keto-7-phenol' using Sprague-Dawley rats as test animals. Three groups, each consisting of 8 males and 16 females, were used. Dietary concentrations of '3-keto-7-phenol' corresponding to 0, 10 and 50 ppm, respectively, were fed to animals in the three groups.

At the time the second litter (F_{1b}) was weaned, the F_O parents had been on test for 224

days (32 weeks). No significant difference between control and treated animals were noted during this period of time with respect to growth, food consumption, reactions, mortality, desire or ability to mate or in the females ability to conceive and carry the reproduction process to successful parturition and nourish their resulting young. Organ weight and ratio data as well as gross and microscopic pathology on parental animals did not reveal any adverse findings. In addition, the progeny of the treated animals were in no way affected either in their physical appearance or in their ability to survive and grow in a normal manner." (quoted from FMC, undated, DPR record #22786)

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

1. Non-oncogenic effects

a. Acute toxicity

Oral exposure. An acute regulatory LED_{05} value of **0.01 mg/kg** was used in this document to characterize acute risk after oral exposure to carbofuran. It was calculated using benchmark dose methodology from the rat developmental toxicity study of WARF (1978a). Statistically significant, dose-dependent stimulation of chewing behavior in pregnant dams was observed at 0.1 mg/kg (lowest dose tested) and above. The acute nature of this sign was explicit in the study report. Other signs, including lacrimation, pale eyes, increased salivation, rough coat, trembling and convulsions, were seen in several animals at the high dose of 1 mg/kg. Lethargy was observed at both the mid dose of 0.3 and at the high dose of 1 mg/kg. The report did not indicate if these other signs were acute responses. However, recognizing that the exposure regimen was for 10 days only (gestation days 6-15), they certainly resulted from short term, if not strictly acute, exposures.

Because chewing behavior incidence was highly dose-responsive, and because more serious signs were observed at somewhat higher doses, it was viewed not only as adverse, but appropriate as a critical endpoint determinant. Risk analyses of several organophosphate compounds submitted to the Department of Pesticide Regulation as part of the registration process indicate that chewing behavior was a critical acute determinant in several cases (acephate, fenthion, azinphosmethyl and mevinphos) and a critical subchronic determinant in one case (dichlorvos) (Reed, 2003). In light of their widely-recognized cholinesterase inhibiting properties, these examples emphasize the possibility that cholinergic activation, either central or peripheral, was responsible for the chewing behavior.

Of the 16 algorithms examined for the benchmark dose analysis, the dichotomous log-transformed logistic plot (with the slope parameter restricted as slope ≥ 1) best approximated the dose-response data, as determined by comparison of AIC numbers. This plot generated the 0.01 mg/kg LED_{05} value (ED_{05}=0.02 mg/kg), as shown below in Figure 4. Details of the log-logistic algorithm and the resultant calculations appear in Appendix I.

Results from several other studies support this critical acute determination. FMC (2002) reported a statistically significant, dose-dependent rise in teeth grinding behavior in Sprague-Dawley rats following acute oral gavage exposure. Teeth grinding was considered equivalent to the abnormal chewing behavior documented in the WARF (1978a) study. Females appeared to be slightly more sensitive than males, though this difference may have reflected the relatively small numbers of test animals in the FMC study. In addition to teeth grinding, dose-dependent tremors were also noted. Benchmark dose analysis of the teeth grinding behavior generated LED_{05} / ED_{05} values of 0.02 mg/kg / 0.03 mg/kg (multistage algorithm), very close to the values generated in the WARF (1978a) study.

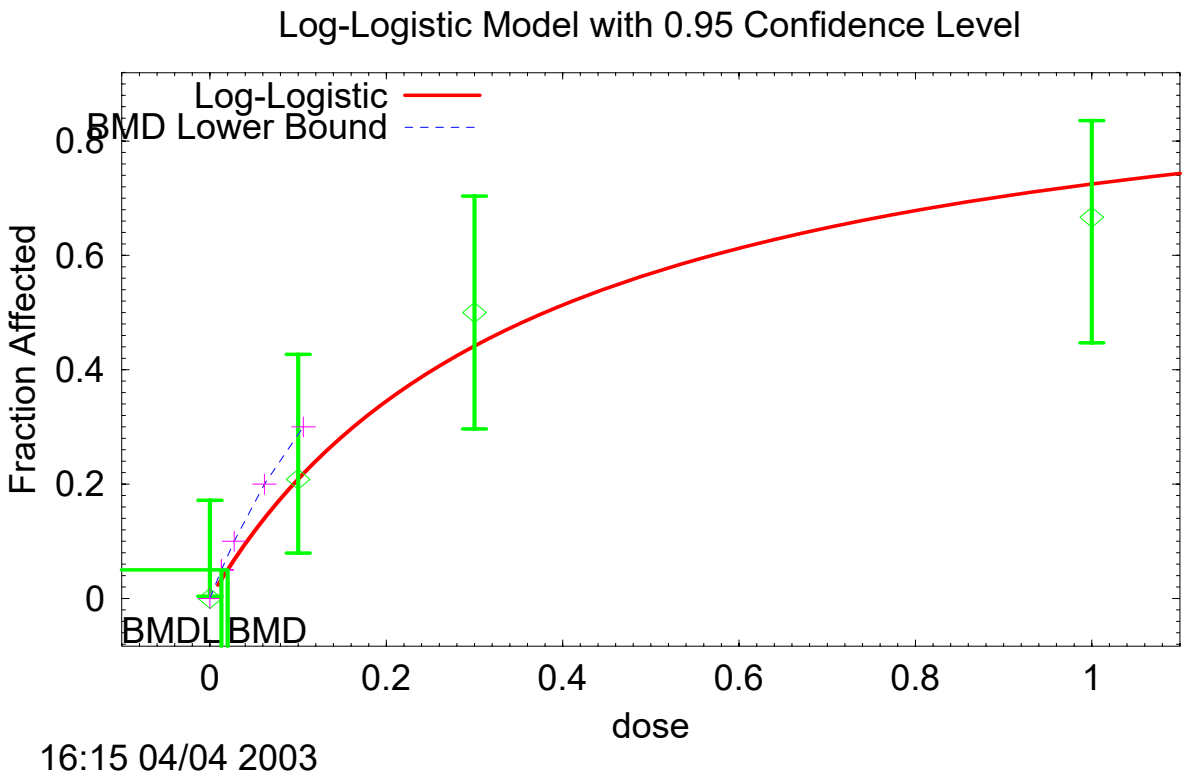
In addition, Moser (1995) pointed out in a study comparing the acute effects of cholinesterase inhbitiors in rats using the functional observational battery, that abnormal chewing behavior, sometimes called mouth-smacking, is a recognized cholinergic response to organophosphates and carbamates. Dose-dependent chewing behavior was observed in response to all of the compounds tested in that study, including aldicarb, carbaryl, parathion, DFP, chlorpyrifos, fenthion and diazinon. As noted on page 623 of that study: "Mouth-smacking, or chewing, is another sign that was consistently observed with these compounds. This sign is elicited by muscarinic agonists such as pilocarpine and oxotremorine, but not by nicotine, and can be blocked by muscarinic antagonists. The pharmacological subtype M_2, but not M_1, muscarinic receptor has been implicated, and the site of action identified as the ventrolateral striatum. This

behavior has been proposed as an indicator of nausea in rats; it is interesting to note that nausea is a common symptom of cholinesterase inhibitors in humans."

A low dose LOEL of 0.2 mg/kg was established in the study of Jayatunga *et al.* (1998a). Pregnant female Wistar rats exposed by daily gavage to 0.2 mg/kg carbofuran on gestation days 1-5 exhibited statistically significant decreases in number of rears, locomotive activity, and number of head dips. Because the relevant tests were performed only on gestation day 5, these signs were interpreted as acute or relatively short-term responses. Carbofuran also induced clinical signs, though precise documentation of the relevant dose and time of appearance was not provided. Nonetheless, the discussion strongly implied that low-dose effects were present from the initial exposure: "...overt signs of cholinergic toxicity was (*sic*) evident (2-3 h) following administration of carbofuran: salivation.... lachrymation, constriction of pupils, convulsions, production of loose stools and frequent urination. These effects were transient (lasting 7-8 h) and *appeared to be dose related*." (Jayatunga *et al.* [1998a], p. 34; emphasis added). Statistically significant bradycardia, decreased water consumption, and piloerection without exophthalmia (considered to be an adrenergic response) were also seen at the LOEL dose, though again, these measurements were made after 5 days of exposure. Similar effects were seen in Jayatunga *et al.* (1998b), where pregnant Wistar rats were exposed to carbofuran on gestation days 8-12. Benchmark dose modeling of both the head dip and locomotor activity data from Jayatunga *et al.* (1998a) using a Hill algorithm (continuous data) generated LED_{05} and ED_{05} values of 0.01 mg/kg and 0.02 mg/kg, respectively, precisely the same as the equivalent values in the critical WARF study.

Cholinergic signs were present in humans at a dose level only 5-fold higher than the WARF LOEL. It must be recognized, however, that the indicated study (FMC, 1976) used only a few male volunteers and the data were only summarily reported. For this reason, the data could be marshaled only as *support* for a critical regulatory value derived elsewhere. Nonetheless, the study established a NOEL of 0.1 mg/kg, based on a LOEL of 0.25 mg/kg. The report summary did not reveal the precise method of exposure, though it is presumed that it occurred by gavage via capsule. The signs included dry mouth, salivation, diaphoresis, abdominal pain, drowsiness, nausea and vomiting. These generally began 0.5 to 3 hours post dose and persisted for up to 3 hours. In addition, miosis was observed within 2 hours of dosing, persisting for 24 hr. Such symptomology was not unexpected in view of the ChE-inhibitory properties of this carbarnate insecticide. Indeed, dose-dependent inhibition of RBC ChE was documented - 33% inhibition was measured at the NOEL dose of 0.1 mg/kg and 57.5% inhibition was measured at the LOEL dose of 0.25 mg/kg. However, the blood ChE data were so incompletely reported that it was even more difficult than usual to gauge their biologic or toxicologic significance. The real significance of the FMC study lay in its demonstration of cholinergic signs in humans at a dose level (0.25 mg/kg) that was only 2.5-fold greater than the LOEL dose in the critical rat study (0.1 mg/kg).

Figure 4. Incidence of chewing behavior in CD rats following gavage dosing with carbofuran (WARF, 1978a): Log-logistic curve fitting with LED_{05} ($BMDL_{05}$) and ED_{05} (BMD_{05}) intercepts



Dermal exposure. An acute dermal study adequate to establish a critical acute dermal NOEL was not identified for this report. The human acute dermal study of Arnold (1977) demonstrated that humans are highly sensitive to carbofuran by the dermal route. Overt cholinergic signs were observed at the high dose of 4 mg/kg and dose-dependent inhibition of RBC AChE occurred from the low dose of 0.5 mg/kg and up. However, this study was inadequate to establish a regulatory NOEL / LOEL for several reasons: (1) there were too few subjects per dose (two), (2) there were no female subjects, (3) there were no subjects outside the 23-53 yr age range, and (4) the study was conducted in 1977, before there was adequate institutional review for human studies.

While the acceptable rabbit 21-day dermal study (FMC, 1985b) was considered for this purpose, the lack of overt toxicity even at the high dose of 1000 mg/kg/day forced the conclusion that rabbits were less sensitive than humans to the systemic effects of dermal carbofuran. Alternatively, the difference in toxicity between the human acute dermal study (Arnold, 1977) and the rabbit 21-day dermal study (FMC, 1985b) could have been due to greater dermal penetration caused by the particular inert ingredients in the end-product formulation (Furadan 4F) used in the human study. In any case, the combined results of these two studies indicated that the rabbit system is inappropriate for evaluating carbofuran's potential for dermal systemic toxicity in humans.

In the absence of a route-specific study, the critical acute oral LED_{05} of **0.01 mg/kg** will be used to assess the potential for acute dermal toxicity. Since it is assumed that the intestinal absorption of carbofuran is 100%, no adjustment to the LED_{05} will be necessary. And as the value of 0.01 mg/kg is $1/50^{th}$ of the LOEL in the human study, which itself was based on marginal inhibition of the RBC ChE, it is likely that 0.01 mg/kg, in the context of the acute dermal assessment, is health-protective. Uncertainties arising with the route extrapolation are summarized in the Risk Appraisal section of this document (section V).

Inhalation exposure. There was insufficient observational detail from the available acute inhalation toxicity studies to establish a critical inhalation NOEL. Instead, potential inhalation health risks were gauged by use of the critical oral LED_{05} of **0.01 mg/kg**. Limited support for this came from the fact that the 4-hr rat inhalation LD_{50}, ~0.1 mg/L, when converted to mg/kg by correcting for the default rat breathing rate of 160 L/kg/4 hr and the default inhalation pulmonary absorption of 100%, was 16 mg/kg. This fell within the acute oral LD_{50} range of 2-30 mg/kg (for LD_{50} values, see Table III-4a):

$$(0.1 \text{ mg/L}) \times (160 \text{ L/kg/4 hr}) = 16 \text{ mg/kg}$$
$$16 \text{ mg/kg} \times 100\% \text{ absorption} = 16 \text{ mg/kg} \approx \text{rat inhalation } LD_{50}$$

However, the value of the LD_{50} correlation should not be overstated. With cholinergic compounds, mortality at high doses is due to a combination of overwhelming peripheral and central nervous effects converging on the lung. On the other hand, individual clinical signs at low doses are likely due to specific interactions at individual anatomic sites. Such effects are dependent on pharmacokinetic factors such as absorption, distribution, metabolism and excretion, all of which are influenced by the route of exposure. A recent review by Rennen *et al.* (2003) confirms this: when inhalation NOELs were estimated from oral data, they were often found to be inaccurate, with common errors in the direction both of over- and underestimation. Nonetheless, oral-to-inhalation route extrapolation appears to be the best recourse in the present case.

b. Subchronic toxicity

Oral exposure. The critical subchronic oral NOEL was set at **0.1 mg/kg/day**. This was based on the 60-day gavage study by Pant *et al.* (1995) in which male reproductive toxicity and suppression of body weight gain in Druckrey rats were noted at the LOEL of 0.2 mg/kg/day. The

male reproductive toxicity was manifested as reductions in the absolute and relative weights of epididymides, seminal vesicles, ventral prostate and coagulating gland, reduced epididymal sperm motility and counts, morphologic sperm abnormalities, changes in testicular enzyme levels, vacuolization of Sertoli cells and spermatids, and testicular congestion. Higher doses caused even more severe responses.

Four additional studies may be brought in support of this NOEL designation.

(1) In a later study by the same authors (Pant *et al.*, 1997), similar degenerative changes in the male reproductive system were demonstrated in 90-day old Druckrey rats that had been exposed to 0.4 mg/kg/day carbofuran, either throughout gestation or for the lactational period of 21 days. The NOEL for that study was, consequently, 0.2 mg/kg/day. In view of the fact that the affected animals had been exposed indirectly (i.e., through placental blood or mother's milk) and the testicular examinations were carried out as long as 90 days after exposure, the slightly higher NOEL was not surprising.

(2) Testicular degeneration was noted at 0.6 mg/kg/day in the dog 1-year chronic dietary study (Toxigenics, 1983), resulting in a NOEL designation of 0.3 mg/kg/day.

(3) Youssef *et al.* (1995, 1996) found evidence for sperm toxicity within 1 week of gavage exposure (the time of first measurement) in rabbits, as well as in rabbit and human sperm *in vitro*.

(4) A single intraperitoneal injection of carbofuran resulted in abnormal sperm production in mice at doses as low as 1 mg/kg (Chauhan *et al.*, 2000). Treatment with 0.5 mg/kg/day for 5 consecutive days also resulted in abnormal sperm.

Dermal exposure. No adequate subchronic dermal study was available to derive a critical NOEL. The critical subchronic oral NOEL of **0.1 mg/kg/day**, based on testicular effects in rats in the 60-day study (Pant *et al.*, 1995), was substituted for a subchronic dermal NOEL in the risk calculations.

It might be argued that the 21-day repeat dose dermal study of FMC (1985b) offered a more appropriate critical subchronic NOEL, particularly as it was route specific. However, evidence presented above suggested that the rabbit was not nearly as sensitive as the human to the adverse effects of carbofuran by the dermal route, and thus may be inappropriate to use in a carbofuran risk assessment. In addition, the strong evidence for testicular effects in the oral study made it unwise to ignore the possibility of such effects by the dermal route. The FMC dermal study did not address the possibility of male reproductive pathology.

c. Chronic toxicity

Oral exposure. Risks from chronic oral exposure to carbofuran were evaluated using the rat subchronic oral NOEL value of **0.1 mg/kg/day**. As noted above, this value came from the study of Pant *et al.* (1995). It was based on male reproductive toxicity and suppression of body weight gain in rats at the LOEL dose of 0.2 mg/kg/day.

Use of a subchronic study to represent chronic toxicity in this assessment may be considered unusual. However, the lowest chronic NOEL was 0.3 mg/kg/day, based on testicular degeneration and clonic convulsions at 0.6 mg/kg/day in the 1-yr dog feeding study (Toxigenics, 1983). The concordance of testicular effects in the rat and dog studies supports use of the rat study in this context. Why the critical chronic NOEL was higher than the critical subchronic NOEL of 0.1 mg/kg/day established in Druckrey rats was not known. It could not be explained

by the choice of doses, since the LOEL of 0.2 mg/kg/day in the rat study was lower than the NOEL if 0.3 mg/kg/day in the dog study. There were two other (non-exclusive) possibilities:

(1) The gavage dosing regimen used in the subchronic study resulted in higher blood levels of carbofuran than were achieved in the dog feeding study.

(2) Rats were more sensitive to the testicular effects of carbofuran than dogs.

It was not possible using current data to distinguish between these possibilities.

Dermal exposure. In the absence of an appropriate dermal study to assess chronic dermal exposure, the subchronic oral NOEL of 0.1 mg/kg/day will be used.

2. Oncogenicity

No evidence for oncogenicity was forthcoming from FIFRA-acceptable chronic studies in rats, mice and dogs (IRDC, 1979a; IRDC, 1980a; Toxigenics, 1983; respectively). Neither was there indication of oncogenicity in humans from illness reporting to the State of California. However, several *in vitro* and *in vivo* studies suggested that carbofuran is genotoxic. This included *in vivo* evidence for induction of chromosome abnormalities and micronucleus formation in mice (Amer *et al.*,. 1997; Chauhan *et al.*, 2000). *N*-nitrosocarbofuran, a possible gastric metabolite, is cytotoxic and mutagenic *in vitro* (Blevins *et al.*, 1977; Nelson *et al.,* 1981; Wang *et al.*, 1998; Yoon *et al.*, 2001). Nitrosocarbamates have been shown to be oncogenic in several studies (*cf.*, Baron, 1991). Finally, a large epidemiologic study suggests an increased risk for lung cancer in populations occupationally exposed to carbofuran (Bonner *et al.*, 2005). These data, while not adequate for quantitative assessment of carcinogenicity, suggest that oncogenic concerns may be relevant to this chemical.

B. EXPOSURE ASSESSMENT

1. Overview

Estimates of potential exposure to carbofuran resulting from various occupational and resident/bystander scenarios were developed by the Worker Health and Safety Branch of DPR. These are contained in a companion document to this report, entitled Estimation of Exposure of Persons in California to Pesticide Products that Contain Carbofuran (DPR, 2006), which is attached to this report as Appendix I. Data from that document are summarized below and are used in the following risk characterization for carbofuran (see section IV.C. below).

Only one carbofuran product, Furadan 4F Insecticide / Nematicide, a 44% flowable liquid concentrate, is currently registered for use in California. Agricultural application techniques include as a foliar spray by aerial or ground equipment, as a soil application, by irrigation, as a dip, or by drenching. Non-agricultural uses are not permitted.

Carbofuran use declined steadily in California between 1999 (138,212 pounds) and 2003 (49,275 pounds). This decline was primarily a function of a decline in use on three of the four major target crops, alfalfa, grapes and rice (use on rice was cancelled after 2000). Use on cotton was higher in 2000-2002 than in 1999 or 2003.

2. Occupational exposure

a. Handlers

Only one study, conducted among prairie grain farmers in Alberta, Canada, was available in which handler exposures to carbofuran were directly monitored (Hussain *et al.*, 1990). It was considered unacceptable by DPR due to small sample sizes. In addition, it was hampered by failure to delineate which of the subjects were exclusively applicators and which were mixer / loader / applicators.

For these reasons, it was concluded that handler exposure would be more effectively characterized through the Pesticide Handler Exposure Database (PHED), a non-chemical-specific program developed by the USEPA, Health Canada and the American Crop Protection Association. The only exceptions to this were (1) the acute dermal estimates for dip/slurry applicators, which came from the equations in the Risk Assessment Guidance for Superfund, Part E (RAGS-E), and (2) the acute inhalation estimates for dip/slurry applicators, which were derived by estimating the air saturation concentration for carbofuran. The air saturation concentration was used because calculations of a theoretical air concentration using the equations in SWIMODEL, a modeling approach for calculating air concentrations over an aqueous solution, generated a value that was greater than the air saturation concentration (for references to RAGS-E and SWIMODEL, see DPR, 2006). In this context it should be noted that the Exposure Assessment Document (DPR, 2006) did not estimate seasonal exposure, as DPR records indicated no evidence for *any* uses on pine seedlings over the 1991-2003 period.

According to the DPR Exposure Assessment document (DPR, 2006), PHED use begins with selection of "a subset of the data having the same or a similar application method and formulation type as the target scenario. The use of non-chemical-specific exposure estimates is based on two assumptions: (1) that exposure is primarily a function of the pesticide application method/equipment and formulation type and not of the physical-chemical properties of the specific AI; and (2) that exposure is proportional to the amount of AI handled."

PHED estimates are subject to uncertainty because they are based on measurements obtained using varying protocols, analytical methods and residue detection limits. Adding to this uncertainty, only small numbers of replicates are used for some target scenarios. For these reasons, the DPR Exposure Assessment uses 90% confidence limits on the 95th percentile to estimate short-term (acute) exposures and 90% confidence limits on the arithmetic mean to estimate intermediate (subchronic) or long-term (chronic) exposures. In order to correct for the fact that PHED supplies only the mean of total dermal exposure, but only the coefficients of variation (*i.e.*, the standard deviation divided by the mean x 100) of separate body regions, a multiplier is applied to estimate the confidence limit for the 95th percentile. The value of this multiplier is determined by the sample size. As stated in the Exposure Assessment (p. 23), "DPR makes the assumption that total exposure is lognormally distributed across persons and has a coefficient of variation of 100 percent. The method of approximation is described in Powell (2002) [for this reference, see DPR (2006)], and uses the fact that in any lognormal distribution with a given coefficient of variation, the confidence limit for the 95th percentile is a constant multiple of the arithmetic mean." For further details on the actual multiplier values, and on the general methods and assumptions required to estimate confidence limits on percentiles from PHED, see DPR (2006).

Five different handler categories relevant to carbofuran application scenarios were identified for this document. These included groundboom, aerial, chemigation, low-pressure handwand and dip/slurry applications. Within these categories, exposures were estimated for different subtasks, including, where appropriate, mixer / loader, applicator, mixer/loader/applicator and flagger. For each subtask, certain assumptions were made regarding the influence of protective gear (*eg.*, clothing, respirators, etc.). The period of seasonal use was determined by reference to the DPR Pesticide Use Report.

The following section is quoted at length from the section of the Exposure Assessment (DPR, 2006) relating to groundboom applications (mixer/loader and applicator; pp. 19-20). This was done in order to clarify how the exposures were estimated from PHED. Because similar considerations apply to the other handler scenarios, it is expected that the groundboom description will give the reader a general idea of the procedures involved. Further details on all of the handler scenarios, as well as further calculation details, can be found in DPR (2006).

> Significant exposure scenarios involving groundboom applications are M/L [mixer/loader] and applicator... For M/L, use of a closed system was assumed, based on California requirements, and M/L were assumed to wear the clothing and PPE [personal protective equipment] listed on product labels. A 90% protection factor was applied to the inhalation PHED results for use of a respirator... Applicators were assumed to use clothing and PPE listed on product labels and California regulations. The groundboom applicator scenario included use of either truck or tractor, and an open cab was assumed as there is no requirement for a closed cab. Two protection factors were applied to PHED results for applicators...: a 90% protection factor was applied to hand exposure for use of gloves, and a 90% protection factor was applied to inhalation exposure for use of a respirator... The protection factor for gloves was needed because the applicator PHED scenario with gloves gave results with insufficient numbers of high-quality observations, and the scenario used did not include gloves. The application rate, 10 lbs/acre, is the rate allowed for field-grown ornamentals to which carbofuran is applied as a high volume spray or drench, which is then watered in...
>
> As shown in Table 5 [of the Exposure Assessment], the Acute Absorbed Daily Dosage (Acute ADD) estimate for the M/L scenario was 0.224 mg/kg/day. For the applicator scenario, the Acute ADD estimate was 0.318 mg/kg/day. Assuming that a M/L/A spends part of a workday mixing/loading and part making the application, exposure of the M/L/A should be less than the applicator exposure and greater than that of the M/L. [*Note: The figures in this paragraph were combined dermal + inhalation values. The present assessment makes use only of the separate exposure values.*]
>
> Groundboom applications are common in row and field crops, such as alfalfa, artichokes, cotton, and soybeans, as well as on grapes. Alfalfa was selected as a representative crop, and all ground applications to alfalfa were assumed to be groundboom applications. Figure 1 [of the Exposure Assessment document] summarizes ground applications of carbofuran to alfalfa in Imperial County, based on pounds applied per month for the most recent six years for which data are available, 1997-2002... Most use during the six-year period occurred in Imperial County.
>
> All applications occurred in the 3-month period of January through March... Ground applications to other crops also tended to occur during two or three months each year..., supporting a seasonal and annual estimate of three months. Both seasonal and annual use were estimated to occur during these three months."

Table IV-1 (using data from Tables 5 and 6 of the DPR Exposure Assessment) presents the data and assumptions used to calculate carbofuran handler dosages, both by the dermal and the inhalation routes. Inspection of the absorbed dosages reveals that the great majority of systemic exposure in handlers occurs by the dermal route. The acute Absorbed Daily Dosage (acute ADD), Seasonal Average Daily Dosage (SADD) and Annual Average Daily Dosage

(AADD) are calculated using the following default values:

- Dermal absorption = 50%
- Body weight = 70 kg
- Inhalation absorption = 100%

Table IV-1. Exposure dosages for workers handling carbofuran: short-term (acute) and seasonal scenarios by the dermal and inhalation routes (data from Tables 5 and 6, DPR, 2006)

Work task	Acute ADD [1] (mg/kg)		SADD [2] (mg/kg/day)		AADD [3] (mg/kg/day)	
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation
Groundboom [4]						
M/L	0.221	0.003	0.055	0.001	0.009	0.0001
Applicator	0.291	0.027	0.073	0.007	0.012	0.001
Aerial [5]						
M/L	0.552	0.008	0.138	0.002	0.023	0.0003
Applicator	6.36	0.041	2.12	0.016	0.354	0.003
Flagger	1.09	0.011	0.271	0.003	0.045	0.001
Chemigation [6]						
M/L	1.16	0.015	0.290	0.004	0.072	0.001
LPHW [7]						
M/L/A	0.002	0.00005	0.0006	0.00002	0.0001	0.00001
Dip/slurry [8]						
M/L	0.002	0.00003	---- [9]	----	----	----
Applicator	1.29	0.001	----	----	----	----

Note: Dermal and inhalation exposures were calculated from surrogate data using the PHED database and software (DPR, 2006). Values from PHED were rounded to three significant figures.

[1] The Acute Absorbed Daily Dosage (acute ADD) is an upper-bound estimate calculated from the short-term exposure (µg/lb AI). The application rate is the maximum on the product labels, which varied for each scenario; acres treated per day varied by scenario. Estimates were rounded to three significant figures. Calculation:

Acute ADD = [(acute exposure) x (absorption) x (acres treated / day) x (application rate)] / 70 kg bw

The acute exposure values and acres treated / day are provided in the EAD (DPR, 2006). Calculation assumptions include:

• Dermal absorption = 50% • Body weight = 70 kg • Inhalation absorption = 100%

[2] The Seasonal Average Daily Dosage (SADD) is a 90% upper confidence estimate calculated from the long-term exposure estimate (µg/lb AI). The application rate is the maximum rate on product labels, which varied for each scenario; acres treated per day varied by scenario. These are found in the EAD (DPR, 2006). Calculation assumptions are the same as in footnote "1". Calculation:

SADD = [(long-term exposure) x (absorption) x (acres treated / day) x (application rate)] / 70 kg bw

[3] The Annual Average Daily Dosage = SADD x (annual use months per year) (12 months/year). Annual use estimates vary for each scenario and can be found in the EAD (DPR, 2006).

[4] Estimates assumed a maximum application rate of 10 lb AI / acre, the maximum rate on field-grown ornamentals. Assumed 40 acres treated / day. Seasonal and annual exposures are estimated to occur over two months.

[5] Estimates assumed a maximum application rate of 1 lb AI / acre, maximum rate on alfalfa. Assumed 1000 acres treated / day. Seasonal and annual exposures are estimated to occur over two months.

[6] Estimates assumed a maximum application rate of 6 lb AI / acre, maximum rate on post-harvest grapes. Assumed 350 acres treated / day. Seasonal exposure is estimated to occur during a two-month period; annual exposure is estimated to occur over a total of three months.

[7] Estimates assumed handling of 40 gal /day, containing 0.0625 lb AI / 100 gal, for a total of 0.025 lb AI / day. Seasonal and annual exposures are estimated to occur over three months.

[8] Estimates assumed handling of 40 gal/day containing 0.1 lb AI/100 gal, for a total of 4 lb AI/day. The M/L estimates were derived from PHED. The applicator dermal exposure estimates were based on Risk Assessment Guidance for Superfund, Part E, while the applicator inhalation exposure estimates were based on USEPA's SWIMODEL, assuming a saturated carbofuran vapor concentration (DPR, 2006).

[9] Seasonal and annual estimates were not made for dip/slurry applications. The Exposure Assessment Document states that this was due to the complete lack of reported uses on pine seedlings over the 1991-2003 period (DPR, 2006).

b. Fieldworkers

Dermal exposure of fieldworkers via dislodgeable foliar residues was expected upon reentry into fields previously treated with carbofuran. Estimates were made for three representative scenarios: scouting cotton, scouting alfalfa and scouting potatoes. Protection of cotton scouts was anticipated to protect all activities in field corn, sweet corn and sugarcane. Protection of alfalfa scouts covered workers in barley, wheat, oats, soybeans and artichokes. Protection of potato scouts was expected to protect only potato workers (DPR, 2006).

The following equation was used to calculate the acute ADD:

$$\text{ADD } (\mu g/kg/day) = \frac{\text{DA x DFR } (\mu g/cm^2) \text{ x TC } (cm^2/hr) \text{ x ED } (hr/day)}{\text{BW } (kg)}$$

DFR (dislodgeable foliar residue): the pesticide residue that can be removed from both sides of treated leaf surfaces using an aqueous surfactant. DFRs were estimated at the expiration of the restricted entry interval for acute estimates and at the expiration of the restricted entry interval plus an additional time period depending on the task for the seasonal and annual estimates. Details relating to the determination of DFR for each exposure scenario are found in Table IV-2 (footnotes 6, 7 and 8) and in DPR (2006).

TC (transfer coefficient): an estimate of the foliage area that comes into contact with the skin. The TC for cotton was the sum of the geometric mean transfer factors for bare hands, clothed upper body and clothed lower body, and assumed a clothing penetration of 10%. The TC for artichokes was a USEPA default value.

ED (exposure duration) was set at a default of 8 hours.

DA (dermal absorption rate) was set at a default of 50%.

BW (bodyweight) was set at a default of 70 kg.

Table IV-2 provides the acute, seasonal, annual and lifetime systemic exposure estimates resulting from dermal contact during cotton, alfalfa and potato scouting. These data are equivalent to Tables 7 and 8 in the Exposure Assessment document (DPR, 2006).

Table IV-2. Acute exposures to carbofuran estimated for reentry workers (from Tables 7 and 8; DPR, 2006)

Exposure scenario	DFR ($\mu g/cm^2$) [1]	TC (cm^2/hr) [2]	Acute ADD (mg/kg/day) [3]	SADD (mg/kg/day) [4]	AADD (mg/kg/day) [5]
Scouting cotton [6]	0.057 (acute) 0.0076 (seasonal-annual)	2000	0.007	0.0009	0.0001
Scouting alfalfa [7]	1.16 (acute) 0.819 (seasonal-annual)	1500	0.099	0.070	0.012
Scouting potatoes [8]	0.186 (acute) 0.111 (seasonal-annual)	1500	0.016	0.010	0.002

[1] Dislodgeable Foliar Residue was estimated at expiration of the restricted entry interval for acute estimates and at the expiration of the restricted entry interval plus an additional time period depending on the task for the seasonal and annual estimates (see footnotes # 6, 7 and 8 below).
[2] Transfer Coefficients were estimates of skin contact with treated foliage.
[3] Acute Absorbed Daily Dosage was calculated as described in the text. Assumptions include:
• Exposure duration = 8 hr • Dermal absorption = 50% • Body weight = 70 kg
[4] Seasonal Average Daily Dosage, a mean estimate of absorbed dose, was calculated as described in the text.
[5] Annual Average Daily Dosage = ADD x (annual use in months per year / 12 months)
[6] Restricted entry interval for acute estimates = 14 days for foliar applications. The seasonal estimates assumed that workers would enter the treated field at 14 days plus an additional 6 days, totaling 20 days. The estimated seasonal and annual exposure is 2 months. For reference citations, see DPR (2006).
[7] Restricted entry interval for acute estimates = 48 hours. The seasonal estimates assumed that workers would enter the treated field at 48 hours plus an additional 3 days, totaling 5 days. The estimated seasonal and annual exposure is 2 months.
[8] Restricted entry interval for acute estimates = 48 hours. The seasonal estimates assumed that workers would enter the treated field at 48 hours plus an additional 3 days, totaling 5 days. The estimated seasonal and annual exposure is 3 months.

3. Ambient air exposure

Potential ambient air exposures were defined as occurring in urban areas, and in areas that are far from application sites. Such exposures were not associated with particular carbofuran applications. Rather, they were an indication of the potential exposure of the general public to carbofuran at locations distal to actual application sites and at points in time not correlated with specific applications.

Monitoring of ambient air was carried out in 1995 in Imperial County and in 1996 and 1997 in downtown Sacramento. Annual use levels during those years, 58,200 pounds in Imperial County and 2750 pounds in Sacramento County, may explain the higher air levels measured there than in Sacramento County (Table IV-3). However, it should also be noted that the monitoring in Imperial County was carried out in February and March, the months of peak usage, while the monitoring in Sacramento County was done throughout the year.

Acute absorbed daily dosages were calculated using the 95% percentile concentrations estimated using lognormal methods (DPR, 2006). Default assumptions were made for infant and adult inhalation rates, as well as for the percent of inhaled carbofuran that is absorbed (see footnotes to Table IV-3). Seasonal and annual estimates were based on the number of months of high use in both counties. No such estimates were made for sites in which carbofuran was either not detected (Site H) or detected only once (Sites C and EC).

Table IV-3 summarizes the acute, seasonal and annual absorbed dose estimates for carbofuran in Sacramento and Imperial Counties.

Table IV-3. Carbofuran exposure estimates, ambient air (DPR, 2006)

Site	N [1]	Air conc. [2] Mean ± SD (µg/m^3)	95% conc. [3]	Acute ADD [4] (µg/kg/day)		Seasonal ADD [5] (µg/kg/day)		Annual ADD [6] (µg/kg/day)	
				Infants	Adults	Infants	Adults	Infants	Adults
Imperial county									
Site C [7]	14	0.007±0.003	0.012	0.007	0.003	n/a [9]	n/a	n/a	n/a
Site M	14	0.014±0.008	0.032	0.019	0.010	0.008	0.004	0.001	0.001
Site EC	14	0.007±0.002	0.010	0.006	0.003	n/a	n/a	n/a	n/a
Site H	14	0.006±0.001	0.006	0.004	0.002	n/a	n/a	n/a	n/a
Site PM	12	0.033±0.037	0.118	0.070	0.034	0.020	0.010	0.003	0.002
Sacramento county [10]									
South winds	66	0.0007±0.0011	0.0024	0.0014	0.0007	0.0004	0.0002	0.0001	0.00007
North winds	50	0.0009±0.0020	0.0027	0.0016	0.0008	0.0005	0.0003	0.0002	0.0001

[1] Total number of observations in the data set (including non-detects). For references, see DPR (2006).
[2] Calculated using ½ detection limit (reporting limit) for non-detects.
[3] Value (in µg/m^3) used for the acute exposure estimate. Calculated using lognormal distribution methods.
[4] Acute Absorbed Daily Dosage (µg/kg/day) = (95% upper bound air concentration) x (inhalation rate). Calculation assumptions include (references in DPR [2006]):

- Infant inhalation rate = 0.59 m^3/kg/day
- Adult inhalation rate = 0.28 m^3/kg/day
- Inhalation absorption = 100%

[5] Seasonal Average Daily Dosage = (mean air concentration) x (inhalation rate).
[6] Annual Average Daily Dosage = SADD x (# of high-use months / 12 months per year)
[7] Site C, Callipatria. Site M, Meadows Union School. Site H, Heber. Site EC, El Centro. Site PM, Air Pollution Control District monitoring station.
[8] Single detect used as upper-bound.
[9] n/a, not applicable. Seasonal and annual exposure estimates were not done at sites with no detects (Site H) or one detect (Sites C and EC).
[10] Metropolitan, downtown

4. Application site (bystander) air exposure

Application site (bystander) exposures occur to individuals living, working or performing other activities near a field undergoing a specific pesticide application. Air sampling was done during and directly after the application.

The estimates in the current assessment were drawn from a 1993 Air Resources Board analysis of a carbofuran application in Imperial County. The study located monitoring stations 20 meters to the north, west, east and south of a 70-acre alfalfa field. Carbofuran was applied by groundboom equipment for 1 hour at a rate of 1 lb ai/acre. The values expressed in Table IV-4 reflected the highest 24-hour time weighted averages (TWA), which were detected by the monitors on the west side of the field (though the TWAs were only slightly less on the north and east sides). Not surprisingly, these high values occurred during the first 24 hours.

As was the case for the ambient air estimates, default assumptions were made for the infant and adult inhalation rates, and for the percent of inhaled carbofuran that is absorbed. Finally, according to DPR (2006), seasonal or annual exposures were not estimated because application site air levels are expected to approach ambient levels within a few days of the application (ambient seasonal and annual levels appear in Table IV-3).

Table IV-4. Carbofuran exposure estimates, application site air (bystander exposures) (DPR, 2006)

	1-hr Air concentration ($\mu g/m^3$) [1]	1-hr Inhalation rate ($m^3/kg/hr$) [2]	1-hr Absorbed dose ($\mu g/kg/hr$) [3]	24-hour TWA concentration ($\mu g/m^3$) [4]	24-hr Inhalation rate ($m^3/kg/day$) [5]	24-hr Absorbed dose ($\mu g/kg/day$) [6]
Infants	2.2	0.25	0.550	0.77	0.59	0.454
Adults	2.2	0.045	0.099	0.77	0.28	0.216

Note: The data in this table are based on air monitoring done 20 meters from an Imperial County alfalfa field in 1993 (see Table 10, DPR, 2006).

[1] The highest detected 1-hr carbofuran concentration (0.66 $\mu g/m^3$, detected in the East monitoring station) was multiplied by the ratio of maximum allowed application rate on alfalfa (1 lb AI/acre) over the 0.3 lb AI/acre used in the ARB report (see Table 10 in DPR, 2006). Thus: (1 lb/acre ÷ 0.3 lb/acre) x 0.66 = 2.2 $\mu g/m^3$.

[2] Hourly inhalation rates for heavy activity were 1.9 m^3/hr and 3.2 m^3/hr for infants and adults, respectively. Default median body weights were 7.6 kg/infant and 71.8 kg/adult. Thus: 1.9 m^3/hr ÷ 7.6 kg/infant = 0.25 m^3/kg/hr for infants; 3.2 m^3/hr ÷ 71.8 kg/adult = 0.045 m^3/kg/hr for adults.

[3] The 1-hr absorbed dose assumes a 1-hr exposure during heavy activity and is based on the highest carbofuran concentration measured by ARB (see footnote 1 above). The 1-hr absorbed dose = (1-hr air concentration) x (1-hr inhalation rate)

[4] The 24-hr TWA concentration was from the West air monitoring station, adjusted as in footnote 1.

[5] Daily inhalation rates are default values (see Table 10, DPR, 2006).

[6] The 24-hr absorbed dose assumes a typical mixture of activity levels throughout the day. The 24-hr absorbed dose (µg/kg/day) = (TWA air concentration) x (inhalation rate).

5. Dietary exposure

a. Introduction

Under the California Food Safety Act (AB-2161), the Department of Pesticide Regulation conducts acute and chronic dietary exposure assessments to evaluate the risk of human exposure to a pesticide in food (Bronzan and Jones, 1989). Two separate approaches are used to estimate the risk: (1) risk is determined for the total dietary exposure based on measured residue levels on all commodities with established tolerances, and (2) risk is estimated for exposure to an individual commodity at the tolerance level (see section VI. Tolerance Assessment).

Dietary exposure is the product of the amount of food that is consumed and the concentration of the pesticide residue in that food. The total exposure in an individual's diet during a defined period of time is the sum of exposure from all foods consumed within that period, in various forms and as ingredients in processed food items.

Two distinct pieces of information are required to assess dietary exposure: (1) the amount of the pesticide residue in food, and (2) the food consumption. For estimating the acute exposure either the highest residue values at or below the tolerance or the distribution of residues are considered. In contrast, for chronic exposure the mean residue values are appropriate. Acute exposure is calculated on a per-user basis, *i.e.*, including in the distribution of exposures only the days of survey that at least one commodity with potential pesticide residues is consumed. Chronic exposure to pesticides is generally calculated using per-capita mean consumption estimates.

b. Consumption data and dietary exposure

The Dietary Exposure Evaluation Model (DEEM™, Exponent Inc., http://www.exposnent.com/home.html), version 7.87, was used as the dietary exposure software in this analysis. The food consumption pattern was based on data generated by the United

States Department of Agriculture (USDA) during the 1994-1998 Continuing Survey of Food Intake by Individuals (CSFII). The 1994-1998 dataset includes the 1994-1996 food consumption survey along with the 1998 Supplemental Children's Survey (CSFII 1998). Risk estimates, expressed as margins of exposure (MOEs), were provided for the average US population and 18 selected population subgroups. These subgroups were defined by geographic regions, gender, ethnicity, or age, and included all infants, nursing or non-nursing infants, and children.

For acute exposure estimates, one-day consumption data comprised all of the more than 20 commodities which carry tolerances for carbofuran (Table IV-5). The consumption of each commodity by each member of a population subgroup was multiplied by a single residue value (point estimate) for a deterministic risk assessment. This single value was either the highest residue value measured or, in cases in which no residues were detected, the LOD (limit of detection). In order to refine the acute assessment, the entire range of measured residue levels was used in a distributional (Monte Carlo) analysis. One-half of the LOD value was assigned to those samples in the residue data file for any particular commodity where the measured level was below the LOD. (*Note*: For many tolerances there was insufficient reason to conduct a distributional analysis, either for lack of residue detections or because the critical exposure analysis suggested that consumption was very low. In those cases, the residue value was left at the full LOD for these commodities, even while other commodities were subjected to distributional analysis.)

For chronic exposure estimates, the average food consumption of each population subgroup was multiplied by the mean residue value. The dosage estimates for both acute and chronic exposure were expressed in µg/kg/day.

c. Exposure to carbofuran in food

Residue levels of carbofuran and its major toxicologically significant degradate, 3-OH-carbofuran, were determined in all food items with carbofuran tolerances, as indicated above. The published tolerances are listed in CFR 40 180.254. They are expressed for plant commodities as combined residues of carbofuran and its carbamate degradates. For all tiers of the analysis, the measured residue or LOD-based levels for the two compounds were added to generate a final single residue value. This was, in turn, used in the DEEM analysis. In the distributional phase, one half of the combined LODs were used for all non-detected samples, as noted in the previous section. However, in listing the residue values for the detects in the residue data file (RDF), the detected value (either carbofuran or 3-OH-carbofuran) was added to the full LOD for the other compound. For example, 2002 and 2003 California-only PDP data on cucumbers generated a highest residue value of 0.53 ppm for carbofuran, while there were no detects for 3-OH-carbofuran. The residue value used for cucumbers was thus 0.53 + 0.021 (*i.e.*, the highest LOD for 3-OH-carbofuran), or 0.55 ppm. The 2002 and 2003 California-only data on sweet bell peppers was the only commodity for which there were residue detects for *both* carbofuran (13 out of 911 total samples) and 3-OH-carbofuran (8 out of 927 total samples). Nonetheless, the final residue value was also set equal to the sum of the detected value, whether it was carbofuran or 3-OH-carbofuran, and the full LOD for the other compound.

The 3-keto-carbofuran degradate, as well as the major carbofuran phenolic degradates (3-keto-7-phenol, 3-OH-7-phenol, and 7-phenol), were not included in the analysis. This was due both to the dearth of toxicity data and to a lack of food tolerances for these compounds, though limited data indicated that 3-keto-carbofuran and the carbofuran phenols were less acutely toxic than either the parent compound or its 3-OH degradate (see section III.J). In addition, sufficient residue data were not available for these compounds.

In view of the USEPA's recently proposed revocation of carbofuran tolerances in meat, milk and eggs (USEPA, 2003), these commodities were not included in the DEEM analysis.

d. Residue data sources

The carbofuran and 3-OH-carbofuran residue data used in this assessment were derived from the USDA Pesticide Data Program (PDP) and from field trial residue studies submitted by carbofuran registrants to support tolerances. In addition, residue levels for cranberry-related food groups (cranberries, cranberry juice and cranberry juice concentrate) were obtained from the USEPA dietary assessment on carbofuran (USEPA, 2000), though it originated in FDA databases. Carbofuran was also included in the DPR-based marketbasket screening program. The available data were not used in this assessment for the reasons detailed below.

The USDA Pesticide Data Program (www.ams.usda.gov/science/pdp/download.htm). The PDP was designed to generate pesticide residue data for risk assessments. Established in 1991, these data are collected on an annual basis from ten states, including California, at produce markets and chain store distribution centers close to the consumer level. About 50 commodities and 290 pesticides have been examined over the 14-year period of PDP's existence. The current assessment includes carbofuran and 3-OH-carbofuran residue data collected between 1995 and 2003.

As noted, PDP provided residue levels both for carbofuran and for its most toxicologically significant degradate, 3-OH-carbofuran. PDP data were available for 17 of the commodities with tolerances. Residue data generated by PDP-sponsored laboratories in California were used in preference to data generated by laboratories outside of the state. This was done because the California laboratories were more likely to sample commodities bound for sale within the state. "Ca-only" PDP data were available for cantaloupe, cucumbers, grapes, grape juice, sweet bell peppers, sweet corn and winter squash.

Carbofuran residues were detected under PDP for cucumbers (CA-only data, 2002 and 2003; two of the cucumber detections exceeded the legal tolerance; for details on how this was handled in the Tier 2 and Tier 4 assessments, see footnote 6, Table IV-5), sweet bell peppers (2002 and 2003) and wheat (1997). 3-OH-carbofuran residues were detected under PDP for sweet bell peppers (CA-only data, 2002 and 2003) and for sweet corn (CA-only data, 2003). PDP also registered carbofuran detections in water (2002 and 2003), though 3-OH-carbofuran was not detected. PDP did not detect either compound in bananas (1995, 2001, 2002), barley (2002, 2003), cantaloupe (CA-only data, 1998, 1999, 2000), corn grain-sugar-high fructose corn syrup (1998, 1999), grapes (CA-only data, 2000), grape juice (CA-only data, 1998, 1999), oats (1999), potatoes (2000, 2001, 2002), rice (2000, 2001), soybeans (1997, 1998), strawberries (1998, 1999, 2000), and winter squash (CA-only data, 1997, 1999). LODs for the PDP measurements ranged between 0.003 and 0.076 ppm.

PDP did not monitor for summer squash and watermelon. However, residue values were derived from the surrogate commodities winter squash and cantaloupe, respectively. These are considered related commodities; as such, they are co-classified in crop groups 9-A and 9-B for the purpose of tolerance establishment (40 CFR 180.41)

DPR Marketbasket Surveillance Program. Carbofuran and 3-OH-carbofuran screening data from wholesale, retail, and chain store distribution centers, as well as points of entry (seaports, airports and state borders) and points of origin (field and packing house samples), were available annually from the DPR Marketbasket Surveillance Program. This program is mainly an enforcement tool, as it focuses on commodities with known violations of tolerance.

The marketbasket program tested 72-119 commodities (2480-7901 total samples) over the 2000-2003 period. Out of all these samples, there was only one residue detection for carbofuran in strawberries in 2001 (707 strawberry samples processed over the 4-year period) and three detections in peppers in 2002 and 2003 (2386 samples over the 4-year period). No other detections were made at any other time for these or any other commodities. Detection limits of

0.02 - 0.05 ppm were provided only for those four samples evidencing residue detections. Consequently, little can be said about the detection limits for the remaining data. Because of the very low detection rate and because the preferred PDP data were available for both commodities, the DPR survey data were not used further in this analysis.

Field trial data. Field trial studies are submitted by the pesticide registrants for support in the setting of tolerances. Because (1) these studies are usually conducted under the maximum application rates for the proposed label and (2) all sampling is done on treated commodities, field trial data are not preferable to PDP or DPR Marketbasket data in the generation of dietary exposure analyses. Thus field trial data were used in this assessment only in cases where PDP or DPR data were not available. These amounted to 9 of the 25 commodities with carbofuran tolerances analyzed: artichokes, coffee, cottonseed, sorghum, sugarbeets, sugarcane, sunflower oil and seeds, and cranberries (as noted, the cranberry data came through an FDA field trial reported in the USEPA dietary assessment [USEPA, 2000]). Field trial data inject an inherently health-conservative note into the risk evaluation. LODs for the field trial data used in this report ranged between 0.01 and 0.025 ppm.

e. Acute exposure

DPR uses a tiered approach to estimate acute dietary exposure to pesticides (DPR, 2002c). For tiers 1-3, point estimates are established for each food group. Such a “deterministic” approach employs the tolerance (Tier 1), the upper bound value (Tier 2) or the mean residue value (Tier 3) to estimate residues for individual food groups. Tier 4 comprises the distributional (Monte Carlo) approach. Monte Carlo is used to refine the assessment by taking into account the distribution of the residue values for a particular commodity, rather than relying on a single point estimate. As is clearly evident for carbofuran, Monte Carlo modeling was necessary to generate a more realistic picture of the acute dietary exposure and potential risk.

Deterministic (point estimate) and Monte Carlo acute dietary exposure assessments. Application of the tier system for acute residue estimation is described in the following paragraphs.

(1) Tier 1. Setting food group residues to tolerance levels resulted in exposure estimates which were higher than the level considered as health protective for all examined subpopulations. Refinement of the exposure estimates in a Tier 2 analysis was therefore necessary.

(2) Tier 2. Tier 2 residue estimates utilize the highest of the measured residue values. In practice, this leads to the following assumptions: (a) all consumed foods contain the highest reported residue below the tolerance, (b) pesticide residues below the LOD are equal to the LOD, (c) all crops with tolerances are treated with the pesticide, and (d) residue concentrations do not vary from the time of sampling to the time of consumption.

Tables IV-5 and IV-6 provide the residue values used in Tier 2 for carbofuran and 3-OH-carbofuran, respectively. As noted above, PDP data were used for 17 of the commodities bearing tolerances, with field trial data (including those from USEPA / FDA) used for the remaining commodities. In all cases, either the highest LOD or the highest measured residue value was used as the final point estimate. An exception was made in the case of strawberries, where the high end of the LOD range over several years was either 0.031 ppm or 0.017 ppm. The latter value was chosen to represent strawberry residues, both because it originated in later assays and because no residues were detected even at the lower LOD value.

Changes in food hydration state can also alter residue concentrations in comparison to the raw monitored commodities. The following default factors provided in the DEEM Acute Module, were utilized to account for concentration or dilution of carbofuran due to hydration changes: 3.9 (dried bananas), 3.3 (cranberry juice concentrate), 4.3 (raisins), 6.5 (dried potatoes) and 0.33

(soybean sprouts).

Based on the paradigms used in this dietary assessment, the 97.5th percentile of user-day exposures to carbofuran + 3-OH-carbofuran ranged from 0.447 µg/kg/day ("females 13+ pregnant/not lactating") to 1.624 µg/kg/day ("children 1-2 yr"). Other population groups receiving exposures similar to the "children 1-2 yr" group included "children 3-5 yr", "all infants" and "non-nursing infants <1 yr. DEEM-generated per-user day exposure values at the 97.5, 99 and 99.9th percentiles are shown in Table IV-7.

The acute Critical Exposure Commodity (CEC) analysis identified several commodities, including bananas, corn grain / high fructose corn syrup, wheat flour, grapes-juice and cucumbers as making substantial contributions to the acute dietary exposure. With the exception of the cucumber and wheat grain data (for which 6 carbofuran residue positives were noted in the 1997 PDP record), these commodities were high contributors by virtue of their consumption patterns and LOD values alone, since there were no residues detected above the LOD.

(3) Tier 3. Tier 3 was designed to utilize the mean, as opposed to the high, residue level for each food group. However, tier 3 analysis was considered impractical in the present case because very few actual residues were measured for carbofuran or 3-OH-carbofuran. This made calculation of mean values virtually meaningless, as most of the food group point estimates were dependent on the LOD values - a situation that was, for the most part, fulfilled by the Tier 2 analysis.

(4) Tier 4. Due to the very low MOEs generated in the Tier 2 analysis (see section IV.C.5.a. below), a distributional analysis was initiated as the next refining step of the acute dietary exposure assessment. Also known as Monte Carlo analysis, the distributional approach combines the distribution of pesticide residues available from the data sources with the distribution of commodity consumption generated from the CSFII 1994-1998 survey to produce the distribution of potential exposures for the selected subpopulations. The Monte Carlo-derived exposure estimates were further refined by incorporating information on the percentage of the crop that was treated (PCT) with carbofuran. This represented an effort to reflect the actual use pattern for that crop. PCT data were derived primarily from the Agricultural Chemical Use Summaries (USDA, 2000-2004) and from the Biological and Economical Analysis Division (BEAD) reports (BEAD data for this report were extracted from the USEPA dietary assessment of carbofuran [USEPA, 2000]). PCT was applied to the following commodities that had detectable residues in the PDP database: cucumbers, sweet bell peppers, and sweet corn. PCT was also applied to the following commodities that had no detectable residues, but were included in the distributional analysis because they ranked high in the CEC (consumption) analysis: bananas, potatoes and watermelon. Several of the commodities (wheat, corn grain / high fructose corn syrup and grape juice) were considered to be "blended", *i.e.*, they contained contributions from many different harvests. PCT was not applied to these commodities (in other words, PCT was set at 100%) because it was assumed that there were potential residues in all samples. PCT adjustments were also not made for commodities which were assigned a single residue value (point estimate) in the context of the Monte Carlo analysis, as a point estimation precluded a distributional analysis.

The number of samples containing carbofuran / 3-OH-carbofuran residues or set at the LOD was based on the number of samples analyzed and the PCT. In the current analysis, the number of samples with measured residues never exceeded the theoretical maximum predicted by the PCT. Consequently, all samples containing residues were assigned their corresponding values, with the additional samples either set to the LOD or zero as determined by the PCT value.

Food processing factors, including the degree of pesticide degradation that occurs upon food washing and cooking, are also useful as a further refinement. However, experimental data to derive such factors were not available for the current analysis.

Monte Carlo analysis showed 97.5th percentile user day exposures ranging between 0.164 µg/kg/day ("Adults 50+") and 0.616 µg/kg/day ("non-nursing infants <1 yr"), with young children registering the higher end exposures (Table IV-7). For the 99th percentile, exposures ranged between 0.212 µg/kg/day ("Adults 50+") and 0.771 µg/kg/day ("children 1-2 yr"), while for the 99.9th percentile, exposures ranged between 0.281 µg/kg/day ("females 13+ lactating") and 1.778 µg/kg/day ("children 1-2 yr"). These values were approximately 2-3-fold lower at the 97.5-99.9th percentiles than the corresponding point estimate (Tier 2) values.

CEC analysis showed corn grain-sugar-high fructose corn syrup, sugar-beet-refined, grapes-juice, cantaloupe, sugar-cane, rice, winter squash, corn grain-sugar-hfcs, strawberries, soybeans and barley-alcohol to be major contributors for most of the subpopulations, with the precise amounts varying with the subpopulation. Except for beet sugar, for which the data from a sugarbeet field trial yielded three residue detects for carbofuran, all of the high contributor contributions were based on LOD determinations. As such, these contributions were considered to be consumption- and LOD-driven.

f. Chronic exposure

For estimates of chronic exposure, the average value of all pesticide residues detected on a commodity was multiplied by the average annual consumption determined for each subpopulation. The population average daily consumption distribution reflected the longitudinal consumption patterns of individuals. Residue levels below the LOD were set at 1/2 of that limit. PCT adjustments were not made, as the high MOEs obtained without such adjustments rendered them unnecessary (see section IV.C.5.b.).

Chronic residues for carbofuran and 3-OH-carbofuran are shown in Tables IV-5 and IV-6. The chronic exposure estimates appear in Table IV-7 for the various subpopulations. "Children 1-2 yr" exhibited the highest exposures (0.234 µg/kg/day), followed closely by "non-nursing infants <1 yr" (0.199 µg/kg/day) and "children 3-5 yr" (0.196 µg/kg/day). Lowest chronic exposures were predicted for "adults 50+ yr" (0.062 µg/kg/day), "females 13-49 yr" (0.064 µg/kg/day) and "adults 20-49 yr" (0.067 µg/kg/day).

Table IV-5. Anticipated **Carbofuran** Residues for Acute and Chronic Dietary Exposure Assessment

Commodity	Source of data	Year	# samples	# detected samples	Detected residues (ppm)	LOD range (ppm)	% crop treated (max. value) [1]	Adj. factor	Acute residue (ppm)		Chronic avg. residue (ppm)
									Point estimate [2]	Monte Carlo	
Artichokes	Field trials McCalley (1983)	1982	8 replicates per study	study #1: 0	n/a	0.05	29%	1	LOD	0.19	0.0575
				study #2: 3	0.05, 0.07, 0.09	0.05			0.09 (**0.19**)		
Bananas	PDP data	1995	486	0	n/a	0.006-0.031	7%	1 (RAC & banana juice) 3.9 (dried bananas)	0.031	RDF8	0.026
	PDP data	2001	702	0	n/a	0.013-0.031			0.031		
	PDP data	2002	727	0	n/a	0.013-0.031			0.031 (**0.052**)		
Barley	PDP data	2002	752	0	n/a	0.012	1%		0.012	0.025	0.0125
	PDP data	2003	452	0	n/a	0.012			0.012 **(0.025)**		
Canola	Field trial (ref. in USEPA (2000)	not given	8	2	0.077, 0.067 (combined w/3-OH-CF) [5]	0.06 (combined w/3-OH-CF) [5]	0.28%		**0.063** [5]	0.063	0.0405
Cantaloupe	Ca-only PDP data	1998	110	0	n/a	0.013	6%	1	0.013	0.026	0.013
	Ca-only PDP data	1999	237	0	n/a	0.013			0.013		
	Ca-only PDP data	2000	220	0	n/a	0.013			0.013 (**0.026**)		
	PDP data	2003	186	0	n/g	0.002-0.013			0.013		
Coffee	Field trial FMC (1996)	1994-6 (Brazil)	3 (roast beans)	0	n/a	0.01	1.5%	1	0.010	0.020	0.010
			3 (instant coffee)	0	n/a	0.01			0.010 (**0.020**)		

Corn grain (including popcorn)	Used sweet corn data						3%				
Corn grain (sugar / hfcs)	PDP data	1998	298	0	n/a	0.001-0.009	blended	1.5	0.009	RDF5	0.009
	PDP data	1999	156	0	n/a	0.009		1.5	0.009 (**0.018**)		
Cottonseed	Field trial FMC (1973)	1973	8 (mature seeds)	0	n/a	0.025	5%	1	0.025 (**0.075**)	0.075	0.0375
Cranberries	FDA field trial (EPA, 2000)	1995-8	35	0	n/a	0.01	0.5% (=1%)	1 (fruit & juice) 3.3 (conc.)	0.01 (**0.020**)	0.020	0.010
Cucumbers	Ca-only PDP data	2002	183	4	0.022-0.14	0.013-0.018	7%	1	0.14	RDF1	0.0223
	Ca-only PDP data	2003	739	3	0.022-0.53	0.013-0.021		1	0.53 (**0.2**)[6]		
Grapes	Ca-only PDP data	2000	142	0	n/a	0.013	1%	1 (table) 4.3 (raisins)	0.013 (**0.026**)	RDF6	0.013
Grape juice	Ca-only PDP data	1998	151	0	n/a	0.013	blended	1	0.013	RDF7	0.013
	Ca-only PDP data	1999	197	0	n/a	0.013			0.013 (**0.026**)		
Oats, grain	PDP data	1999	332	0	n/a	0.005	1%	1	0.005 (**0.010**)	0.010	0.005
Potatoes	PDP data	2000	369	0	n/a	0.008-0.013	13%	1 (whole) 6.5 (dry)	0.013	RDF9	0.013
	PDP data	2001	733	0	n/a	0.008-0.013			0.013		
	PDP data	2002	370	0	n/a	0.008-0.013			0.013 (**0.026**)		
Rice, grain	PDP data	2000	178	0	n/a	0.012	15%	1	0.012	0.025	0.0125
	PDP data	2001	689	0	n/a	0.012			0.012		
	PDP data	2002	495	0	n/a	0.012			0.012 (**0.025**)		

Sorghum	Field trial (EPA, 2000)	no year given	10 samples?	0	n/a	0.01	4%	1	0.01 (**0.020**)	0.020	0.010
Soybeans	PDP data	1997	159	0	n/a	0.006	1%	1 (flour) 0.33 (sprouts)	0.006 (**0.013**)	0.013	0.0065
	PDP data	1998	590	0	n/a	0.005-0.006			0.006		
Strawberries (fresh)	PDP data	1998	610	0	n/a	0.010-0.031	1%	1	0.031	0.037	0.0185
(fresh)	PDP data	1999	640	0	n/a	0.010-0.031			0.031		
(fresh)	PDP data	2000	518	0	n/a	0.013-0.017			0.017		
(frozen)	PDP data	1998	47	0	n/a	0.010-0.017			0.017		
(frozen)	PDP data	1999	71	0	n/a	0.013-0.031			0.031		
(frozen)	PDP data	2000	37	0	n/a	0.013-0.017			0.017[3] (**0.037**)		
Sugarbeets	Field trial #1 FMC (1986)	1986	12	2	0.01 & 0.03 (10 non-detects)	0.01	1%	1	0.030 (**0.040**)	RDF5	0.0202
	Field trial #2 FMC (1992a)	1992	12	1	0.01 (11 non-detects)	0.01			0.010		
Sugarcane	Field trial FMC (1992b)	1990-2	4 samples per process level	0-sugar	n/a	0.01		1	0.01 (**0.020**)	0.020	0.010
				0-molasses	n/a	0.01			0.01		
Summer squash	Used winter squash data						6%				0.013
Sunflower oil	Field trial FMC (1981c)	1981	2	2	0.01, 0.01 (2 detects)	0.01		1	0.010 (**0.020**)	0.020	0.015

Sunflower seeds	Field trial FMC (1981d)	1981	oilseeds, 26 samples	26 (all detects)	oilseeds, Total CF: .03, .05, .05, .04, .05, .06, .03, .03, .22, .26, .04, .04, .07, .10, .03, .03, .08, .13, .10, .16, .04, .03, .03, .02, .02, .03	0.01	5%	1	0.26 (**0.33**)	0.33	0.0847
			confectionary seeds, 8 samples	8 (all detects)	confect. seeds, Total CF: 07, .05, .04, .05, .03, .05, .06, .09, no non-detects				0.09		
Sweet bell pep.	Ca-only PDP data	2002	186	3	0.003-0.015	0.002	4%	1	0.015	RDF2	0.033
	Ca-only PDP data	2003	741	10	0.003-0.088	0.000-0.004			0.008 **(0.143)**		
Sweet corn	Ca-only PDP data	2002	727	0	n/a	0.008-0.013	4%	1	0.013 (**0.052**)	RDF4	0.013
	Ca-only PDP data	2003	547	0	n/a	0.008-0.013			0.013		
Water (drinking)	PDP data	2001	296	0	n/a	20-22.5 ppt	n/a	1	0.000022 **(0.000197)**	0.000197[4]	0.000127
	PDP data	2002	550	6	1.0-79 ppt	0.6-22.5 ppt	n/a		0.000022		
	PDP data	2003	583	8	5.0-20 ppt	0.6-16 ppt	n/a		0.000016		
Watermelon	Used cantaloupe data						7%			RDF10	0.013
Wheat grain	PDP data	1995	600	0	n/a	0.005	blended	1	0.005	RDF3	0.005
	PDP data	1996	340	0	n/a	0.005			0.005		
	PDP data	1997	623	6	0.008-0.022	0.005			0.022 (**0.028**)		
	PDP data	2003	5664	0	n/a	0.023			0.023		

W squash (fresh)	Ca-only PDP data	1997	156	0	n/a	0.013	6% 49% (pumpkin)	1	0.013 (**0.026**)		0.013
(fresh)	Ca-only PDP data	1999	83	0	n/a	0.013			0.013		
(frozen)	Ca-only PDP data	1997	2	0	n/a	0.013			0.013		
(frozen)	Ca-only PDP data	1999	5	0	n/a	0.013			0.013		

[1] Percent crop treated data were derived from several sources as indicated here. Commodities subjected to distributional analysis, indicated by their RDF designation, are listed first: cucumbers (RDF1) - Agricultural Chemical Usage Report (USDA, 2000, 2002, 2004); sweet bell peppers (RDF2) - maximum USDA BEAD (Biological and Economical Analysis Division) estimates derived from the USEPA dietary assessment on carbofuran (USEPA, 2000); wheat (RDF3) - considered a "blended" commodity and thus assigned a PCT of 100%; sweet corn (RDF4) - Agricultural Chemical Usage Report (USDA, 2000, 2002, 2004); corn grain/sugar/high fructose corn syrup (RDF5) - considered a "blended" commodity and thus assigned a PCT of 100%; grapes (RDF6) - Agricultural Chemical Usage Report (USDA, 1999, 2001, 2003); grapes/juice (RDF7) - considered a "blended" commodity and thus assigned a PCT of 100%; bananas (RDF8) - maximum USDA BEAD (Biological and Economical Analysis Division) estimates derived from the USEPA dietary assessment on carbofuran (USEPA, 2000); potatoes (RDF9) - Agricultural Chemical Usage Report (USDA, 2000, 2002, 2004); watermelon (RDF10) - maximum USDA BEAD (Biological and Economical Analysis Division) estimates derived from the USEPA dietary assessment on carbofuran (USEPA, 2000). PCT values are listed for the remaining commodities, though they were not used in either the acute or chronic analyses: artichokes - California Dept. of Food and Agriculture's Resource Directory 2002; barley, canola, cantaloupe, coffee, cottonseed, cranberries, oats, rice sorghum, soybeans, strawberries, sugarbeets, sugarcane, summer and winter squash, sunflower seeds - maximum USDA BEAD (Biological and Economical Analysis Division) estimates derived from the USEPA dietary assessment on carbofuran (USEPA, 2000).

[2] Parenthetic numbers in bold print represent the sum of the highest residue and/or LOD values for carbofuran and 3-OH-carbofuran. It is this value that was used for the point estimate.

[3] Despite the fact that this value was not the highest measured for strawberries, it was chosen to represent the point estimate because it was the most recent.

[4] The point estimates for water in 2001 and 2002 included 3-ketocarbofuran in addition to carbofuran and 3-OH-carbofuran. In each of those years, the LOD for 3-ketocarbofuran was 20 ppt, which was added to the final point estimate.

[5] The point estimate for canola was based on field trial results reported in USEPA (2000). In that reference, residues were expressed as the combined values for carbofuran + 3-OH carbofuran, with the combined LOD expressed as "<0.06 ppm". Because the only anticipated consumption of canola is through the processed oil, a blended commodity, the acute residue was calculated as the mean of the 8 samples measured, with the non-detects set at the LOD. Thus the acute point estimate was (0.06 + 0.06 + 0.06 + 0.06 + 0.06 + 0.06 + 0.077 + 0.067) ÷ 8 = 0.063 ppm.

[6] PDP residue data for cucumbers showed two carbofuran detect values (0.53 and 0.43 ppm) that exceeded the carbamate-only tolerance of 0.2 ppm. However, according to DPR policy, it was considered inappropriate to use an over-tolerance value in the Tier 2 point estimate process, as such residues were illegal. Consequently, the over-tolerance value was substituted by the tolerance value of 0.2 ppm. However, for the Tier 4 distributional analysis, *all* of the residue detect values were used to generate the distribution (see RDF1 file in Appendix III.2).

Table IV-6. Anticipated **3-OH-Carbofuran** Residues for Acute and Chronic Dietary Exposure Assessment

Commodity	Source of data	Year	# samples	# detected samples	Detected residues (ppm)	LOD range (ppm, except where indicated)	% crop treated [1]	Adj. factor [1]	Acute residue (ppm)		Chronic avg. residue (ppm) [1]
									Point estimate [2]	Monte Carlo [1]	
Artichokes	Field trials McCalley (1983)	1982	8 replicates per study	study #1: 0 (no detects)	study #1, 0 (no detects)	0.05			LOD		
				study #2: 3 detects	study #2, 3 detects: 0.05, 0.05, 0.10	0.05			0.10		
Bananas	PDP data	1995	486	0	n/a	0.009-0.031			0.021[3]		
	PDP data	2001	702	0	n/a	0.013-0.017					
	PDP data	2002	727	0	n/a	0.013-0.021					
Barley	PDP data	2002	662	0	n/a	0.013			0.013		
	PDP data	2003	392	0	n/a	0.013			0.013		
Barley	Used wheat data										
Canola	Field trial (ref. in USEPA (2000)	see carbofuran residue table (Table IV-5), including footnote #5 on that table									
Cantaloupe	Ca-only PDP data	1998	110	0	n/a	0.013			0.013		
	Ca-only PDP data	1999	237	0	n/a	0.013					
	Ca-only PDP data	2000	120	0	n/a	0.013					
	PDP data	2003	186	0	n/g	0.004-0.013					
Coffee (roast beans & coffee)	Field trial FMC (1996)	1994-6 (Brazil)	3 (roast beans)	0	n/a	0.01			0.010		
			3 (instant coffee)	0	n/a	0.01					

Corn, grain (including popcorn)	Used sweet corn data										
Corn grain (sugar / hfcs)	PDP data	1998	298	0	n/a	0.001-0.009		1.5	0.009		0.009
	PDP data	1999	156	0	n/a	0.009		1.5			
Cottonseeds	Field trial FMC (1973)	1973	8 (mature seeds)	0	n/a	0.05			0.05		
Cranberries	(EPA, 2000)	1995-8	35	0	n/a	0.01			0.01		
Cucumbers	Ca-only PDP data	2002	183	0	n/a	0.013-0.021			0.021		
	Ca-only PDP data	2003	739	0	n/a	0.013-0.021					
Grapes	Ca-only PDP data	2000	142	0	n/a	0.013			0.013		
Grape juice	Ca-only PDP data	1998	151	0	n/a	0.013			0.013		
	Ca-only PDP data	1999	198	0	n/a	0.013					
Oats, grain	PDP data	1999	323	0	n/a	0.005			0.005		
Potatoes	PDP data	2000	369	0	n/a	0.012-0.013			0.013		
	PDP data	2001	733	0	n/a	0.012-0.013					
	PDP data	2002	370	0	n/a	0.012-0.013					
Rice, grain	PDP data	2000	178	0	n/a	0.013			0.013		
	PDP data	2001	689	0	n/a	0.013			0.013		
	PDP data	2002	495	0	n/a	0.013			0.013		
Sorghum	(EPA, 2000)	no year given	10 samples?	0	n/a	0.01			0.01		
Soybeans	PDP data	1997	159	0	n/a	0.007			0.007		
	PDP data	1998	590	0	n/a	0.005-0.007					

Strawberries (fresh) (fresh) (fresh)	PDP data PDP data PDP data	1998 1999 2000	610 640 518	0 0 0	n/a n/a n/a	0.010-0.020 0.010-0.020 0.013-0.020			0.020		
(frozen) (frozen) (frozen)	PDP data PDP data PDP data	1998 1999 2000	47 71 37	0 0 0	n/a n/a n/a	0.010-0.020 0.013-0.020 0.013-0.020					
Sugarbeets	Field trial #1 FMC (1986) Field trial #2 FMC (1992a)	1985 (Calif.) 1992	12 12	0 0	n/a n/a	0.01 0.01			0.01		
Sugarcane	FMC (1992b)	1990-2 (LA)	4 samples per process level	0-sugar 0-molasses	n/a n/a	0.01 0.01			0.01		
Summer squash	Used winter squash data										
Sunflower oil	Field trial FMC (1981c)	1981	2	0	n/a	0.01			0.01		
Sunflower seeds	Field trial FMC (1981d)	1981	oil seeds, 26 samples confection ary seeds, 8 samples	24 8 (all detects)	oilseeds, Total 3-OH-CF: nd, .01, .02, .01, .01, .01, .01, .01, .06, .07, .01, .01, .04, .04, .03, .03, .02, .03, .01, .03, .01, .01, .02, .02, .01, nd confect. seeds, Total 3-OH-CF: .01, .01, .01, .01, .02, .03, .02, .02, no non-detects	0.01			0.07		
Sweet bell pep.	Ca-only PDP data Ca-only PDP data	2002 2003	186 741	2 6	0.009-0.010 0.003-0.055	0.002 0.001-0.002			 0.055		

Sweet corn	Ca-only PDP data	2002	727	2	0.020-0.039	0.012-0.013			0.039		
	Ca-only PDP data	2003	547	0	n/a	0.012-0.013					
Water (drinking)	PDP data	2001	296	0	n/a	20-97.5 ppt	n/a	1	0.0000975		
	PDP data	2002	550	0	n/a	6.0-97.5 ppt	n/a		0.0000975		
	PDP data	2003	572	0	n/a	6.0-68 ppt	n/a		0.000068		
Watermelon	Used cantaloupe data										
Wheat grain	PDP data	1995	600	0	n/a	0.005			0.006		
	PDP data	1996	340	0	n/a	0.005					
	PDP data	1997	623	0	n/a	0.005					
	PDP data	2003	594	0		0.006					
W squash (fresh)	Ca-only PDP data	1997	156	0	n/a	0.013			0.013		
(fresh)	Ca-only PDP data	1999	83	0	n/a	0.013					
(frozen)	Ca-only PDP data	1997	2	0	n/a	0.013					
(frozen)	Ca-only PDP data	1999	5	0	n/a	0.013					

[1] See Table IV-5.

[2] The point estimate values in this column were added to the point estimates for carbofuran (Table IV-5) to produce the total point estimate used in the estimation of residues for all food groups. The total point estimates are found in Table IV-5.

[3] For bananas, the highest of the 2002 and 2003 LODs was used to calculate the acute point estimate and chronic estimates.

Table IV-7. Dietary exposure to carbofuran + 3-OH-carbofuran: Acute (point estimate and Monte Carlo) and chronic estimates

Population subgroup	Acute (point estimate) exposure [1], µg/kg/day			Acute (Monte Carlo) exposure [1], µg/kg/day			Chronic exposure [2], µg/kg/day
	97.5th percentile [3]	99th percentile	99.9th percentile	97.5th percentile [3]	99th percentile	99.9th percentile	
1. US population	0.804	1.073	2.062	0.282	0.389	0.796	0.085
2. Western region	0.859	1.198	2.382	0.303	0.419	0.881	0.092
3. Hispanics	0.879	1.157	1.787	0.311	0.460	0.744	0.095
4. Non-hispanic whites	0.780	1.032	1.915	0.273	0.381	0.881	0.084
5. Non-hispanic blacks	0.801	1.060	1.794	0.282	0.372	0.692	0.079
6. Non-hispanic / non-white / non-black	1.080	1.679	2.553	0.323	0.421	0.817	0.101
7. All infants	1.236	1.519	2.315	0.603	0.717	1.156	0.166
8. Nursing infants <1 yr	1.147	1.486	2.168	0.483	0.669	0.978	0.081
9. Non-nursing infants <1 yr	1.247	1.536	2.355	0.616	0.739	1.160	0.199
10. Females 13+ (preg./not lact.) [4]	0.447	0.610	0.615	0.210	0.263	0.281	0.070
11. Females 13+ (lactating) [4]	0.597	0.955	1.033	0.301	0.905	0.916	0.083
12. Children 1-2 yr	1.624	2.115	3.558	0.565	0.771	1.778	0.234
13. Children 3-5 yr	1.371	1.842	3.346	0.473	0.608	1.009	0.196
14. Children 6-12 yr	0.944	1.222	2.556	0.329	0.417	1.066	0.124
15. Youth 13-19 yr	0.605	0.882	1.899	0.230	0.295	1.062	0.077
16. Adults 20-49 yr	0.536	0.683	1.210	0.199	0.265	0.563	0.067
17. Adults 50+ yr	0.488	0.643	1.171	0.164	0.212	0.416	0.062
18. Females 13-49 yr	0.508	0.641	1.252	0.195	0.262	0.546	0.064
19. Males/Females 16-70 yr	0.532	0.681	1.281	0.196	0.259	0.537	not calculated

[1] The DEEM program was used with the following input parameters: (a) food consumption data came from the USDA CSFII, 1994-1998, (b) Monte Carlo analysis used 500 iterations, a seed number of 10, and incorporated PCT analysis on non-blended distributional commodities (PCT was set to 100% for blended commodities).

[2] The chronic exposure estimates do not include PCT adjustments (see text).

[3] Estimated percentile of user-days falling below the calculated exposure.

[4] The total number of user days for "Females 13+ (preg./not lactating)" and "Females 13+ (lactating)" were 139 and 80, respectively. These sample sizes were very small compared to the other subpopulations, for which the total user days ranged between 586 ("Nursing infants <1 yr") and 40,224 ("US population"). The representativeness of the two former populations was therefore subject to uncertainty.

C. RISK CHARACTERIZATION

1. Overview

The potential for non-oncogenic health effects resulting from carbofuran exposure was expressed as the margin of exposure (MOE). The MOE is the ratio of the critical NOEL or LED value, as derived from the definitive acute, subchronic or chronic studies, over the estimated exposure.

$$\text{Margin of Exposure (MOE)} = \frac{\text{NOEL or LED (mg/kg)}}{\text{Exposure dose (mg/kg)}}$$

In general, MOEs of 10 or more are considered protective of human health if the relevant adverse effects were observed in human experimental toxicity studies. This reflects the default assumption that a 10-fold range of sensitivity exists within the human population. MOEs of 100 are considered to be protective of human health if the relevant adverse effects were observed in experimental animal studies. This reflects the default assumptions that (1) humans are 10-fold more sensitive than animals and (2) that a 10-fold range of sensitivity exists within the human population. All of the critical endpoints used in this report were derived from animal studies.

As noted in the accompanying exposure assessment document (DPR, 2006; attached as Appendix I to this report) and summarized above in section IV.B., the exposure estimates for carbofuran were derived from four sources: (1) surrogate data in the pesticide handlers database (PHED), which predicts both dermal and inhalation exposure to handlers, (2) plausible reentry scenarios involving dermal exposure to fieldworkers through contact with dislodgeable foliar residues, (3) air monitoring studies designed to estimate ambient and bystander exposures by the inhalation route, and (4) residue studies on food items. The following sections provide the MOE values generated by these exposure scenarios.

2. Occupational exposure

a. Handlers

MOEs for handlers appear in Table IV-8. As handler exposure was predicted by both the dermal and inhalation routes, handler risk was evaluated by both of these routes. The acute MOE calculations utilized the critical oral LED_{05} value of 0.01 mg/kg established in section IV.A.1 as appropriate to both exposure routes. Seasonal and annual MOEs utilized the critical subchronic NOEL of 0.1 mg/kg/day.

Handler dermal MOEs were consistently below one for all of the acute scenarios except low pressure handwand mixer / loader / applicators and dip-slurry mixer / loaders (MOE = 5 in both cases). Seasonal dermal exposure scenarios evidenced MOEs between <1 and 2, again with the exception of low pressure handwand use (MOE = 167) (dip-slurry uses were not predicted for seasonal and annual scenarios). Inhalation MOEs ranged between <1 and 333 for acute scenarios and between 6 and 5000 for seasonal scenarios.

Table IV-8. Margins of exposure (MOEs) for handlers calculated using the rabbit dermal NOELs to estimate dermal risk and the appropriate oral NOELs to estimate inhalation risk

	Acute MOE		Seasonal MOE		Annual MOE	
Work task	**Dermal [1]**	**Inhalation [2]**	**Dermal [3]**	**Inhalation [4]**	**Dermal [3]**	**Inhalation [4]**
Groundboom						
M/L	<1	3	2	100	11	1000
Applicator	<1	<1	1	14	8	100
Aerial						
M/L	<1	1	<1	50	4	333
Applicator	<1	<1	<1	6	<1	33
Flagger	<1	<1	<1	33	2	100
Chemigation						
M/L	<1	<1	<1	25	1	100
Low pressure handwand						
M/L/A	5	200	167	5000	1000	10,000
Dip/slurry						
M/L	5	333	---- [5]	---- [5]	---- [5]	---- [5]
A	<1	10	---- [5]	---- [5]	---- [5]	---- [5]

Note: The acute, seasonal and annual exposure values used to calculate handler MOEs are found in Table IV-1. Occupational details also appear in the footnotes to that table.

[1] The acute oral LED_{05} of 0.01 mg/kg (rat study; WARF [1978a]) was used to estimate acute dermal risk.

[2] The acute oral LED_{05} of 0.01 mg/kg (rat study; WARF [1978a]) was used to estimate acute inhalation risk.

[3] The subchronic oral NOEL of 0.1 mg/kg (rat study; Pant *et al.* [1995]) was used to estimate seasonal and annual dermal risk.

[4] The subchronic oral NOEL of 0.1 mg/kg (rat study; Pant *et al.* [1995]) was used to estimate seasonal and annual inhalation risk.

[5] Seasonal and annual estimates were not made for dip/slurry applications. The Exposure Assessment Document states that this was due to the complete lack of reported uses on pine seedlings over the 1991-2002 period (DPR, 2006).

b. Fieldworker reentry scenarios

Fieldworker exposure estimates were limited to three reentry scenarios, scouting cotton, scouting alfalfa and scouting potatoes. The only plausible exposure route was dermal. MOEs of 1 or less were found for all acute scenarios and for seasonal exposure related to alfalfa scouting. Alfalfa scouting also generated an annual MOE of 8. Potato scouting generated seasonal and annual MOEs of 10 and 50, while the values for cotton scouting were 111 and 1000.

Table IV-9. Margins of exposure (MOEs) for fieldworker reentry scenarios

Reentry scenario	Acute MOE [1]	Seasonal MOE [2]	Annual MOE [2]
Scouting cotton	1	111	1000
Scouting alfalfa	<1	1	8
Scouting potatoes	1	10	50

Note: The acute, seasonal and annual exposure values used to calculate fieldworker reentry MOEs are found in Table IV-2.

[1] The acute oral LED_{05} of 0.01 mg/kg (rat study; WARF, 1978a) was used to estimate acute dermal risk.

[2] The subchronic oral NOEL of 0.1 mg/kg (rat study; Pant *et al.,* 1995) was used to estimate seasonal and annual dermal risk.

3. Ambient air exposure

Ambient air measurements at five sites in Imperial County and under two different wind conditions in metropolitan Sacramento County indicate a potential for inhalation exposure to the general public distal to application sites (Table IV-3). MOEs for these ambient exposure scenarios were calculated using the oral LEDs and NOELs, as appropriate inhalation studies were not available. Distinction between adult and infant systemic exposures were made in recognition of the different breathing rates of these two subpopulations. The acute MOE values ranged between 143 and 7143 for infants and between 294 and 14,286 for adults. Seasonal MOEs ranged between 5000 and 250,000 for infants and between 10,000 and 500,000 for adults. Annual MOEs ranged between 33,333 and 1,000,000 for infants and between 50,000 and 1,428,571 for adults. These MOEs appear in Table IV-10.

Table IV-10. Margins of exposure (MOEs) for the general public under ambient exposure conditions

Site	Acute MOE [1]		Seasonal MOE [2]		Annual MOE [2]	
	Infants	Adults	Infants	Adults	Infants	Adults
Imperial county						
Site C [3]	1429	3333	n/a [4]	n/a	n/a	n/a
Site M	526	1000	12,500	25,000	100,000	100,000
Site EC	1667	3333	n/a	n/a	n/a	n/a
Site H	2500	5000	n/a	n/a	n/a	n/a
Site PM	143	294	5000	10,000	33,333	50,000
Sacramento county						
South winds	7143	14,286	250,000	500,000	1,000,000	1,428,571
North winds	6250	12,500	200,000	333,333	500,000	1,000,000

Note: For a description of the various ambient exposure scenarios, see section IV.B.3 and the footnotes to Table IV-3.

[1] Acute oral LED_{05} = 0.01 mg/kg (rat study; WARF [1978a]).

[2] Subchronic oral NOEL = 0.1 mg/kg, used for seasonal and annual evaluations (rat study; Pant *et al.*, 1995).

[3] For details on the sites measured, see Table IV-3.

[4] n/a, not applicable. Seasonal and annual exposure estimates were not made at sites with no detects (Site H) or one detect (Sites C and EC).

4. Bystander (application site) exposure

As was the case for the ambient air determinations, application site determinations in Imperial County indicated a potential for inhalation exposure near to fields under treatment with carbofuran (for details of the particular application, see section IV.B.4). Because application site air levels were expected to approach ambient levels within a few days of the application, only acute exposure was expected for bystanders. MOEs for both the highest 1-hour exposures and for the 24-hr time-weighted average exposures were calculated. They were 18 and 101 for infants and adults, respectively, at the 1-hr maximum exposure level. At the 24-hr TWA, they were 22 and 46.

Table IV-11. Margins of exposure (MOEs) for the general public under application site (bystander) exposure conditions (using 24-hr TWA exposure values)

	Acute MOE [1] - 1-hr maximum exposure	Acute MOE [1] - 24-hr TWA exposure
Infants	18	22
Adults	101	46

Note: For details on the exposure conditions, see table IV-4.

[1] Acute oral LED_{05} = 0.01 mg/kg (rat study; WARF, 1978a).

5. Dietary exposure

a. Acute risk estimation - deterministic and distributional approaches

Acute dietary risk estimates using both the deterministic (point estimate) and distributional (Monte Carlo) exposure predictions appear in Table IV-12. The acute LED_{05} used to assess acute dietary risk was 0.01 mg/kg. It was based on the induction of a presumptively cholinergic sign, chewing behavior, at a low dose of 0.1 mg/kg in Wistar rats. This endpoint was relevant to dietary assessment because it was established using oral gavage as the route of exposure. As the data will show, all subpopulations exhibited acute MOEs less than the standard health-protective cut-off of 100, regardless of whether they were based on point estimates or distributional analysis. Thus a health concern exists in all of these groups based on dietary consumption of carbofuran.

The lowest MOEs were associated with infants and young children less than 6 years old, as predicted by their relatively higher exposure values. For the Tier 2 analysis, MOEs at the 97.5th user day percentile ranged between 6 ("children 1-2") and 22 ("females 13+ pregnant / not lactating"). At the 99th percentile, the Tier 2 MOEs ranged between 4 ("children 1-2") and 15 ("adults 50+" and "females 13-49"). At the 99.9th percentile, the Tier 2 MOEs ranged between 2 ("children 1-2" and "children 3-5") and 16 ("females 13+ preg. / not lactating").

For the distributional analysis, MOEs at the 97.5th user day percentile ranged between 16 ("non-nursing infants <1 yr") and 60 ("adults 50+"). At the 99th percentile, the distributional MOEs ranged between 11 ("females 13+ / lactating") and 47 ("adults 50+"). At the 99.9th percentile, the distributional MOEs ranged between 5 ("children 1-2 yr") and 35 ("females 13+ preg./not lactating").

In assessing acute dietary exposure from pesticide residues, the point estimate-Tier 2 analysis considered the highest residue level below tolerance that was found in crops, assuming that 100% of the crop was treated. In general, this approach allows a rapid evaluation of dietary exposure in cases where risks are low. Monte Carlo analysis refined the point estimate approach by combining residue and consumption distributions. As discussed in the previous paragraph, both approaches predict a potential human health concern from exposure to

residues of carbofuran + 3-OH-carbofuran when all crops with existing tolerances were examined (*i.e.*, MOEs are less than 100 at the 97.5th-99th percentile levels).

"Reality check". In an acute point estimate analysis, single residue values are applied to the distribution of population consumption rates. The size of the user-day population increases as more commodities are added to a single commodity exposure analysis. The change in reference population between the single and multiple commodity analyses is likely to result in a shift of the distributional placement of individuals who have high, yet reasonable, exposure from a particular commodity alone. Since the high end of exposure from these analyses is represented at predetermined percentiles, a "reality check" procedure is necessary to ensure that the exposure of such individuals is captured within the specified percentile of the multiple commodity analysis.

Among the high contributors for most subpopulations in the point estimate analysis were bananas, corn grain / high fructose corn syrup, cucumbers and wheat flour. The Tier 2 point estimates for the latter two commodities were based on actual residue detections recorded in the PDP database, while the estimates for the former two commodities were based on reported LOD values in the same database. (Note, however, that both the tolerance value and the highest overtolerance value are used for cucumbers.) These commodities were chosen for the reality check, as they were prominent representatives of the residue-positive and residue-negative foods that contributed to the estimated carbofuran exposure.

The 97.5th percentile MOEs were lower for all commodities combined than for the single commodity when assessing wheat grain, bananas and corngrain / sugar / hfcs (Table IV-13). Thus high end consumers of these commodities were included in the combined analysis. With the exception of the "non-hispanic non-white non-black" population, this was also the case for cucumbers when tested at tolerance. On the other hand, when tested at the overtolerance value of 0.551 ppm, the single commodity MOEs were consistently lower than the all-commodities MOEs. This continued to be the case even at the 99.9th percentile in many subpopulations (data not shown). Thus if illegal cucumber residues are considered, high-end consumers of cucumbers may exceed the exposures indicated in the combined analysis at the chosen percentile.

b. Chronic risk estimation

Chronic dietary risk estimates also appear in Table IV-12. The subchronic NOEL of 0.1 mg/kg was used to assess chronic dietary risk. It was based on the induction of male reproductive toxicity and suppression of body weight gain in Druckrey rats under a gavage exposure regime at a LOEL dose of 0.2 mg/kg. As no MOE was lower than 427 ("children 1-2 yr"), a chronic dietary health concern was not indicated. Consequently, further refinement of the chronic risk estimation, particularly with respect to including percent crop treated considerations, was considered unnecessary.

6. Aggregate exposure

Because toxicologically significant acute exposures to carbofuran were predicted by the dermal, respiratory and dietary routes, determination of the risk from combined exposures ("aggregate" risk) might also be appropriate. However, each exposure route was associated with MOEs that were already below the health-protective benchmarks of 10 or 100 necessitated by the relevant human or animal toxicity studies, respectively. It was, therefore, considered unnecessary to calculate aggregate risk values, as they would not add significantly to the overall assessment.

Aggregate risk calculations were also not necessary for chronic exposure, as such a scenario was not considered likely by any except route except the dietary.

Table IV-12. Dietary risk estimates for carbofuran + 3-OH-carbofuran: MOEs for acute (point estimate and Monte Carlo) and chronic exposures

Population subgroup	MOE [1], Acute (point estimate)			MOE [1], Acute (distributional)			MOE [2], Chronic
	97.5th percentile [3]	99th percentile	99.9th percentile	97.5th percentile	99th percentile	99.9th percentile	
US population	12	9	4	35	25	12	1172
Western region	11	8	4	32	23	11	1089
Hispanics	11	8	5	32	21	13	1054
Non-hispanic whites	12	9	5	36	26	11	1189
Non-hispanic blacks	12	9	5	35	26	14	1262
Non-hispanic / non-white / non-black	9	5	3	30	23	12	992
All infants	8	6	4	16	13	8	601
Nursing infants <1 yr	8	6	4	20	14	10	1235
Non-nursing infants <1 yr	8	6	4	16	13	8	503
Females 13+ (preg./not lactating)	22	16	16	47	38	35	1419
Females 13+ (lactating)	16	10	9	33	11	10	1207
Children 1-2 yr	6	4	2	17	12	5	427
Children 3-5 yr	7	5	2	21	16	9	510
Children 6-12 yr	10	8	3	30	23	9	805
Youth 13-19 yr	16	11	5	43	33	9	1307
Adults 20-49 yr	18	14	8	50	37	17	1489
Adults 50+ yr	20	15	8	60	47	24	1623
Females 13-49 yr	19	15	7	51	38	18	1550
Males/Females 16+ yr	18	14	7	51	38	18	**not caculated**

[1] Acute oral LED_{05} = 0.01 mg/kg (WARF, 1978a).
[2] The subchronic oral NOEL of 0.1 mg/kg/day (Pant *et al.*, 1995) was used to calculate chronic risk.
[3] The estimated percentage of user days that were at or above the indicated MOE value.

Table IV-13. Dietary risk estimates for carbofuran + 3-OH-carbofuran: comparison of 97.5th percentile MOEs (point estimate and Monte Carlo) with MOEs generated using point estimates on four single commodities

Population subgroup	Acute MOEs, point estimates, 97.5th percentile [1]				
		Single commodities			
	All commodities	Cucumbers [2]	Wheat grain [3]	Bananas [4]	Corn hfcs [5]
US population	12	20 (7)	59	21	102
Western region	11	14 (5)	60	21	104
Hispanics	11	18 (6)	60	18	102
Non-hispanic whites	12	23 (8)	60	22	103
Non-hispanic blacks	12	32 (11)	56	21	90
Non-hispanic / non-white / non-black	9	6 (2)	58	21	107
All infants	8	11 (4)	44	11	29
Nursing infants <1 yr	8	363 (131)	51	10	56
Non-nursing infants <1 yr	8	11 (4)	42	11	29
Females 13+ (preg. / not lactating)	22	28 (10)	93	52	109
Females 13+ (lactating)	16	38 (13)	90	39	160
Children 1-2 yr	6	8 (3)	32	12	53
Children 3-5 yr	7	7 (2)	35	14	58
Children 6-12 yr	10	12 (4)	48	21	76
Youth 13-19 yr	16	18 (6)	78	41	111
Adults 20-49 yr	18	26 (9)	92	50	170
Adults 50+ yr	20	27 (9)	117	53	243
Females 13-49 yr	19	27 (9)	96	52	164
Males/Females 16+ yr	18	26 (9)	93	50	172

[1] Acute oral LED_{05} = 0.01 mg/kg (WARF, 1978a).
[2] For cucumber, the carbofuran + 3-OH-carbofuran residue was set at the tolerance of 0.2 ppm. This was done because the high residue value of 0.551 (PDP tests from 2003-2003) was over the tolerance and therefore illegal. However, MOEs generated by use of 0.551 ppm were calculated as well - these MOEs are in parentheses.
[3] Wheat grain, carbofuran + 3-OH-carbofuran high detect value = 0.028 ppm (PDP tests from 1997-1999, 2003)
[4] Bananas, carbofuran + 3-OH-carbofuran point estimate = 0.052 ppm (high LOD, PDP tests from 1995, 2001-2002)
[5] Corngrain / sugar / hfcs, carbofuran + 3-OH-carbofuran point estimate = 0.018 ppm (high LOD, PDP tests from 1995 and 2001

V. RISK APPRAISAL

Risk assessment is the process by which the toxicity of a compound is compared to the potential for human exposure under specific conditions, in order to estimate the possible risk to human health. Every risk assessment has inherent limitations relating to the relevance and quality of the available toxicity and exposure data. Assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment and exposure-assessment processes. This results in uncertainty in the risk characterization, which integrates the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, the magnitude of the uncertainty varies with the availability and quality of toxicity and exposure data, and the relevance of that data to the anticipated exposure scenarios.

In the following sections, the specific areas of uncertainty associated with the characterization of health risks from exposure of both workers and the general public to carbofuran and its metabolites and degradation products are described. The exposure scenarios examined include dermal and inhalation exposure to workers, inhalation exposure to the general public, and dietary exposure to the general public.

A. HAZARD IDENTIFICATION

Selection of the appropriate laboratory animal toxicity studies to characterize human risk is a central task of pesticide risk assessment. Two factors influence the selection process: (1) the scientific quality of the studies in question, including the reliability of the data used to support the critical LOELs and NOELs, and (2) the relevance of the routes of exposure employed in those studies to the anticipated routes of human exposure. These factors are discussed in the following sections as they relate to acute, seasonal and annual exposure to carbofuran.

1. Acute toxicity

a. Oral and inhalation exposure

The statistically significant increase in incidence of chewing motions in rats observed by WARF (1978a) - 0/24, 5/24*, 12/24** and 16/24** at 0, 0.1, 0.3 and 1 mg/kg, respectively (*$p \leq 0.05$; **$p \leq 0.001$) - was the basis of the critical acute LED_{05} designation. Abnormal chewing behavior was considered to be an acute neurotoxic response to exposure. The acuteness was explicit in the study report, which described chewing behavior as occurring “for a short period of time immediately following dosing each day”. Because of the low dose incidence, benchmark dose analysis was performed to establish an LED_{05} of 0.01 mg/kg (see section IV.A.1 for a complete discussion). The clear dose-response pattern, combined with the statistical significance, were strong evidence that the incidence at all doses was due to carbofuran exposure. Nonetheless, for such an effect to merit regulatory attention there should be a reasonable possibility of adverseness. There is precedent for identifying unusual chewing behavior as an adverse effect. DPR risk analyses of several organophosphate compounds indicate that unusual chewing behavior was a critical acute determinant in several cases and a critical subchronic determinant in one case (see discussion, section IV.A.1). In light of their widely-recognized cholinesterase inhibiting properties, these examples emphasize that cholinergic activation, either central or peripheral, was the likely driving force.

Even so, none of the previous studies identified unusual chewing behavior as the *only* neurotoxic sign at the critical dose. In each of those cases, chewing behavior was aligned with other signs at the same dose. It is thus helpful to examine the WARF study at higher doses, to certify that unusual chewing behavior was part of a cassette of neurotoxic responses. The appearance of lethargy at the mid dose, and trembling, convulsions, lacrimation and salivation

at the high dose, all within an order of magnitude of the LOEL dose, made it likely that the observed unusual chewing behavior was an early indicator of neurotoxicity. Taken in conjunction with the evidence for acute neurotoxicity at the low dose of 0.2 mg/kg in the Jayatunga *et al*. (1998a) rat developmental toxicity study (see below), the low dose effect in WARF (1978a) appears both to be related to carbofuran exposure and serious enough to merit regulatory attention.

The absence of unusual chewing behavior (or, for that matter, any other neurotoxic sign) at doses as high as 1.2 mg/kg in the follow-up study (IRDC, 1980b) or in the Pant (1995) subchronic study at doses as high as 0.6 mg/kg injected an element of uncertainty into the critical acute determination. These negative observations suggested that the WARF observation was not robust, casting question on its reliability. Furthermore, since dosing analyses were not reported for any of these studies, there was no way to confirm the accuracy of the nominal doses (though, to be sure, WARF provided a detailed account of how the suspensions were made and how uniformity of suspension was ensured). Finally, the inability to trace the chewing response in each rat (time of appearance, severity, number of incidents per rat) decreased the reliability of the critical endpoint observation. These deficiencies emphasized that both the WARF (1978a) and Pant (1995) studies were not conducted according to Good Laboratory Practice guidelines, which establish that dosing analyses are carried out and individual animal data are presented.

However, the GLP-compliant FMC (2002) study evidenced teeth grinding at a similar dose range as the WARF (1978a) study. Teeth grinding was considered to be equivalent to the abnormal chewing behavior noted in the latter study. In addition, as discussed in section IV.A.1.a., Moser (1995) stated that “mouth smacking” is a commonly observed response to cholinergic compounds in rats, likely originating in the ventrolateral striatum. Interestingly, Moser speculated that mouth smacking is a direct consequence of activation of the M_2 muscarinic receptor, implying that the role of cholinesterase inhibition may be secondary at best.

Further uncertainties resided in the benchmark dose methodology used to determine the LED. For example, the choice of algorithm to model dose-responses at sub-empirical levels reflected substantial uncertainty. In this case, the dichotomous log-transformed logistic algorithm was chosen to represent the low-dose behavior. This was based on AIC analysis, which suggested that, among the 16 algorithms tested, log logistic modeling best described the data at higher doses. Even in light of the AIC analysis, however, the shape of the dose-response curve at very low doses may not be predictable from the empirically-determined curve shape at the higher doses. Access of carbofuran to the target tissue or enzyme is undoubtedly affected by dose, since dose would affect the processes of absorption, distribution, metabolism and excretion. For carbofuran, none of these pharmacokinetic processes is understood to a level necessary to reliably predict low-dose effects, leaving us with benchmark dose / AIC analysis as the lone determinant.

The choice of benchmark response level also added uncertainty to the risk analysis because it was dependent on a judgement of endpoint severity. DPR uses a 5% response level as an initial default, but selects a 1% or 10% level in cases of high or low severity, respectively. The chewing effect observed in the WARF (1978a) study might be interpreted as a low-severity sign since (1) it did not overtly compromise the organism and (2) other signs were not observed until higher doses. Yet the distinct possibility of central nervous system involvement, with the attendant possibility that other centrally coordinated, but difficult-to-document, processes such as learning or perception were also affected, suggested the possibility that the effect was more severe.

Had a 10% benchmark response been chosen to model the chewing effect (*i.e.*, had the affect

been judged non-severe), the LED_{10} and ED_{10} would have been 0.03 and 0.04, respectively, raising the MOEs by threefold. This would have made little difference under any of the considered exposure scenarios - most of the MOEs would still have been less than 100, indicating the presence of a potential health concern. In the end, because there was a balance of "non-severe" *vs.* "severe" health implications, the default benchmark response level of 5% was chosen, in full recognition of the uncertainties.

Regardless of these quantitative considerations, the view that the chewing effect was a sufficient critical endpoint was supported by the results of Jayatunga *et al.* (1998a) in Wistar rats. These investigators demonstrated putatively neurotoxic signs at a low gavage dose of 0.2 mg/kg. Benchmark dose analysis resulted in precisely the same LED_{05} as for the WARF chewing data. Furthermore, not only did the these signs increase in severity with dose, but serious impacts on pregnancy outcome were noted starting at 0.4 mg/kg (*i.e.*, just twice the LOEL dose).

In the absence of a critical acute or subchronic inhalation toxicity study, the same WARF (1978a) rat oral gavage study was used to assess risks from anticipated inhalation exposure. Applying an LED from an oral bolus dosing study to estimate human inhalation risk adds uncertainty to the risk assessment. Such an exposure technique results in high initial systemic pesticide concentrations, which increases the potential for acute toxicity. Inhalation exposure may result in dose internalization over a longer time period, with consequent lower systemic concentrations and decreased toxicity. On the other hand, rapid uptake through the lungs could elicit more severe initial systemic toxicity than a slower digestive uptake process. Contributing to this, intestinal absorption results in immediate delivery to the liver via the hepatic portal vein (the "first pass" effect), where metabolic transformations would likely lower the ultimate toxicity of carbofuran by creating less toxic metabolites and enhancing excretion. Evidence from one pharmacokinetic study indicates, however, that carbofuran enters the enterohepatic circulation, which may increase its residence time in the body and thus lengthen its period of toxicity (Marshall and Dorough [1979]). In sum, it is not currently possible to say whether using a route extrapolation in this case increases or decreases the perception of risk.

b. Dermal exposure

In the absence of an appropriate dermal toxicity study, the WARF (1978a) rat critical oral toxicity study was also used to assess the risks from human dermal exposure to carbofuran. In general, a route extrapolation of this nature carries similar uncertainties to the oral-to-inhalation extrapolation discussed in the preceding paragraph. Using an oral bolus dose to assess systemic toxicity by the dermal route may overestimate the potential toxicity by generating a more precipitous rise in blood concentrations. The extent to which various inert ingredients in the Furadan 4F formulation might counteract or promote this is unknown, though RBC ChE activity was inhibited within 2 hours at the high dose (4 mg/kg) in the human dermal study (Table III-2; Arnold, 1977). This suggested that dermal carbofuran had relatively quick access to the circulation. In any case, the question of the appropriateness of the oral study to the dermal toxicity assessment cannot be resolved until an acceptable dermal study is conducted and submitted for review.

2. Subchronic toxicity

a. Oral and inhalation exposure

Damage to the male rat reproductive system after daily gavage administration of carbofuran for 60 days was clearly in evidence at the mid dose of 0.2 mg/kg/day in the study of Pant *et al.* (1995). This resulted in a NOEL of 0.1 mg/kg/day. Significant organ weight reductions occurred in the epididymides, seminal vesicles, ventral prostate and coagulating gland; epididymal sperm motility and counts were significantly reduced; testicular enzyme levels were altered; Sertoli cells and spermatids were vacuolated; and testicular congestion and edema were present. The

dose response was excellent. These observations were supported by similar observations in at least three other species (mouse, rabbit, and dog), and in human sperm *in vitro* (see complete discussion in section IV.A.1.b). In addition, the same investigators reported testicular effects in rat offspring after exposure of the mother during gestation or lactation (Pant *et al.*, 1997).

Despite the strength of the Pant observations, the issue of the relevance of bolus gavage dosing to inhalation exposure scenarios, raised above with respect to the acute assessment, is potentially valid in the subchronic case as well. NOELs derived from a gavage study might over- or underestimate the inhalation risk if the build-up of internal levels is different than for inhalation exposure. Nonetheless, for many compounds, repeated dosing results in the establishment of steady state blood concentrations, which would minimize daily dosing extremes. This would also tend to minimize potential differential effects based on exposure route, though it is not known if steady states are approached with carbofuran under the dosing regime used by Pant.

It is also worth noting that the Pant study, which appeared in the open literature, was not conducted according to GLP guidelines. Nonetheless, one guideline-compliant dog subchronic study (RCC, 1987a) generated a similar NOEL to that of the Pant *et al.* (1995) rat study (0.15 mg/kg/day and 0.1 mg/kg/day, respectively). In the dog study, the estimated NOEL was based on inhibition of RBC cholinesterase. However, based on the clear toxicologic potential of the testicular effects in the rat study, as opposed to the unclear toxicologic potential of RBC ChE inhibition in the dog study, the rat study was designated as the critical one.

Setting the subchronic (and chronic) critical NOEL one order of magnitude higher than the critical acute level, while unusual in a risk assessment, is not likely to compromise human health. Protection against untoward acute effects at the lower dose level would ensure protection against subchronic / chronic effects, regardless of their nature, occurring at higher doses.

b. Dermal exposure

The uncertainties and caveats inherent in using a subchronic oral NOEL (0.1 mg/kg/day from the Pant *et al.* [1995] study) to estimate seasonal dermal risk were similar to those discussed above for the estimation of acute and subchronic inhalation risk using oral studies.

3. Chronic toxicity

a. Oral exposure

The subchronic critical oral NOEL of 0.1 mg/kg/day from the Pant *et al.* (1995) rat study was used to evaluate the risks from chronic exposure to carbofuran. Choice of a subchronic NOEL to evaluate chronic risk injected a clear uncertainty into the analysis, as chronic exposure might be expected to result in lower NOELs than subchronic. However, the reverse may be true in the present case: the lowest NOEL from a chronic study was 0.3 mg/kg/day, based on a LOEL of 0.6 mg/kg/day established in the Toxigenics 1-year dog (1983) study. Significantly, the testicular degeneration noted as the principal LOEL determinant in that study was reminiscent the testicular damage underlying the LOEL determination of 0.2 mg/kg/day in the critical subchronic rat study. Using 0.1 mg/kg/day instead of 0.3 mg/kg/day might therefore be viewed as a health-protective position. The uncertainty resides in the possibilities, discussed above in section IV.A.1.c, that dogs were less sensitive to carbofuran's testicular impacts than rats and that the dietary route used in the dog study was less toxicologically effective than the gavage route used in the rat study.

b. Dermal exposure

The uncertainties and caveats inherent in using an oral NOEL (0.1 mg/kg/day from the Pant *et al.* [1995] subchronic study) to estimate chronic dermal risk were similar to those discussed above for the estimation of acute and seasonal inhalation risk using oral studies. In addition, while extrapolating from seasonal (subchronic) to annual (chronic) exposure scenarios might recommend imposition of an uncertainty factor, this was considered unnecessary in this case - the critical subchronic oral NOEL was lower than the lowest chronic oral NOEL. As mentioned in the Hazard Identification section (section IV.A.c.), this may be due to use of gavage dosing in the subchronic case as opposed to the dietary dosing employed in the chronic case. Even so, use of a subchronic study to estimate chronic risk carries at least the possibility of chronic risk underestimation.

B. EXPOSURE ASSESSMENT

1. Occupational and resident / bystander exposure

Many of the uncertainties associated with the occupational and resident / bystander exposure assessment have been discussed in the accompanying Exposure Assessment document (DPR, 2006; attached to this report as Appendix I). The following paragraphs summarize the most prominent of those uncertainties.

Handler estimates. Most of the handler estimates were based on surrogate data from the Pesticide Handlers Exposure Database (PHED). Reliance on surrogates for this purpose was replete with uncertainties. PHED generates exposure estimates using data from many different compounds and studies. These studies utilize different analytical methodologies and detection limits, and incorporate data from exposure to different body regions. PHED also considers only the physical state of a compound (*i.e.,* liquid, powder, flowable concentrate, etc.), not its physico-chemical properties. Potential validation for the PHED-based estimates was forthcoming from only one carbofuran handler study (Hussain *et al.* [1990]). This study was rejected for use in the Exposure Assessment document due to its small sample size. Nonetheless, several of the measured handler exposures were much higher than the mean PHED values used in this assessment, and several were lower, suggesting that PHED may under- or overestimate actual carbofuran exposure.

Erroneous handler exposure estimates may also result from misapprehensions concerning the number of acres treated / day and the number of days in which workers were exposed. For most applications, unverifiable USEPA defaults were used to estimate acres treated, leaving open the possibility that there were under- or overestimates in this parameter. Also, the number of exposure days was estimated using Pesticide Use Report data, which were based on applications distributions in California during high-use periods. PUR's reliance on "a recent work history of the handler population" rather than on individual data may foster overestimations in this parameter as well (DPR, 2006).

Finally, several default values were used in the handler assessment, each of which contained assumptions that were not verifiable. (1) A dermal penetration default of 50% was used in lieu of an adequate experimental study. The studies by Shah *et al*. in mice (1981) and rats (1987) were conducted using acetone as a vehicle instead of with the formulated product or with water as recommended by USEPA. An extractive and disruptive organic solvent (Merck, 2001), acetone is likely to over-promote the dermal absorption of carbofuran, though there are no compound-specific data to substantiate this. Also, the doses tested were generally too high to be relevant to exposures in the workplace. Finally, the treatment areas were somewhat lower than those recommended by USEPA. Taking all of these factors into account, the accuracy of the 50% default is very unclear. (2) An inhalation absorption value of 100% was used in the absence of a direct measurement of this parameter. (3) A default body weight of 70 kg was

used in the absence of direct field determinations. Such a default assumed that all of the workers were average-sized males.

The exposure estimates for dip/slurry applicators, in contrast to the PHED-based estimates used for the rest of the occupational exposure scenarios (including dip/slurry mixer/loaders), were based on the RAGS-E model equations for the dermal estimates and a calculation of

carbofuran's air saturation concentration for the inhalation estimates. As the air saturation calculations were greatly exceeded by a parallel estimates generated by SWIMODEL, a USEPA program for calculating theoretical air concentrations at aqueous-air interfaces, the air saturation concentration was used in this document (for references on RAGS-E and SWIMODEL, see DPR, 2006). These mathematical modeling approaches describe the ideal behavior of surrogate organic chemicals in aqueous solutions and at aqueous-air interfaces. As such, the resultant estimates were subject to pronounced uncertainties. These were delineated in the Exposure Assessment document (DPR, 2006), with the major uncertainties summarized here: (1) The use of surrogates may not adequately predict the behavior of carbofuran under the various potential exposure routes. (2) The RAGS-E method for calculating the dermal permeability, K_p, assumed that the carbofuran exists in aqueous solution, without other solutes. However, this was violated in the dip/slurry case. First, the only available carbofuran formulation from which to make the slurry contains additives designed to increase water solubility and dispersibility. These are likely to elevate the flux across the dermal barrier, making the K_p value calculated from RAGS-E artificially low. Second, the presence of clay in the slurry may partition the carbofuran in such a way that it becomes less available to the skin (*i.e.*, the calculated K_p would be artificially high). (3) The K_p determinations in RAGS-E were based on equations that considered only *in vitro* permeability measurements using surrogate chemicals with defined physico-chemical properties. *In vitro* measurements may not reflect the actual *in vivo* permeability of human skin. (4) The air saturation concentration used with respect to the dip/slurry application was very likely an overestimate. Such calculated values assume a closed system, with no means of egress for the volatilized carbofuran. Such would not be the case for the dip/slurry task, which is carried out in an open vat with ventilation available in the case of indoor treatments.

Fieldworker estimates. In the absence of direct monitoring data, fieldworker exposures were estimated using an equation that incorporated dislodgeable foliar residue values (DFR) and transfer coefficients (TC), as well as defaults for exposure duration (8 hours), dermal absorption (50%), and body weight (70 kg). The non-specificity and consequent uncertainty in some of these default values was noted above in relation to the handlers (see also section IV.B.2.b and DPR, 2006). The DFR and TC values were crop-specific for the three reentry crops examined, though the fieldworker estimates for additional crops with carbofuran tolerances were subsumed under those three scenarios.

There were some cotton fieldworker tasks that may not have been perfectly represented by the assumptions underlying the cotton scouting task. These included weeding, roguing (removal of diseased plants) and harvesting. In the absence of such data, scouting was considered most appropriate to the assessment, though the potential for error is recognized.

Finally, the Exposure Assessment document recognized that translocation after a soil application from the roots to the leaves could conceivably result in residues at the leaf surface. It is not clear if such translocated residues might be dislodgeable. However, the EAD considered that even if they are, they are not likely to result in significant exposures.

Ambient and application site air estimates. As no biomonitoring was available, ambient and application site exposures were based both on measured air concentrations and on assumptions about carbofuran uptake by adults and infants from the air. In addition, while

ambient monitoring sites were selected based on anticipated nearby carbofuran use, actual applications were not confirmed. The fact that a number of samples were negative for carbofuran even in Imperial County where use was high, suggests the possibility that carbofuran levels were occasionally not measured at sites and times of peak use. This would result in underestimates of potential ambient levels.

Seasonal and annual application site air values were not estimated because it was assumed that, within a few days of an application, application site levels would approximate seasonal ambient levels. This appears to be a reasonable assumption in view of the estimated vapor phase photooxidation half-life of 4.6 hours (HEFED, 1991). In addition, application site estimates were corrected for submaximal application rates. It is not known if actual air levels would increase proportionately to increases in application rate.

2. Dietary exposure

Uncertainties in the dietary exposure assessment fall into three major categories: (1) parameter uncertainty, (2) model uncertainty, and (3) scenario uncertainty (Peterson *et al.*, 2001).

a. Parameter uncertainty

Sources of parameter uncertainty in the dietary exposure assessment included the degree of completeness of the food residue database, the use of surrogate data, the possible presence of sampling or reporting errors, and the routine summing of carbofuran plus 3-OH-carbofuran residues for all estimates. The latter factor, which represents the explicit assumption that both chemical entities are always present in toleranced commodities, may overestimate the carbamate residues, particularly as detections of either compound (not to mention simultaneous detections of both compounds) were rare. On the other hand, it should be noted that the contributions of the phenolic (non-carbamate) degradates, were not considered for this analysis. This was due both to the extremely limited toxicity evaluations available for these compounds and to the dearth of phenolic residue data in the available databases. In addition, the phenolic compounds were not included in the current tolerances.

Carbofuran / 3-OH-carbofuran residue estimates were based largely on PDP data. PDP was the database of preference because it was specifically designed to generate data relevant to risk assessment and contained the most extensive residue database. Most of the commodity residue data for this report came from this source, contributing to the reliability of the analysis. However, the vast majority of residue assays were negative, resulting in the setting of those levels at the limit of detection (LOD) for the point estimate approach. Consequently, the *actual* residue level could be anywhere between zero and the LOD. The distributional (Monte Carlo) approach was less problematic in this regard because non-blended commodity estimates were based on an assumption that only a fraction of the non-detects were at the LOD, depending on the percentage of the crop that was treated (PCT) (see discussion below). The remaining samples were set to zero.

The DPR Marketbasket Surveillance database, of next preference as a residue data source in DPR dietary assessments, showed only a minimal number of residue detections, and only for strawberries and peppers. As noted above in the dietary exposure section, this very low detection rate combined with the fact that PDP data were available for both commodities, obviated the need for this data in the current analysis.

Residue data from field trials were employed in the current assessment for artichokes, coffee, cottonseed, sugarbeets, sugarcane, and sunflower oil and seeds. Such studies were conducted to determine the highest residue level that can result from maximal legal use of the pesticide. As such, they did not necessarily reflect the actual use patterns and were used only when PDP data were not available. As none of these commodities emerged as major contributors in the point estimate analysis, it was not expected that field trial data significantly affected the outcome

of the assessment. In the distributional analysis, both sugarbeets and sugarcane emerged as high contributors in many of the analyzed subpopulations, though these contributions never rose above 19% for the former and 11% for the latter commodity. It was thus unlikely that exposure from these commodities significantly affected the risks estimated from distributional analysis.

Surrogate data were used when neither PDP nor field trial data were available. This included the use of sweet corn data for corn grain (including popcorn), winter squash data for summer squash and for pumpkin, and cantaloupe data for other melons. As none of these commodities were particularly high contributors, there was little chance that the use of surrogates had an appreciable effect on the analysis.

Uncertainty in the dietary exposure assessment also can arise from the consumption data contained in the 1994-1998 CSFII survey. There are several possible sources for this type of uncertainty: misrepresentation of actual dietary consumption, reporting errors, or variation in dietary habits during or after the consumption period. For example, critical exposure commodity analysis for the population “Females 13+ (lactating)” showed a different profile than any of the remaining 18 subpopulations; however, the data on this subpopulation were less convincing than data for other subpopulations because, as indicated in Table IV-7, the number of user days in the dietary record for this population (80) was small relative to most of the other populations (586-40,224; except for “Females 13+ preg/not lactating”=139). Such a small sample size may skew the consumption pattern for that particular population.

b. Model uncertainty

The 97.5th, 99th and 99.9th user day percentiles are presented in this assessment as estimated high-end exposures when single upper bound residues and 100%-crop-treated assumptions were employed. Acute dietary exposures to carbofuran + 3-OH-carbofuran, calculated at those exposure levels using the point estimate method, indicated a potential health concern in every subpopulation examined, with acute MOEs ranging between 6 and 22 (97.5th percentile), 4 and 16 (99th percentile), and 2 and 16 (99.9th percentile) (Table IV-12). As a result, a more refined distributional modeling approach (Monte Carlo) was initiated. Residue distribution and PCT information were incorporated into the analysis for those commodities considered to be high contributors using the DEEM point estimate critical exposure commodities (CEC) report. The remaining commodities retained their point estimate values, though it was assumed that, by virtue of their lower contributions, they would not make a substantial contribution to the total carbofuran + 3-OH-carbofuran consumption. As it turns out, this assumption may not be precisely true (see next paragraph).

The distributional refinement did result in lower predicted exposures in virtually every subpopulation and percentile exposure category. Correspondingly higher MOEs at each percentile were generated: 16 - 60 at the 97.5th (mean increase: 2.7±0.4-fold), 11 - 47 at the 99th (mean increase: 2.7±0.7-fold) and 5 - 35 at the 99.9th (mean increase: 2.6±0.76-fold) percentiles (Table IV-13).

If all commodities not subjected to distributional analysis were removed (*i.e.*, their point estimates were set to zero), the resultant MOEs increased to 28 - 153 at the 97.5th percentile (mean increase over the complete distributional analysis: 2.5±0.5-fold). Thus even though the non-RDF commodities were not major contributors in the Tier 2 point estimate analysis, they did have a substantial contribution in the context of the Tier 4 distributional analysis.

It is also worth noting that the distributional data included several blended commodities. As such, the “distributions” for those commodities did not include any samples that were set to zero, since PCT considerations were not taken into account. Thus little effect would be expected of Monte Carlo analysis for these commodities, since there was little distribution to

speak of and no “zero” values.

c. Scenario uncertainty

Three residue scenarios were examined in the current dietary analysis: (1) a refined point estimate analysis for each commodity with tolerance, (2) a distributional analysis, incorporating percent crop treated for non-blended commodities, and (3) a point estimate analysis in which pesticide residues were contributed by one commodity only (the “reality check”). These approaches represented different ways of viewing, refining and checking the same residue database. As the purpose and implications of the first two approaches were discussed in detail above, only the third approach will be examined here.

Scenario 3 was, in effect, a test of the adequacy of the consumption distributions to include all members of a particular subpopulation. This was a concern because of the inevitability of a distribution shift between analyses that considered only a single commodity and analyses that examined all of the toleranced commodities together, especially for those commodities that exhibited a low percentage of user days. If a case arose whereby high consumers of such a commodity evidenced higher exposure (lower MOE) with the commodity alone than in the combined analysis, then we would conclude that the combined distribution at that percentile of user days did not include the single commodity consumer. Tests of three high-contributing commodities - wheat grain, bananas and corngrain / sugar / high fructose corn syrup (hfcs) - showed that this was not the case. MOEs were higher for each commodity analyzed singly than for all commodities analyzed together (Table IV.13 - only the 97.5th percentile data are shown). Cucumbers, which evidenced the highest individual residues of any commodity, also showed higher exposures (lower MOEs) for 18 of the 19 subpopulations analyzed at the 97.5th percentile. Only the “non-hispanic / non-white / non-black” subpopulation showed lower MOEs for the cucumber-alone data than for the combined. Interestingly, such was also the case for “children 6-12 yr” and “youth 13-19 yr” at the 99th percentile (data not shown), but not for any population at the 99.9th percentile. Thus some very high consumers of cucumbers in these subpopulations would not be included in the all-commodities distribution, at least through the 99th percentile.

C. RISK CHARACTERIZATION

Risk is characterized in this document by using the margin of exposure ratio, which is equal to the critical NOEL or LED divided by the anticipated exposure. When the NOEL or LED is established in a human study, an MOE of 10 or greater is usually considered to be protective of human health. This is based on the health-conservative assumption that the most sensitive human is 10-fold more sensitive than the average human. When the NOEL or LED comes from a laboratory animal study, as was the case under all exposure scenarios considered for this document, an MOE of 100 or greater is considered to be protective of human health. This is based on the additional health-conservative assumption that humans are 10-fold more sensitive than the most sensitive animal.

The health risks from acute occupational dermal exposure were assessed using the rat critical oral toxicity study (WARF, 1978a) and surrogate exposure modeling from PHED and RAGS-E. MOEs of at least 100 were required to ensure human health. As each term in the MOE ratio was fraught with uncertainty (see discussions in sections V.A.1.b. and V.B.1.), the resultant MOEs, many of which were less than one, were at best only a first approximation of risk. Examination of DPR’s Pesticide Illness Surveillance Program (PISP) showed only 120 reports of illness or injury with definite, probable or possible relation to carbofuran exposure over the 1982-2001 period (section II.E.). While it is certainly possible that many adverse incidents have gone unreported, the PISP record does not suggest imminent danger. Even so, the apparently high human dermal sensitivity suggests that extreme caution is in order when use of carbofuran is

considered.

The health risks from acute inhalation exposure were assessed using the rat critical oral study, necessitating MOEs of at least 100 to ensure human health. All handler tasks exhibited MOEs of less than 10 by the inhalation route, except those of the low pressure handwand and dip/slurry workers. One bystander scenario, infants at application sites, also registered an MOE below 100. While the toxicity endpoint, abnormal chewing behavior, was considered serious because it reflected a possible neurological insult, a major uncertainty resided in the relevance of bolus oral dosing to inhalation exposure (see discussion, section V.A.1.b). Because it was not known if the bolus oral dose was more toxic than the anticipated inhalation exposure in the field, it was not possible to judge the reliability of the MOEs.

Risk from acute dietary exposures was also evaluated using the WARF (1978a) rat acute oral study. MOEs fell below the benchmark level of 100 for every subpopulation regardless of the percentile user days, indicating the presence of a potential health risk. A route extrapolation was not necessary, arguing in favor of the use of the rat study in this instance. However, the appropriateness of the bolus dose to human dietary exposure was very much in question, as dietary exposure would suggest a more gradual systemic entry. Also, the exposure values, with their overwhelming dependence on limits of detection in the absence of residue detections, were very likely to be overestimates. For both of these reasons, the acute dietary MOEs are likely to be artificially low, though it is not presently known by how much.

The health risks inherent in the anticipated seasonal dermal and inhalation exposures were assessed using a rat subchronic study (Pant, 1995). This necessitated MOEs of at least 100 to ensure human health. Most handler seasonal MOEs were under 100 by both routes, with many dermal MOEs under 1. Artichoke fieldworkers also registered MOEs under 100. Nonetheless, the relevance of the route extrapolation once again injected substantial uncertainty into the analysis.

Risk from chronic dietary exposure was evaluated using the same rat subchronic study (Pant, 1995). Most of the subpopulation MOEs were greater than 1000, with the lowest at 711, implying a low chronic risk. It should be recalled, however, that use of a subchronic study to estimate chronic risk injected an uncertainty due to the longer-term human exposure. However, as was the case for the acute dietary assessment, the reliance on LODs may have resulted in overly high exposure values, with the opposite effect, overestimating risk.

D. CRITICAL TOXICITY ENDPOINTS - USEPA *vs.* DPR

USEPA issued a Revised Preliminary Risk Assessment for carbofuran in September, 2005 (USEPA, 2005). On the conviction that cholinesterase inhibition was the most sensitive toxicity endpoint in mammals, USEPA identified a critical LOAEL of 0.25 mg/kg, based on inhibition of plasma ChE in the dog chronic study (Toxigenics, 1983). This LOAEL was applied both to acute and chronic exposure scenarios. Using an uncertainty factor of 3, a critical acute and chronic NOAEL of 0.08 mg/kg was estimated. In both the acute and chronic cases, USEPA applied an uncertainty factor of 100 to the LOAEL (10-fold for intrahuman and and 10-fold for interspecies variability, but no factor to account for the lack of a NOAEL) to generate an acute RfD of 0.0025 mg/kg (2.5 µg/kg).

DPR set a critical acute LED_{05} of 0.01 mg/kg based on abnormal chewing behavior in rats at a LOEL of 0.1 mg/kg (*i.e.*, 40% of the USEPA LOAEL concentration). Uncertainties regarding this designation were discussed above. Application of the 100-fold uncertainty factor to this value led to an acute oral RfD of 0.1 µg/kg. The 25-fold difference between acute RfDs from the two agencies was due (1) to selection of different endpoints (plasma cholinesterase in dogs at a

LOAEL of 0.25 mg/kg by USEPA *vs.* abnormal chewing behavior in rats at a LOEL of 0.1 mg/kg by DPR) and (2) to the lack of a LOAEL-to-NOAEL uncertainty factor in USEPA's calculation (DPR calculated an LED_{05} from the LOEL). However, USEPA also calculated an acute Population Adjusted Dose (aPAD) of 0.00025 mg/kg (0.25 µg/kg), which used an additional 10x uncertainty factor to account both for the LOAEL-to-NOAEL extrapolation and for an FQPA factor based on the evidence for male reproductive system toxicity. This value was used in the USEPA dietary risk evaluation. Even with the additional factor, the USEPA aPAD was 2.5-fold higher than the DPR RfD.

DPR set a critical subchronic / chronic NOEL of 0.1 mg/kg based on male reproductive toxicity and suppression of body weight gain in rats at a LOEL of 0.2 mg/kg/day. Application of the 100-fold uncertainty factor to this value led to a seasonal / annual RfD of 1 µg/kg/day, 2.5-fold lower than USEPA's chronic value. The difference between the RfDs generated by the two agencies resided almost solely in the lack of a LOAEL-to-NOAEL extrapolation in USEPA's calculation, as the LOELs in the two critical studies were similar (0.25 mg/kg/day in the USEPA critical study, 0.2 mg/kg/day in the DPR critical study). However, as with the acute value, USEPA also calculated an acute Population Adjusted Dose of 0.00025 mg/kg (0.25 µg/kg), which used an additional uncertainty factor to account both for the LOAEL-to-NOAEL extrapolation and for an FQPA factor based on the evidence for male reproductive system toxicity.

Like DPR, USEPA used their acute and chronic RfDs to calculate risk by the dermal route, as well as by the oral route. Unlike DPR, USEPA did not calculate a separate inhalation RfC value, opting instead to use the oral systemic value.

VI. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

The Food Quality Protection Act of 1996 mandated the USEPA to "upgrade its risk assessment process as part of the tolerance setting procedures" (USEPA, 1997a and b). The improvements to risk assessment were based on recommendations made in the 1993 National Academy of Sciences report, "Pesticides in the Diets of Infants and Children" (NAS, 1993). The Act required an explicit finding that tolerances are safe for children. USEPA was required to use an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data, unless USEPA determined, based on reliable data, that a different margin would be safe. In addition, the USEPA must consider available information on: 1) aggregate exposure from all non-occupational sources; 2) effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity; 3) the effects of *in utero* exposure; and 4) the potential for endocrine disrupting effects. A final risk assessment on carbofuran is not yet available from the USEPA. It is thus unknown how that agency will handle the issue of the safety of present tolerances.

Aggregate exposure. The evidence from the exposure assessment (DPR, 2006) suggests a potential for aggregate exposure, since carbofuran or 3-OH-carbofuran are predicted in the air and, to some extent, in food. However, as suggested above in section IV.C.6, both exposure routes were associated with acute MOEs that were already below the health-protective benchmarks of 10 or 100 necessitated by the relevant human or animal toxicity studies, respectively. It was thus unnecessary to calculate aggregate risk values, as they would not add significantly to the overall assessment. Chronic aggregate exposure was not considered likely because chronic exposure was not expected by any route except for the dietary.

Cumulative exposure. USEPA is currently evaluating the potential for cumulative exposure to carbamate pesticides. We will await the outcome of that evaluation before rendering a judgement on cumulative risk.

In utero effects. As noted in the study by Jayatunga *et al.* (1998a), exposure of pregnant Wistar rats to carbofuran at maternal doses as low as 0.4 mg/kg/day during the first 5 days of gestation resulted in the termination of pregnancy. Even so, neuro-behavioral effects were noted in the dams at a lower dose of 0.2 mg/kg/day, resulting in an LED_{05} of 0.01 mg/kg/day. This was considered to be protective against the possibility of spontaneous early term abortion.

In a separate study, Pant *et al. (*1997) showed that exposure of fetal Druckrey rats throughout pregnancy to carbofuran (0.4 mg/kg/day and above) resulted in lowered sperm counts, increased numbers of abnormal sperm, and altered testicular enzyme activities in male offspring. These measurements were conducted 90 days after termination of exposure. Similar results were seen in 90-day old males if carbofuran exposure occurred during the day 0-21 lactation period (*i.e.*, the sperm measurements were carried out 69 days after the end of exposure). Maternal toxicity was not noted in the Pant *et al. (*1997) study. These results, reminiscent of the testicular and epididymal toxicity detected in adult rats following exposure to 0.2 mg/kg/day for 60 days, indicate that oral carbofuran exposure to pregnant or lactating mothers may pose a risk to fetuses or young animals. They should be considered when evaluating the need for additional uncertainty factors for carbofuran.

Endocrine effects. The mechanisms by which carbofuran disrupts pregnancies or induces testicular toxicity are unknown, though it remains possible that endocrine pathways are involved. Nonetheless, the extent of endocrine involvement, if any, in such effects should be approached with specifically designed studies.

VII. REFERENCE DOSES AND CONCENTRATIONS

A. REFERENCE DOSES (RfDs) - oral exposures

Oral doses of carbofuran below a calculated reference dose (RfD) are considered unlikely to pose a risk to human health. RfDs were calculated for acute, seasonal and annual (s/a) oral exposure scenarios by dividing the critical oral NOEL by an uncertainty factor of 100. All of the uncertainties that accompanied selection of this endpoint, including the use of values derived from oral gavage studies to model what were likely to be more gradual exposures and the necessity of calculating an appropriate acute LED value due to the absence of a critical acute NOEL, were equally applicable to this calculation (see section V.A.1.a.). Potential exposures sustained under occupational scenarios, either by the dermal or inhalation routes, were not considered for this analysis. The RfDs calculated below were considered most relevant to the general population exposed through the diet.

RfD = critical oral NOEL or LED ÷ 100

critical acute oral LED_{05} = 0.01 mg/kg
RfD_{acute} = 0.01 mg/kg ÷ 100 = 0.0001 mg/kg = **0.1 µg/kg**

critical subchronic & chronic oral NOEL = 0.1 mg/kg/day
$RfD_{s/a}$ = 0.1 mg/kg/day ÷ 100 = 0.001 mg/kg/day = **1 µg/kg/day**

In Table VII-1, the calculated oral RfDs for carbofuran are compared with the anticipated dietary exposure ranges for the various DEEM subpopulations. Acute dietary exposures calculated using the point estimate and the Monte Carlo approaches notably exceeded the RfD_{acute}. In contrast, chronic dietary exposure estimates were less than the $RfD_{s/a.}$

Table VII-1. Oral reference doses (RfDs) for carbofuran

Exposure time and species	Endpoint	LOEL and NOEL (or ENOEL)	RfD	Anticipated exposures
Acute **rat gavage developmental study, gestation days 6-15 (WARF, 1978a)**	chewing behavior	**LOEL** 0.1 mg/kg	0.1 µg/kg	**dietary, 97.5th percentile, PE** [1] 0.447 - 1.624 µg/kg/day
		LED_{05} 0.01 mg/kg		**dietary, 97.5th percentile, MC** [1] 0.164 - 0.616 µg/kg/day
Seasonal **rat gavage 60-day study (Pant *et al.*, 1995)**	male reproductive toxicity, weight decrements	**LOEL** 0.2 mg/kg/day **NOEL** 0.1 mg/kg/day	1 µg/kg/day	**dietary (chronic)** [1] 0.062 - 0.234 µg/kg/day
Annual **rat gavage 60-day study (Pant *et al.*, 1995)**	male reproductive toxicity, weight decrements	**LOEL** 0.2 mg/kg/day **NOEL** 0.1 mg/kg/day	1 µg/kg/day	**dietary (chronic)** [1] 0.062 - 0.234 µg/kg/day

[1] PE, point estimate; MC, Monte Carlo estimate. The dietary subpopulations examined are those covered in the DEEM dietary analysis. The dietary exposure values were taken from Table IV-7. The range of exposures at the 99th percentile, as predicted by point estimate analysis was 0.610 - 2.113 µg/kg/day. At the 99.9th percentile, the pointe estimate range was 0.615 - 3.558 µg/kg/day. The range of exposures at the 99th percentile, as predicted by Monte Carlo analysis, was 0.212 - 1.905 µg/kg/day. At the 99.9th percentile, the Monte Carlo range was 0.281 - 1.778 µg/kg/day.

B. REFERENCE CONCENTRATIONS (RfCs) - inhalation exposures

Air concentrations of carbofuran below a calculated reference concentration (RfC) are considered unlikely to pose a risk to human health in the general population. RfCs were calculated for acute and seasonal / annual inhalation exposures in the following manner:

1. Human equivalent NOELs were calculated from the critical oral NOEL or LED by dividing the appropriate value by the respiratory rate for humans (using the adult respiratory rates of 0.045 m^3/kg/hr or 0.28 m^3/kg/day or the infant rates of 0.25 m^3/kg/hr or 0.59 m^3/kg/day, as appropriate - see Table IV-4 for details), then multiplying by the inhalation absorption factor (for carbofuran, the AF=1, equivalent to 100% absorption):

$$\text{human inhalation NOEL } (mg/m^3) = \frac{\text{oral NOEL or } LED_{05} \text{ (mg/kg)}}{\text{respiratory rate}} \times \text{AF (=1)}$$

2. RfCs were then calculated by dividing the human inhalation NOEL by an uncertainty factor of 100 (to account for inter- and intraspecies variation in sensitivity):

$$\text{RfC } (mg/m^3) = \frac{\text{human inhalation NOEL } (mg/m^3)}{\text{uncertainty factor of 100}}$$

For **acute** inhalation exposures, the critical LED_{05} was 0.01 mg/kg. The resultant calculations are:

Infants - 1-hr exposures

acute human inhalation LED_{05} (mg/m^3) = $\frac{0.01\ mg/kg \times 1}{0.25\ m^3/kg/hr}$ = 0.040 mg/m^3

1-hr RfC_{acute} (mg/m^3) = $\frac{0.040\ mg/m^3}{100}$ = **0.4 µg/m³**

Infants - 24-hr exposures

acute human inhalation LED_{05} (mg/m^3) = $\frac{0.01\ mg/kg \times 1}{0.59\ m^3/kg/day}$ = 0.017 mg/m^3

24-hr RfC_{acute} (mg/m^3) = $\frac{0.017\ mg/m^3}{100}$ = **0.17 µg/m³**

Adults - 1-hr exposures

acute human inhalation LED_{05} (mg/m^3) = $\frac{0.01\ mg/kg \times 1}{0.045\ m^3/kg/hr}$ = 0.222 mg/m^3

1-hr RfC_{acute} (mg/m^3) = $\frac{0.222\ mg/m^3}{100}$ = **2.22 µg/m³**

Adults - 24-hr exposures

acute human inhalation LED_{05} (mg/m^3) = $\frac{0.01\ mg/kg \times 1}{0.28\ m^3/kg/day}$ = 0.036 mg/m^3

24-hr RfC_{acute} (mg/m^3) = $\frac{0.036\ mg/m^3}{100}$ = **0.36 µg/m³**

For **seasonal** and **annual (s/a)** inhalation exposures, the critical NOEL was 0.1 mg/kg. The resultant calculations are:

Infants

s/a human inhalation NOEL (mg/m^3) = $\frac{0.1\ mg/kg \times 1}{0.59\ m^3/kg/day}$ = 0.17 mg/m^3/day

$RfC_{s/a}$ (mg/m^3) = $\frac{0.17\ mg/m^3}{100}$ = **1.7 µg/m³**

Adults

s/a human inhalation NOEL (mg/m^3) = $\frac{0.1\ mg/kg \times 1}{0.28\ m^3/kg/day}$ = 0.36 mg/m^3/day

$RfC_{s/a}$ (mg/m^3) = $\frac{0.36\ mg/m^3}{100}$ = **3.6 µg/m³**

The calculated RfCs for carbofuran are summarized in Table VII-2. They are compared with the anticipated air level ranges under ambient and application site scenarios to residents and bystanders. For acute scenarios, the 1-hr and 24-hr application site exposures exceeded the RfCs established for infants. The 24-hr application site exposures also exceeded the adult 24-hr RfC, while the 1-hr application site exposure level was equal to the 1-hr adult RfC. Ambient

exposures did not exceed the infant or adult RfCs under any exposure duration. Occupational scenarios were not considered for this analysis.

Table VII-2. Reference air concentrations (RfCs) for carbofuran

Exposure time and species	Endpoint	LOEL and NOEL or LED	RfC (reference air concentration)	Anticipated air concentrations [1]
Acute **rat gavage developmental study, gestation days 6-15 (WARF, 1978a)**	chewing behavior	**LOEL** 0.1 mg/kg/day **LED_{05}** 0.01 mg/kg/day	**infants** - 1-hr 0.4 µg/m^3 **infants** - 24-hr 0.17 µg/m^3 **adults** - 1-hr 2.22 µg/m^3 **adults** - 24-hr 0.36 µg/m^3	**ambient** (24-hr) [2] 0.0024-0.118 µg/m^3 **application site** (1-hr) 2.2 µg/m^3 **application site** (24-hr) 0.77 µg/m^3
Seasonal **rat gavage 60-day study (Pant *et al.*, 1995)**	male reproductive toxicity, weight decrements	**LOEL** 0.2 mg/kg/day **NOEL** 0.1 mg/kg/day	**infants** 1.7 µg/m^3 **adults** 3.6 µg/m^3	**ambient** 0.0007-0.033 µg/m^3
Annual **rat gavage 60-day study (Pant *et al.*, 1995)**	male reproductive toxicity, weight decrements	**LOEL** 0.2 mg/kg/day **NOEL** 0.1 mg/kg/day	**infants** 1.7 µg/m^3 **adults** 3.6 µg/m^3	**ambient** 0.0002-0.006 µg/m^3

[1] Ambient air levels appear in Table IV-3. The acute levels are the 95% percentile of the measurements taken. The seasonal levels are the mean of the measurements taken. The annual levels are the mean x (2 months / 12 months) for the high value (from Imperial County) or the mean x (4 months / 12 months) for the low value (from Sacramento County). These latter factor represents the number of months per year of high usage in Imperial Sacramento and Counties, where the high and low values originated, respectively. Application site air levels, for which only acute levels were available, appear in Table IV-4.

[2] The time length value, either 1-hr or 24-hr, appearing in parentheses next to the acute air exposure scenarios in the far right-hand column (ambient or application site) refers the reader to the RfC value appearing in the mid-right column most relevant to the expressed air concentrations. Thus the 1-hr application site concentration should be compared to the 1-hr RfCs (infant or adult) and the 24-hr ambient and application site concentrations should be compared to the appropriate 24-hr RfCs.

Note: The "24-hr" acute ambient air concentrations actually include both 24-hr values (Imperial County) and 1-week values (Sacramento County), which were combined under the 24-hr rubric because it was assumed that the default breathing rates over a 24-hr period would equal those over a 1-week period. Consequently, the air levels measured under both time periods were relevant to the 24-hr ambient RfC value.

VIII. TOLERANCE ASSESSMENT

A tolerance is the legal maximum residue concentration of a pesticide, which may exist in or on a raw agricultural commodity or processed food. USEPA is reponsible under the Federal Food, Drug and Cosmetic Act (FFDCA) for setting tolerances for pesticide residues (Section 408). The tolerances are established at levels necessary for the maximum application rate and frequency, and are not expected to produce deleterious health effects in humans from chronic dietary exposure (USEPA, 1991).

The data requirements for the registration of pesticides and for establishment of tolerances include: (1) residue chemistry (including measured residue levels from field studies), (2) environmental fate, (3) toxicology, (4) product performance (*i.e.*, efficacy), and (5) product chemistry. The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications and the proposed formulations (USEPA, 1982).

In 1996, the Food Quality Protection Act (FQPA) amended the overall regulation of pesticide residues under FIFRA and FFDCA (USEPA, 1997a). Significantly, the Delaney Clause, which prohibited residues of cancer-causing pesticides in processed foods, was removed. However, FQPA requires scientific evidence to show that tolerances are safe for children. USEPA must consider applying an additional uncertainty factor of up to 10-fold to take into account potential pre- and post-natal developmental toxicity and completeness of the database.

FQPA also requires USEPA to reassess existing tolerances and tolerance exemptions for active and inert ingredients by 2006 (USEPA, 1997b). Tolerance reassessments had previously been executed as part of USEPA's re-registration and Special Review processes. All label-use commodities are evaluated using a tiered approach similar to that used for the general dietary assessments.

In California, Assembly Bill 2161 (The Food Safety Act) requires DPR to "conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides" (Bronzan and Jones, 1989). In situations whereby "any pesticide represents a dietary risk that is deleterious to health of humans, the DPR shall prohibit or take action to modify that use or modify the tolerance".

A. ACUTE EXPOSURE

A separate acute tolerance assessment was conducted for each "high-contributor" commodity (*i.e.*, those commodities providing greater than 5% of the total carbofuran + 3-OH-carbofuran consumption in the DEEM Tier II point estimate). The DEEM dietary exposure software and the USDA Continuing Survey of Food Intakes of Individuals 1994-1998 (CSFII) were used in this assessment. The acute tolerance assessment did not address simultaneous consumption of multiple commodities at tolerance levels. The probability of consuming multiple commodities at such levels significantly decreases as the number of commodities included in the assessment increases. Consumption of even two commodities at tolerance was considered unlikely.

The range of exposure and MOE values at the 97.5th exposure percentile for each analyzed commodity is shown in Table VIII-1. The consumption patterns of a given population subgroup is better represented when the survey sample size is large (*i.e.*, >100 user days). Those subgroup-commodity pairs with less than 25 user days were excluded from the analysis due to the high uncertainty associated with the consumption data. Several subpopulation / commodity pairs were excluded from the tolerance analysis based on this parameter (see footnote 3, Table VIII-1).

MOEs of less than 100 were indicated for every commodity and population group examined,

indicating a health concern in each case. Squash, with its high projected exposures (1.480 - 17.288 µg/kg/day) and high tolerance (0.6 ppm) resulted in very low MOEs (<1 - 6) at tolerance. Similarly low MOEs for grapes-juice were more consumption-driven, as it exhibited a lower tolerance (0.2 ppm).

B. CHRONIC EXPOSURE

A chronic exposure assessment using residue levels set to the established carbofuran tolerances was not attempted. It was considered improbable that single or multiple commodities containing pesticide levels at tolerance would be consumed habitually. This conclusion was supported by data from both the federal and DPR pesticide monitoring programs which indicated that less than 1% of all sampled commodities contained residue levels at or above the established tolerance (DPR, 1997).

Table VIII-1. Acute dietary risk estimates for carbofuran + 3-OH-carbofuran residues for high contributing commodities (>5%) at the tolerance level; 97.5th percentile user days

Commodity	Range of Exposures [1] (µg/kg/day)	Range of MOEs [2, 3]	Tolerance [4] (ppm)
Cucumbers	0.306 - 1.454	6 - 32	0.2 [5]
Bananas	0.357 - 1.782	5 - 27	0.1
Corn / sugar / hfcs	0.228 - 1.904	5 - 43	0.1 [5,6]
Wheat grain	0.341 - 1.101	9 - 29	0.1 [5]
Grapes-juice	1.355 - 7.293	1 - 7	0.2 [5,7]
Squash	1.480 - 17.288	<1 - 6	0.6 [5]
Sunflower seeds	0.618 - 3.976	2 - 16	0.5 [5]

[1] An acute tolerance assessment was conducted for carbofuran + 3-OH-carbofuran residues on each commodity which registered higher than 5% dietary contribution in the Tier II DEEM point estimate. The carbofuran + 3-OH-carbofuran residue level for each commodity was set at the tolerance. The DEEM program was used with the following input parameters: (1) USDA CSFII 1994-1998, and (2) an acute LED_{05} of 0.01 mg/kg (chewing behavior in the rat at a low dose tested of 0.1 mg/kg [WARF, 1978a]). The acute dietary exposure was calculated at the 97.5th percentile of user days for all 19 population subgroups examined in the dietary assessment.

[2] The MOE (margin of exposure) is defined as NOEL / acute dietary intake. The number of user days ranged between 25 and 39,967.

[3] The same 19 subpopulations were considered as for the dietary assessment (sections IV.B.5. and IV.C.5.). The following subgroups had less than 25 user days and were not included in the tolerance assessment: females 13+ / preg. / not lactating (squash, bananas, grapes-juice, sunflower seeds); females 13+ / lactating (squash, cucumbers, bananas, grapes-juice, sunflower seeds); nursing infants <1 yr (cucumbers, sunflower seeds); non-hispanic blacks, non-hispanic whites, all infants, non-nursing infants <1 yr, children 1-2 yr (sunflower seeds).

[4] Tolerances were listed in the Code of Federal Regulations 40, July 1, 2004, p. 390.

[5] Carbamate-only tolerance (*i.e.*, does not include phenolic metabolites).

[6] Tolerance established on corn grain.

[7] Tolerance established on grapes.

IX. CONCLUSIONS

A human health risk characterization was carried out for carbofuran. It included acute, seasonal and chronic exposure scenarios for the following categories: occupational (dermal and inhalation exposures for handlers and fieldworkers), residents / bystanders (inhalation exposures under ambient and application site scenarios), and dietary (19 different subpopulations). Laboratory investigations indicated the potential for toxicity under acute, seasonal and annual exposure scenarios. Cholinergic toxicity was a concern particularly under acute exposure scenarios, though longer exposures may also present problems. One human study demonstrated toxicity by the dermal route, though this study was unacceptable for regulatory purposes. Toxicity to the male reproductive system, which occurred in rats after oral exposure, was a seasonal and annual exposure concern, though the mechanism was unknown. Impacts of short oral exposures on pregnancy outcome were also noted. Because all of the critical LEDs and NOELs were based on laboratory animal studies, a margin of exposure (MOE) of 100 was considered sufficiently protective of human health. As noted below, many exposure scenarios resulted in MOEs lower than this value.

Critical NOELs and LEDs. A critical acute LED_{05} of 0.01 mg/kg was used in this document to characterize acute risk after acute oral, dermal and inhalation exposure to carbofuran. It was calculated using benchmark dose methodology from a CD rat oral developmental toxicity study. Statistically significant, dose-dependent induction of chewing behavior in pregnant dams was observed at doses as low as the low dose of 0.1 mg/kg.

The critical subchronic oral NOEL was set at 0.1 mg/kg/day based on testicular toxicity and suppression of body weight gain in Druckrey rats in a 60-day study. This NOEL was also used to evaluate subchronic dermal and inhalation exposure, as well as oral exposure.

The critical chronic oral NOEL was also set at 0.1 mg/kg/day based on testicular toxicity and suppression of body weight gain in Druckrey rats in the same 60-day study as was used for determination of the subchronic value. This NOEL was also used to evaluate chronic oral exposure and subchronic dermal exposure. A subchronic study was used because the lowest chronic NOEL, 0.3 mg/kg/day, was not only higher than the subchronic value, but also based partly on the same endpoint, testicular toxicity.

Risk characterization. *Handlers.* Dermal and inhalation exposures to handlers were estimated using the Pesticide Handlers Exposure Database (PHED), a surrogate approach. Five different carbofuran handler categories were examined: groundboom, aerial, chemigation, low-pressure handwand and dip/slurry.

The dermal acute absorbed daily dosages (acute ADDs) for handlers ranged between 0.002 and 6.36 mg/kg/day, generating acute dermal MOEs of <1-5. The inhalation acute ADDs ranged between 0.00003 and 0.041 mg/kg/day, generating acute inhalation MOEs of <1-333.

The dermal seasonal average daily dosages (SADDs) for handlers ranged between 0.0006 and 2.12 mg/kg/day, generating seasonal dermal MOEs of <1-167. The inhalation SADDs ranged between 0.00002 and 0.016 mg/kg/day, generating seasonal inhalation MOEs of 6-5000.

The annual dermal average daily dosages (AADDs) for handlers ranged between 0.0001 and 0.354 mg/kg/day, generating annual dermal MOEs of <1-1000. The inhalation ADDs ranged between 0.00001 and 0.003 mg/kg/day, generating annual inhalation MOEs of 33-10,000.

Fieldworkers. Fieldworker exposures were predicted to occur only upon reentry into treated fields and only by the dermal route. Three scenarios, scouting cotton, scouting alfalfa and scouting potatoes, were examined as plausible sources of dermal contact to fieldworkers.

Acute ADDs for all of these activities ranged between 0.007-0.099 mg/kg/day. These exposures generated acute MOEs of <1-1. SADDs ranged between 0.0009-0.070 mg/kg/day, generating seasonal MOEs of 1-111. AADDs ranged between 0.0001 and 0.012 mg/kg/day, generating annual MOEs of 8-1000.

General public, ambient air. Inhalation exposure of the general public to carbofuran was predicted via the ambient air, *i.e.*, air distal to an application site that was not associated with a particular application. Ambient air estimates were based on measurements in Imperial County and Sacramento County. Acute ADDs ranged between 0.0014 and 0.070 µg/kg/day for infants and between 0.0007 and 0.034 µg/kg/day for adults. These estimates generated MOE values between 143 and 7143 for infants and 294 and 14,286 for adults. SADDs ranged between 0.0004 and 0.020 µg/kg/day (infants) and between 0.0002 and 0.010 µg/kg/day (adults), resulting in MOEs of 5000-250,000 and 10,000-500,000, respectively. AADDs ranged between 0.0001 and 0.003 µg/kg/day (infants) and between 0.00007 and 0.002 µg/kg/day (adults), resulting in MOEs of 50,000-1,000,000.

General public, application site (bystander) air. Inhalation exposure of the general public was also predicted via application site air, *i.e.*, air close to an application site that was associated with a particular application. Application site estimates were based on air monitoring 20 meters west of an Imperial County alfalfa field in 1993. They were associated with a groundboom application for 1 hour at a rate of 1 lb ai/acre.

Acute 1-hr ADDs were estimated at 0.550 µg/kg/hr in infants and 0.099 µg/kg/hr in adults, generating 1-hr MOEs of 18 and 101, respectively. Acute 24-hr ADDs were estimated at 0.454 in infants and 0.216 in adults, generating 24-hr MOEs of 22 and 46, respectively. Seasonal and annual exposures were not estimated because application site air levels were expected to approach ambient levels within a few days of the application.

Dietary exposure and risk. A dietary exposure and risk evaluation was conducted for 19 subpopulations, and included all 26 commodities for which carbofuran tolerances exist, in addition to drinking water. Exposure to carbofuran's most toxic degradate, 3-OH-carbofuran, was also accounted for in the dietary analysis. Acute and chronic risks were estimated using the DEEM package.

A tiered approach was used to estimate acute dietary exposure. For tiers 1-3, point estimates were established for each food group. Such a "deterministic" approach employed the tolerance (Tier 1), the highest measured residue value or LOD (Tier 2), and the mean residue value (Tier 3) to estimate residues for individual food groups. Tier 4 comprised the distributional (Monte Carlo) approach. Monte Carlo was used to refine the assessment by taking into account the distribution of the residue values for a particular commodity, rather than relying on a single point estimate. Only data from Tiers 2 and 4 were expressed in the current assessment, as Tiers 1 and 3 were not considered to contribute substantially to the analysis.

The lowest MOEs were associated with infants and children, as predicted by their relatively higher exposure values. For the Tier 2 (point estimate) analysis, MOEs at the 97.5th user day percentile ranged between 6 (children 1-2 yr) and 22 (females 13+ preg./not lactating). At the 99th percentile, point estimate MOEs ranged between 4 and 16. At the 99.9th percentile, point estimate MOEs ranged between 2 and 16. For the Tier 4 (distributional) analysis, MOEs at the 97.5th user day percentile ranged between 16 (non-nursing infants <1 yr) and 60 (adults 50+). At the 99th percentile, the distributional MOEs ranged between 11 and 47. At the 99.9th percentile, the distributional MOEs ranged between 5 and 35. As the MOEs for the acute dietary analysis fell well below the benchmark of 100 for both the Tier 2 and Tier 4 analyses, an acute dietary health concern was indicated.

The chronic dietary analysis produced lower exposure values and utilized a 10-fold higher critical NOEL. Correspondingly, the chronic MOEs were notable higher, 427 - 1623. A chronic dietary health concern was, therefore, not indicated for carbofuran.

Reference doses (RfDs). Reference doses for potential oral exposures to the general population were calculated by dividing the critical acute oral LED_{05} or the critical subchronic oral NOEL by an uncertainty factor of 100 to account for possible intra- and interspecies variations in sensitivity. The resulting oral RfD_{acute} was 0.1 µg/kg and the $RfD_{s/a}$ was 1 µg/kg/day. The predicted acute dietary exposure for each of the examined subpopulations exceeded the RfD_{acute} even when the distributional (Monte Carlo) refinement was used to estimate exposure. Conversely, chronic dietary exposures did not exceed the $RfD_{s/a}$ (the DEEM dietary exposure module did not estimate seasonal dietary exposures). Dermal and inhalation exposures sustained under occupational scenarios were not considered for this analysis.

Reference air concentrations (RfCs). In the absence of appropriate inhalation toxicity studies, RfC values for the general population were based on the critical oral acute and subchronic studies. Consequently, they required both an uncertainty factor of 100 to ensure health protection and the use of default respiratory rate values relevant to infants and adults. The resultant 1-hr acute RfCs were 0.4 and 2.22 µg/kg for infants and adults, respectively, while the 24-hr acute RfCs were 0.17 and 0.36 $\mu g/m^3$. The seasonal / annual RfCs were 1.7 and 3.6 $\mu g/m^3$ for infants and adults. For acute scenarios, both the 1-hr and 24-hr application site exposures exceeded the relevant infant RfCs. The 24-hr application site exposures also exceeded the adult 24-hr RfC, while the 1-hr application site exposure level was equal to the 1-hr adult RfC level. Ambient exposures did not exceed the infant or adult RfCs under any exposure duration. Inhalation exposures sustained under occupational scenarios were not considered for this analysis.

Risk appraisal. There was substantial uncertainty relating both to the toxicologic assessment and to the exposure assessment aspects of this risk characterization. This was due to the considerable number of poorly documented assumptions that underlaid the requisite determinations.

X. REFERENCES

Abdel-Aal, Y.A.I. and T.Y. Helal. 1980. Relative toxicity and anticholinesterase activity of phosfolan and carbofuran to four rodent species. *Intern. Pest Control* **22**:40-41

Ahdaya, S.M., R.J. Monroe and F.E. Guthrie. 1981. Absorption and distribution of intubated insecticides in fasted mice. *Pesticide Biochem. Physiol.* **16**:38-46

Alvarez, M. 1989. Analytical support of carbofuran vapor pressure determination. Laboratory study #078AF88121, DPR Vol. #254-133, Rec. #72981

Amer, S.M., E.I. Aboul-Ela and K.M. EI-Sherbeny. 1997. Induction of micronuclei in mouse bone-marrow by the carbarnate insecticide carbofuran. *Egypt. J. Pharm. Sci.* **38**:487-494

Arnold, J.D. 1977. Comparison of cholinesterase inhibition and effects of Furadan 4F and FMC 35001 4 EC. Quincy Res. Ctr. study #ACT 152.03. DPR Vol. #254-171, Rec. #182335

Baban, NX, D.L. Nunley, A.S. Borges and T.M. Roy. 1998. Human sequelae of severe carbarnate poisoning. *Tennessee Medicine*, pp. 103-106, March 1998

Bailey, H.C., C. DiGiorgio, K. Kroll, J. Miller, D.E. Hinton and G. Starrett. 1996. Development of procedures for identifying pesticide toxicity in ambient waters: carbofuran, diazinon, chlorpyrifos. *Environ. Toxicol. Chem.* **15**:837-845

Baligar, P.N. and B.B. Kaliwal. 2003. Temporal effect of carbofuran, a carbamate insecticide, in the interruption of estrous cycle and follicular toxicity in female Swiss albino mice. *Bull Environ. Contam. Toxicol.* **71**:422-428

Barnett, J.B., J.M. Spyker-Cranmer, D.L. Avery and A.M. Hoberman. 1980. Immunocompetence over the lifespan of mice exposed in utero to carbofuran or diazinon: 1. Changes in serum immunoglobulin concentrations. *J. Environ. Path. Toxicol.* **4**:53-63

Baron, R.L. 1991. Carbamate insecticides. in: Handbook of Pesticide Toxicology, Volume 3 (ed. by W.J. Hayes, Jr. & E.R. Laws, Jr.). Academic Press, Inc. pp. 1125-1189

Bartow, T.A., G.A. Lawrence, U.A. Pillai, H.R. Ferrington, B.K. Shipp and P.W. Ferguson. 1994. Comparative in vitro hepatic and pulmonary metabolism of carbofuran. *The Toxicologist* **14**:387 (a meeting abstract)

Bio/dynamics. 1982. An acute dietary pilot study of carbofuran in mice. B/d project #77-1763; ACT 128.22. DPR Vol. #254-136, Record #87709

Blevins, R.D., W. Lijinsky and J.D. Regan. 1977. Nitrosated methylcarbamate insecticides: effect on the DNA of human cells. *Mutation Research* **44**:1-7

Bonner, M.R., W.J. Lee, D.P. Sandler, J.A. Hoppin, M. Dosemeci and M.C.R. Alavanja. 2005. Occupational exposure to carbofuran and the incidence of cancer in the Agricultural Health Study. *Environ. Health Persp.* **113**:285-289

Brahmaprakash, G.P., S. Panda, N. Sethunathan. 1987. Relative persistence of hexachlorocyclohexane, methyl parathion, and carbofuran in an alluvial soil under flooded and non-flooded conditionns. *Agricultural Ecosystems and the Environment* **19**:29-39

Bronzan and Jones. 1989. Assembly Bill 2161, Addition to the Food and Agriculture Code SEC

8, section 13060. California Food and Agriculture Code, Sacramento, CA

Canna-Michaelidou, S. and A-S. Nicolaou. 1996. Evaluation of the genotoxicity potential (by Mutatox test) of ten pesticides found as water pollutants in Cyprus. *The Science of the Total Environment* **193**:27-35

Cambon, C., C. Declume and R. Derache. 1979. Effect of the insecticidal carbarnate derivatives (carbofuran, pirimicarb, aldicarb) on the activity of acetylcholinesterase in tissues from pregnant rats and fetuses. *Toxicol. and Appl. Pharmacol.* **49**:203-208

Caro, J.H., A.W. Taylor and H.P. Freeman. 1976. Comparative behavior of dieldrin and carbofuran in the field. *Arch. Environ. Contam.* **3**:437-447

Chauhan, L.K.S., N. Pant, S.K. Gupta and S.P. Srivastava. 2000. Induction of chromosome aberrations, micronucleus formation and sperm abnormalities in mouse following carbofuran exposure. *Mutation Res*. **465**:123-129

Chiron, S., J.A. Torres, A. Fernanadez-Alba, M.F. Alperdurada and D. Barcelo. 1996. Identification of carbofuran and methiocarb and their transformation products in estuarine waters by on-line solid phase extraction liquid chromatograhy-mass spectrometry. *J. Environ. Anal. Chem.* **65**:37-52

Cohen, S.Z. 1996. Pesticides in ground water in the United States: monitoring, modeling, and risks from the U.S. perspective. *Environ. Sci. Health* **B31**:345-352

Courtney, K.D., J.E. Andrews, J. Springer and L. Dalley. 1985. Teratogenic evaluation of the pesticides Baygon, carbofuran, dimethoate and EPN. *J. Environ. Sci. Health* **B20**:373-406

CSE (Cosmopolitan Safety Evaluation). 1979. Acute oral toxicity study (FIFRA-EPA) in rats (author, P.N. Elleman). Study #0180. DPR Volume #254-171, Record #178470

de Saint-Georges-Gridelet, D., A. Leonard and P. Lebrun. 1982. Cytogenetic effects of carbofuran in mammals. *Mutation Res*. **97**:244-245

Dorough, H.W. 1968. Metabolism of furadan (NIA-10242) in rats and houseflies. *J. Agr. Food Chem*. **16**:319-325

DPR. 1997. Residues in Fresh Produce 1994-1997. Pesticide Enforcement Branch, Sacramento, CA http://mitra:8080/3pubs-annreports.htm

DPR. 2002a. Pesticide chemistry, surface water and ground water databases. Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency.

DPR. 2002b. Interim cholinesterase policy. Memo from G. Patterson to J. Gee, P. Leung, K. Pfeifer, and J. Schreider. Medical Toxicology Branch, Dept. of Pesticide Regulation, Cal-EPA. August 2, 2002

DPR. 2002c. DPR dietary exposure assessment. Report by S. Koshlukova, R. Duncan and R. Reed (Health Assessment Group, Medical Toxicology Branch)

DPR. 2006. Estimation of Exposure of Persons in California to Pesticide Products that Contain Carbofuran. Document #HS-1803 (authors: S. Beauvais and J. Johnson), Worker Health and Safety Branch, Dept. of Pesticide Regulation, Cal-EPA. January 6, 2006

DPR. *in draft.* Cholinesterase Inhibition and Its Application in Risk Assessment, report of the Medical Toxicology Branch, Dept. of Pesticide Regulation, Cal-EPA.

Deuel, L.E.Jr., J.D. Price, F.T. Turner and K.W. Brown. 1979. Persistence of carbofuran and its metabolites, 3-keto and 3-hydroxy carbofuran, under flooded rice culture. *J. Environ. Qual.* **8**:23-26

Eisler, R. 1985. Carbofuran Hazards to Fish, Wildlife, and Invertebrates: A Synoptic Review *U.S. Fish and Wildlife Service Biol. Rep.* **85**(1.3) 36 pp.

Ellison, T. 1980. Review and audit of the [IBT] acute aerosol inhalation toxicity study with NIA 10242 50 WP. IBT #N5183. FMC #NCT 162.11. DPR Vol. #254-044 (no Record #)

Erwin, N. 1991. Carbofuran and bird kills: regulation at a snail's pace. *J. Pesticide Reform* **11**:15-17

Extoxnet. 1996, 2001. Pesticide Information Profile: Carbofuran. Extension Toxicology Network. http://ace.ace.orst.edu/info/extoxnet/pips/carbofur.htm

Farm Chemicals Handbook. 2002. Entry for carbofuran. pp. C84-C85

FDRL, Inc. (Food and Drug Research Laboratories, Inc.). 1980a. Acute oral LD_{50} in young adult male and female Sprague-Dawley rats (authors, G. Rucci and P.J. Becci). Study #6540a & 6540b. DPR Vol. #254-171, Record #183333

FDRL, Inc. (Food and Drug Research Laboratories, Inc.). 1980b. Study of cholinesterase activity inhibition by carbofuran in neonate, weanling and adult rats (authors, G. Rucci and P.J. Becci). Study #6337; DPR Vol. #254-171, Record #182334

Ferguson, P.W., S.A. Jewell, R.I. Krieger and O.G. Raabe. 1982. Carbofuran disposition in the rat after aerosol inhalation. *Environ. Toxicol. Chem.* **1**:245-258

Ferguson, P.W., M.S. Dey, S.A. Jewell and R.I Krieger. 1984. Carbofuran metabolism and toxicity in the rat. *Fundamental and Appl. Toxicol*. **4**:14-21

Ferslew, K.E., A.N. Hagardom and W.F. McCormick. 1992. Case report: Poisoning from oral ingestion of carbofuran (Furadan 4F), a cholinesterase-inhibiting carbamate insecticide, and its effects on cholinesterase activity in various biological fluids. *J. Forensic Sci*. **37**:337-344

FMC. 1964. Acute oral administration [of carbofuran and 8 other active ingredients] - rats (author, M.B. Powers, Hazleton Laboratories, Inc.). NIOSH #00067161

FMC. 1967a. Acute aerosol inhalation toxicity study on NIA 10242 50 WP (author, D. Hathaway, IBT Laboratories). NIOSH#00067164

FMC. 1967b. Acute aerosol and acute dust inhalation toxicity studies on NIA 10242 75 WP (author, D. Hathaway, IBT Laboratories). NIOSH #00067166

FMC. 1967c. Acute dust inhalation toxicity study on Furadan Insecticide 75 WP (author, D. Hathaway, IBT Laboratories). NIOSH #00067167

FMC. 1971a. Eye irritation (rabbit) [carbofuran]. No FMC study number provided. DPR Vol. #254-002, Record #022857

FMC. 1971b. Dominant-lethal mutagenicity study [carbofuran] (summary only). NCT. 438.99. DPR Vol. #254-029, Record #939879

FMC. 1973. Determination of carbofuran and 3-hydroxy carbofuran residues in cottonseeds, meats, hulls and cotton plants. (Authors: M.H. Gruenauer, J.M. Shuttleworth, M.J. Stodolka and T.E. Uebler). Project #M-3334. DPR Vol #254-174, Record #203106

FMC. 1976. Oral toxicity study (human) [carbofuran] (summary only). Quincy Research Center. ACT 152.03. DPR Vol. #254-029, Record #46697

FMC. 1979. Acute oral toxicity of Furadan 1 OG in rats. FMC ref. #A79-344. DPR Vol. #254-029, Record #46698

FMC. 1981a. Summaries of acute toxicity studies on Furadan 5 Granules (rat acute oral toxicity study [Record #23157], rabbit acute dermal toxicity study [Record #23155], and rabbit primary dermal irritation study [Record #23156]) and Furadan 10 granules (rat acute oral toxicity study [Record #23153], rabbit acute dermal toxicity study [Record #23152] and rabbit primary dermal irritation study [Record #23154]). DPR Vol. #254-30

FMC. 1981b. Summaries of acute toxicity studies on Furadan 15G (rabbit acute dermal toxicity study [Record #939866], rabbit eye irritation study [Record #939869], rabbit dermal irritation study [Record #939871], and rabbit acute oral toxicity study [Record # not provided]. FMC #A80-399. DPR Vol. #254-025

FMC. 1981c. Determination of carbofuran and 3-hydroxy carbofuran residue levels in products from oil and confectionary sunflower seed processing studies. (author: M.A. Tilka). Project #G078, RAN-023. DPR Vol. #254-048 [Record # not provided]

FMC. 1981d. Determination of carbofuran carbamate residues in oil and confectionary sunflower seeds. (author: M.A. Tilka). Project #G078, RAN-022. DPR Vol. #254-048 [Record # not provided]

FMC. 1983a. Acute oral toxicity of FMC 10242 [technical (E2915) ONP-derived] in rats. FMC Corporation. FMC reference #A83-1101. DPR Vol. #254-130, Record #47756

FMC. 1983b. Acute oral toxicity of FMC 10242 [technical (RHB-11) catechol-derived] in rats. FMC Corporation. FMC reference #A83-1102. DPR Vol. #254-130, Record #47757

FMC. 1984. Summaries of acute toxicity studies on Furadan 4 Flowable (rat acute oral, dermal and inhalation toxicity, and eye and dermal irritation - no DPR Record #s or FMC study #s provided). DPR Vol. #254-048

FMC. 1985a. Seven-day repeated dose dermal toxicity range-finding study in rabbits with FMC 10242 technical (carbofuran). FMC study #A85-1645. DPR Vol. #254-085, Record #60424

FMC. 1985b. Twenty-one day repeated dose dermal toxicity study in rabbits with FMC 10242 technical (carbofuran). FMC study #A85-1678. DPR Vol. #254-086, Record #60425

FMC. 1986. Determination of carbofuran and its carbamate and phenol metabolite residues in/on sugarbeets and sugarbeet tops. (Author: J.W. Stearns). Study #078SBEER06, RAN-0189. DPR Vol. #254-144, Record #89945

FMC. 1992a. Magnitude of the residue of carbofuran and its carbamate and phenolic metabolites in/on sugarbeet tops and roots treated with Furadan 4F insecticide postemergence

or at planting. (Author: G.M. Singer). Study #078SBE91R1. DPR Vol. #254-175, Record #203107

FMC. 1992b. Magnitude of the residue of carbofuran and its carbamate and phenolic metabolites in/on the processed parts of sugarcane treated with Furadan 4F. (Authors: G.M. Singer & N.A. Shevchuk). Study #078SCA90R2. DPR Vol. #254-177, Record #203109

FMC. 1993. Twenty-eight day neurotoxicity range-finding study in rats with carbofuran technical (author, C. Freeman). FMC #A92-3704. DPR Vol. #254-172, Record #178468

FMC. 1994. Carbofuran technical subchronic neurotoxicity screen in rats. FMC study #A92-3705. DPR Vol. #254-170, Record #178009

FMC. 1996. Magnitude of the residue of carbofuran and its carbamate and phenolic metabolites in/on processed parts of coffee treated with Furadan 5G. (Author: M.W. Brooks). Study #078BCF94R1. DPR Vol. #254-182, Record #203114

FMC. 2002. The toxicokinetics of peripheral cholinesterase inhibition from orally administered carbofuran in adult male and female CD rats. FMC study #A2001-5379. DPR Vol. #254-184, Record #203585

FMC. Undated. Skin and eye irritation [carbofuran]. No FMC study number provided. DPR Vol. #254-030, Record #46702

FMC. undated. Acute and subchronic toxicity of carbofuran metabolites. No FMC study number provided. DPR Vol. #254-030. Record #22786, 23158-23164

Getzin, L.W. 1973. Persistence and degradation of carbofuran in soil. *Environ. Entomol.* **2**:461-467

Getzin, L.W. and C.H. Shanks. 1990. Enhanced degradation of carbofuran in Pacific Northwest soils. *J. Environ. Sci. Health* **B25**:433-446

Gupta, R.C. 1994. Carbofuran toxicity. *J. Toxicol. Environ. Health* **43**:383-418

Gupta, R.C., J.T. Goad and W.L. Kadel. 1991a. Carbofuran-induced alterations (*in vivo*) in high-energy phosphates, creatine kinase (CK) and CK isoenzymes. *Arch. Toxicol*. **65**:304-310

Gupta, R.C., J.T. Goad and W.L. Kadel. 1991b. *In vivo* alterations in lactate dehydrogenase (LDH) and LDH isoenzymes (sic) patterns by acute carbofuran intoxication. *Arch. Environ. Contam. Toxicol.* **21**:263-269

Gupta, R.C., J.T. Goad and W.L. Kadel. 1994b. *In vivo* effects of carbofuran on protein, lipid, and lipoproteins in rat liver and serum. *J. Toxicol. Environ. Health* **42**:451 -462

Gupta, R.C., J.T. Goad and W.L. Kadel. 1994c. Cholinergic and noncholinergic changes in skeletal muscles by carbofuran and methyl parathion. *J. Toxicol. Environ. Health* **43**:291-304

Harris, C.R., R.A. Chapman, C. Harris and C.M. Tu. 1984. biodegradation of pesticides in soil: rapid induction of carbamate degrading factors after carbofuran treatment. *J. Environ. Sci. Health* **B19**:1-11

HEFED. 1991. Handbook of Environmental Fate and Exposure Data **3**:73-83

Hirom, P.C., P. Milburn and R.L. Smith. 1972. Species variation in the threshold molecular-weight factor for biliary excretion of organic anions. *Bioch. J.* **129**:1071 -??

Hour, T-C., L. Chen and L-K. Lin. 1998. Comparative investigation on the mutagenicities of organophosphate, phthalimide, pyrethroid and carbarnate insecticides by the Ames and lactarn tests. *Mutagenesis* **13**:157-166

Hussain, M., K. Yoshida, M. Atiemo and D. Johnston. 1990. Occupational exposure of grain farmers to carbofuran. *Arch. Environ. Contam. Toxicol.* **19**:197-204

IRDC. 1979a. Two-year dietary toxicity and carcinogenicity study in rats [carbofuran technical]. International Research and Development Corporation. IRDC #167-115. DPR Vol. #254-096-098, Record #47717-19

IRDC. 1979b. Three generation reproduction study in rats [carbofuran technical]. International Research and Development Corporation. IRDC #167-114. DPR Volume #254-91-93, Record #47712-14

IRDC. 1980a. Two-year dietary toxicity and carcinogenicity study in mice [carbofuran technical]. International Research and Development Corporation. IRDC #167-116. DPR Volume #254-104-108, Record #47725-29

IRDC. 1980b. Teratology study in the rat with carbofuran. International Research and Development Corporation. IRDC #167-155. DPR Volume #254-094, Record #47715

IRDC. 1980c. Pilot teratology study in the rat with carbofuran in the diet. International Research and Development Corporation. IRDC #167-116. Only the summary is available to DPR: DPR Vol. #254-029, Record #939873

IRDC. 1981 a. Teratology and postnatal study in the rat with carbofuran. International Research and Development Corporation. IRDC #167-154. DPR Volume #254-113, Record #50381

IRDC. 1981 b. Teratology study in the rabbit with carbofuran. International Research and Development Corporation. IRDC #167-156. DPR Volume #254-095, Record #47716

Ivie, C.W. and H.W. Dorough. 1968. Furadan-C^{14} metabolism in the lactating cow. *J. Agr. Food Chem.* **16**:849-855

Jayatunga, Y.N.A., C.D. Dangalle and W.D. Ratnasooriya. 1998a. Hazardous effects of carbofuran on pregnancy outcome of rats. *Medical Science Research* **26**:33-37

Jayatunga, Y.N.A., C.D. Dangalle and W.D. Ratnasooriya. 1998b. Effects of mid-term exposure to carbofuran on pregnancy outcome of rats. *Medical Science Research* **26**:679-683

JMPR. 1996. Carbofuran. In: Pesticide Residues in Food - 1996. Toxicological Evaluations, Joint meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group, Rome, 16-25 September 1996). pp. 23-43

Johnson, W.G. and T.L. Lavy. 1995. Organic chemicals in the environment. *J. Environ. Qual.* **24**:487-493

Kitagawa, K., M. Wakakura and S. Ishikawa. 1977. Light microscopic study of endocrine organs of rats treated by carbamate pesticide. *J. Toxicol. Sci.* **2**:53-60

Klys, M., J. Kosun, J. Pach and A. Kamenczak. 1989. Case report: Carbofuran poisoning of pregnant woman and fetus per ingestion. *J. Forensic Sci*. **34**:1413-1416

Knaak, J.B., D.M. Munger, J.F. McCarthy and L.D. Satter. 1970. Metabolism of carbofuran alfalfa residues in the dairy cow. *J. Agr. Food Chem*. **18**:832-837

Kross, B.C., A. Vergara and L.E. Raue. 1992. Toxicity assessment of atrazine, alachlor, and carbofuran and their respective environmental metabolites using Microtox. *J. Toxicol. Environ. Health* **37**:149-159

Kumari, K., R.P. Singh and S.K. Saxena. 1988. Movement of carbofuran (nematicide) in soil columns. *Ecotoxicol. Environ. Saf.* **16**:36-44

Lalah, J.O., S.O. Wandiga and W.C. Dauterman. 1996. Mineralization, volatilization, and degradation of carbofuran in soil samples from Kenya. *Bull. Environ. Contam. Toxicol.* **56**:37-41

Lewis, R.J.Sr. 1996. Sax's Dangerous Properties of Industrial Materials, 9th Edition. Van Nostrand Reinhold. entry for carbofuran, p. 661

Litton Bionetics. 1983a. Mutagenicity evaluation of FMC 10242 in the Ames Salmonella / microsome plate test. FMC #A83-1037. LBI project #20988. DPR Vol. #254-109, Record #47738

Litton Bionetics. 1983b. Mutagenicity evaluation of FMC 10242 lot no. RHB-11 for the sex-linked recessive lethal test in *Drosophila melanogaster*. LBI project #22205. FMC #A83-1060. DPR Vol. #254-109, Record #47744

Marshall, T.C. and H.W. Dorough. 1979. Biliary excretion of carbarnate insecticides in the rat. *Pesticide Biochem. Physiol*. **11**:56-63

MB Res. (MB Research, Inc.). 1979. Test for oral toxicity in rats (author, M.T. Moreno). Project #MB 79-4009. DPR Vol. #154-171, Record #182330

McCalley, N. 1983. The results of tests on the amount of carbofuran residues remaining in or on artichokes including a description of the analytical method used. (Author: N. McCalley). Project #1361.

Merck. 2001. The Merck Index, 13th Edition (senior editor: M.J. O'Neil). Entry for acetone, p. 68

Metcalf, R.L., T.R. Fukuto, C. Collins, K. Borck, S. Abd El-Aziz and C.C. Cassil. 1968. Metabolism of 2,2-dimethyl-2,3-dihydrobenzofuranyl-7 N-methylcarbamate (Furadan) in plants, insects, and mammals. *J. Agr. Food Chem*. **16**:300-311

Microbiological Associates. 1983a. *Salmonella* / mammalian - microsome plate incorporation mutagenicity assay (Ames test). FMC #A83-868. MA #T1921.501. DPR Vol. #254-109, Record #47731

Microbiological Associates. 1983b. *Salmonella* / mammalian - microsome plate incorporation mutagenicity assay (Ames test). FMC#A83-913. MA#T1934.501. DPR Vol. #254-109, Record #47732

Microbiological Associates. 1983c. *Salmonella* / mammalian - microsome plate incorporation mutagenicity assay (Ames test). FMC #A83-948. MA #T1938.501. DPR Vol. #254-109,

Record #47733

Microbiological Associates. 1983d. *Salmonella* / mammalian - microsome plate incorporation mutagenicity assay (Ames test). FMC#A83-949. MA#T1936.501. DPR Vol. #254-109, Record #47734

Microbiological Associates. 1983e. *Salmonella* / mammalian - microsome plate incorporation mutagenicity assay (Ames test). FMC #A83-950. MA #T1935.501. DPR Vol. #254-109, Record #47735

Microbiological Associates. 1983f. *Salmonella* / mammalian - microsome plate incorporation mutagenicity assay (Ames test). FMC #A83-951. MA #T1937.501. DPR Vol. #254-109, Record #47736

Microbiological Associates. 1983g. *Salmonella* / mammalian - microsome plate incorporation mutagenicity assay (Ames test). FMC #A83-973. MA #T1982.501. DPR Vol. #254-109, Record #47737

Microbiological Associates. 1983h. *Salmonella* / mammalian - microsome plate incorporation mutagenicity assay (Ames test). FMC #A83-1063. MA #T2124.501. DPR Vol. #254-109, Record #47739

Microbiological Associates. 1983i. L5178Y TK+/- mouse lymphoma mutagenesis assay. FMC #A83-962 and A83-988. MA #T1982.701. DPR Vol. #254-109, Record #47740

Microbiological Associates. 1983j. L5178Y TK+/- mouse lymphoma mutagenesis assay. FMC #A83-1064. MA #T2124.701. DPR Vol. #254-109, Record #47741

Microbiological Associates. 1983k. Chromosome aberrations in Chinese hamster ovary cells (FMC 10242). FMC #A83-1094. MA #T1982.337. DPR Vol. #254-110, Record #47747

Microbiological Associates. 1983l. Chromosome aberrations in Chinese hamster ovary cells (FMC 10242). FMC #A83-1096. MA #T2124.337. DPR Vol. #254-110, Record #47748

Microbiological Associates. 1983m. Sister chromatid exchange assay in Chinese hamster ovary cells (FMC 10242). FMC #A83-1097. MA #T2124.334001. DPR Vol. #254-110, Record #47755

Microbiological Associates. 1983n. Sister chromatid exchange assay in Chinese hamster ovary cells (FMC 10242). FMC #A83-1095. MA #T1982.334001. DPR Vol. #254-110, Record #47754

Microbiological Associates. 1983o. Activity of FMC 10242 (T1982) in the *in vivo* cytogenetics assay in Sprague-Dawley rats. FMC #A83-972. MA #T1982.102. DPR Vol. #254-109, Record #47745

Microbiological Associates. 1983p. Activity of FMC 10242, E2915-100A (A83-1065) in the subchronic *in vivo* cytogenetics assay in male rats. FMC # A83-1065. MA #T2124.102. DPR Vol. #254-109, Record #47746

Microbiological Associates. 1983q. Unscheduled DNA synthesis in rat primary hepatocytes. FMC # A83-969. MA #T1982.380. DPR Vol. #254-110, Record #47750

Miles, J.R.W., C.M. Tu and C.R. Harris. 1981. A laboratory study of the persistence of

carbofuran and its 3-hydroxy- and 3-keto- metabolites in sterile and natural mineral and organic soils. *J. Environ. Sci. Health* **B16**:409-417

Mineau, P. 1993. The Hazard of Carbofuran to Birds and Other Vertebrate Wildlife Technical Report Series No. 177, Canadian Wildlife Service

Moser, V.C. 1995. Comparisons of the acute effects of cholinesterase inhibitors using a neurobehavioral screening battery in rats. *Neurotoxicology and Teratology* **17(6)**:617-625

Mostafa, I.Y., S.M.A.D. Zayed, M. Farghaly and F. Mahdy. 1992. Bioavailability to rats and toxicity in mice of carbofuran residues bound to faba beans. *J. Environ. Sci. Health* **B27**:399-405

Nelson, J., E.A. MacKinnon, H.F. Mower and L. Wong. 1981. Mutagenicity of *N*-nitroso derivatives of carbofuran and its toxic metabolites. *J. Toxicol. Environ. Health* **7**:519-531

Nicosia, S., N. Carr, D.A. Gonzales and M.K. Orr. 1991. Off-field movement and dissipation of soil-incorporated carbofuran from three commercial rice fields. *J. Environ. Qual.* **20**:532-539

Nostrandt, A.C., J.A. Duncan and S. Padilla. 1993. A modified spectrophotometric method appropriate for measuring cholinesterase activity in tissue from carbaryl-treated animals. *Fund. Appl. Toxiocol.* **21**:196-203

NRCC. 1979. Carbofuran: Criteria for Interpreting the Effects of its Use On Environmental Quality National Research Council Canada, publication #NRCC 16740

OEHHA. 2000. Carbofuran. *in*: Public Health Goals for Chemicals in Drinking Water prepared by the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, September 2000.

Padilla, S. and M.J. Hooper. 1992. Cholinesterase measujrements in tissues from carbamate-treated animals: cautions and recommendations. *Proc. of the USEPA Workshop on Cholinesterase Methodologies*. prepared for: Office of Pesticide Programs, US Environmental Protection Agency. pp. 63-81

Pant, N., A.K. Prasad, S.C. Srivastava, R. Shankar and S.P. Srivastava. 1995. Effect of oral administration of carbofuran on male reproductive system of rat. *Human & Experimental Toxicol.* **14**:889-894

Pant, N., R. Shankar and S.P. Srivastava. 1997. *In utero* and lactational exposure of carbofuran to rats: Effect on testes and sperm. *Human & Experimental Toxicol*. **16**:267-272

Peterson, B., Yougre and C. Walls. 2001. Modeling dietary exposure and special section on modeling aggregate and cumulative exposure. *in*: Handbook of Pesticide Toxicology, vol. 1 (R. Kreiger, ed.). Academic Press, San Diego, CA

Parkin, T.B. and D.R. Shelton. 1994. Modeling environmental effects on enhanced carbofuran degradation. *Pesticide Sci.* **40**:163-168

Pharmaco LSR. 1994. A developmental neurotoxicity study of carbofuran in the rat via dietary administration. Study #93-4506 (FMC study #A93-3746). DPR Volume #254153, Record #138360

Pilinskaya, M.A. and L.S. Stepanova. 1984. Effect of biotransformation of the insecticide

Furadan on its cytogenetic activity *in vivo* and *in vitro*. *Tsitol. Genet*. **18**:16-19

Raha, P. and A.K. Das. 1990. Photodegradation of carbofuran. *Chemosphere* **21**:99-106

Rawlings, N.C., S.J. Cook and D. Waldbillig. 1998. Effects of the pesticides carbofuran, chlorpyrifos, dimethoate, iindane, triallate, trifluralin, 2,4-D, and pentachlorophenol on the metabolic endocrine and reproductive endocrine system in ewes. *J. Toxicol. Environ. Health* **54**:21-36

RCC. 1987a. 13-Week oral toxicity (feeding) study with carbofuran (D1221) in the Dog. Research & Consulting Company AG. Project #077837. DPR Vol. #254-165, Record #175906

RCC. 1987b. 4-Week toxicity (feeding) study with carbofuran (D 1221) in male dogs. Research & Consulting Company AG. Project #087963. DPR Vol. #254-166, Record #175907

Reed, N.M. 2003. Cholinesterase discussion paper (Topic 2B): Neurobehavioral effects and cholinesterase inhibition. Medical Toxicology Branch, Dept. of Pesticide Regulation, California Enviornmental Protection Agency.

Rotaru, G., S. Constantinescu, G. Filipescu and E. Ratea. 1981. Experimental research on chronic poisoning by carbofuran. *La Medicina del Lavoro* **72**:399-403

Sancewicz-Pach, K., B. Groszek, D. Pach and M. Klys. 1997. Acute pesticides (*sic*) poisonings in pregnant women. *Przeglad Lekarski* **54**:741-744

Scow, K.M., R.R. Merica and M. Alexander. 1990. Kinetic analysis of enhanced biodegradation of carbofuran. *J. Agricult. Food Chem.* **38**:908-912

Seiber, J.N., M.P. Catahan and C.R. Barril. 1978. Loss of carbofuran from rice paddy water: chemical and physical factors. *J. Environ. Sci. Health* **B13**:131-148

Shah, P.V., R.J. Monroe and F.E. Guthrie. 1981. Comparative rates of dermal penetration of insecticides in mice. *Toxicol. Appl. Pharmacol*. **59**:414-423

Shah, P.V., H.L. Fisher, N.J. Month, M.R. Sumler and L.L. Hall. 1987. Dermal penetration of carbofuran in young and adult Fischer 344 rats. *J. Toxicol. Environ*. *Health* **22**:207-223

Shain, S.A., J.C. Shaeffer and R. W. Boesel. 1977. The effect of chronic ingestion of selected pesticides upon rat ventral prostate homeostasis. *Toxicol. Appl. Pharmacol.* **40**:115-130

Sharom, M.S., J.R.W. Miles, C.R. Harris and F.L. McEwen. 1980. Behaviour of 12 insecticides in soil and aqueous suspensions of soil and sediment. *Water Res.* **14**:1095-1100

Shibamoto, T., C. Mourer and G. Hall. 1993. Pilot monitoring of two pesticides in air. California Air Resources Board, California Environmental Protection Agency. Report #R-95/581

Singh, N. and N. Sethunathan. 1999. Degradation of carbofuran by and enrichment culture developed from carbofuran-treated *Azolla* plot. *Pesticide Sci.* **55**:740-744

Sobarzo, C. and E. Bustos-Obregon. 2000. Sperm quality in mice acutely treated with parathion. *Asian J. Androl.* **2**:147-150

Soliman, A.A. and L.M. El-Zalabani. 1977. Impairment of Spermatogenesis by organophosphorus pesticides. *Bull. Alex. Fac. Med.* **17**:125-130

Spencer, E.T. 1981. Carbofuran. *in*: Guide to the Chemicals used in Crop Protection (7th edition) Publication 1093, Research Branch, Agriculture Canada

SRI. 1979. *In vitro* microbiological mutagenicity and unscheduled DNA synthesis studies of eighteen pesticides. Contract #68-0102458. DPR Vol. #254-110, Record #47751 (*E. coli* & *B. subtilis*), #47752 (*S. cerevisiae*), #47753 (WI-38)

Stillmeadow, Inc. 1979. Rat acute oral toxicity (author, R.J. Sabol). Project #1121-79. DPR Vol. #24-171, Record #182331

Stillmeadow, Inc. 1981. Acute dermal toxicity study in rabbits, carbofuran technical 96.1% M607210 (author, C.S. Mehta). Study #2142-81. DPR Vol. #254-172, Record # 178469

Szeto, S.Y. and P.M. Price. 1991. Persistence of pesticide residues in mineral and organic soils in the Frasier Valley of British Columbia. *J. Agricult. Food Chem.* **39**:1679-1684

Talebi, K. and C.H. Walker. 1993. A comparative study of carbofuan metabolism in treated and untreated soils. *Pesticide Sci.* **39**:65-69

Tejada, A.W., N.A. Samaniego, T.E. Sanchez and E.D. Magallona. 1988. Fate of ^{14}C-carbofuran in lactating goats. *The Philippine Agriculturist* **71**:149-155

Tobin, J.S. 1970. Carbofuran: a new carbamate insecticide. *J. Occup. Med.* **12**:16-19

Toxigenics. 1982. 14-Day oral toxicity (range finding) study in beagle dogs of carbofuran. Toxigenics study #410-0714. DPR Vol. #254-169, Record #175910

Toxigenics. 1983. One-year chronic oral toxicity study in beagle dogs with carbofuran. Toxigenics study #410-0715. DPR Vol. #254-099-103, Record #47720-24

Turco, R.F. and A. Konopka. 1990. Biodegradation of carbofuran in enhanced and non-enhanced soils. *Soil Biol. Bioch.* **22**:195-201

University of Wisconsin. 1983. *Drosophila* sex-linked recessive lethal assay of 2,3dihydro-2,2-dimethyl-7-benzofuranyl N-methyl carbamate (carbofuran, T-2047). Lab. Project #103c. DPR Vol. #254-109, Record #47742

USDA. 2000-2004. Agricultural Chemical Use Reports - National Agricultural Statistics Service. http://usda.mannlib.cornell.edu/reports/nassr/other/pcu-bb/#vegetables

USEPA. 1982. Pesticide Assessment Guidelines, Subdivision) - Residue Chemistry. Office of Pesticides and Toxic Substances, #EPA-540/9-82-023. United States Environmental Protection Agency

USEPA. 1991. For Your Information - Pesticide Tolerances. Pesticide and Toxic Substances (H7506C), August 1991. United States Environmental Protection Agency

USEPA. 1997a. The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and Federal Food, Drug and Cosmetic Act (FFDCA) as Amended by the Food Quality Protection Act (FQPA) of August 3, 1996. Doc. #730L97001, March 1997. Office of Pesticide Programs, United States Environmental Protection Agency

USEPA. 1997b. Raw and Processed Food Schedule for Pesiticide Tolerance Reassessment. Federal Register 62(149):42020-42030. United States Environmental Protection Agency

USEPA. 2000. Carbofuran Anticipated Residues, Acute and Chronic Dietary Analyses, Chemical 090601. Case #819321. Submission #S575483. DP Barcodes D263393, D263394.

USEPA. 2002. Carbofuran: Receipt of Application for Emergency Exemption. Solicitation of Public Comment, United States Environmental Protection Agency, Docket ID #OPP-2002-0124

USEPA. 2003. Aldicarb, cacodylic acid, carbofuran, *et al.*; Proposed tolerance actions. *Federal Register* **68**:41989-41996 (July 16, 2003)

USEPA. 2005. HED Revised Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) Document (Phase 2). Chemical Number 090601. DP Barcode: D319934. September 1, 2005

Wang, T.C., C.M. Chiou and Y.L. Chang. 1998. Genetic toxicity of *N*-methylcarbamate insecticides and their *N*-nitroso derivatives. *Mutagenicity* **13(4)**:405-408

WARF. 1978a. Teratogenicity of carbofuran in rats. WARF Institute, Inc., Madison, WI. No study date provided. WARF #T-730. DPR Volume #254-138, Record #87711

WARF. 1978b. Teratogenicity of carbofuran in rabbits. WARF Institute, Inc., Madison, WI. No study date provided. WARF #T-731. DPR Volume #254-137, Record #87710

WARF. 1981. Mutagenesis screening of pesticides using *Drosophila*. WARF Institute, Inc., Madison, WI. February, 1981. Contract #68-01-2474. DPR Volume #254-109, Record #47743

Wolfe, J.L. and R.J. Esher. 1980. Toxicity of carbofuran and lindane ion the old-field mouse (*Peromyscus polionotus*) and the cotton mouse (*P. gossypinus*). *Bull. Environm. Contam. Toxicol.* **24**:894-902

Yang, P-Y., C.Y. Thomas, J-L. Lin, R-K. Lyu and P-C Chiang. 2000. Carbofuran-induced delayed neuropathy. *Clinical Toxicology* **38**:43-46

Yen, J-H., F-L. Hsiao, Y-S. Wang. 1997. Assessment of the insecticide carbofuran's potential to contaminate groundwater through soils in the subtropics. *Eocotox. Environ. Saf.* **38**:260-265

Yoon, J-Y., S-H. Oh, S-M. Yoo, S-J. Lee, H-S. Lee, S-J. Choi, C-K. Moon and B.H. Lee. 2001. *N*-Nitrosocarbofuran, but not carbofuran, induces apoptosis and cell cycle arrest in CHL cells. *Toxicology* **169**:153-161

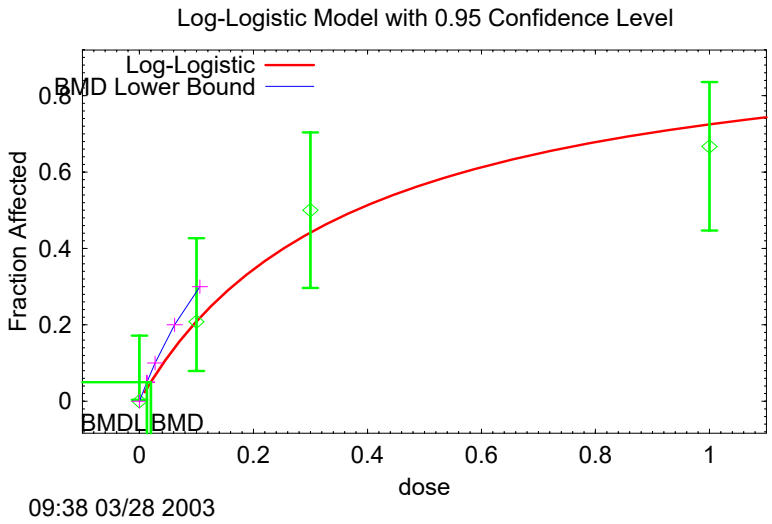
Yousef, M.I., M.H. Salem, H.Z. Ibrahim, S. Helmi, M.A. Seehy and K. Bertheussen. 1995. Toxic effects of carbofuran and glyphosate on semen characteristics in rabbits. *J. Environ. Sci. Health* **B30**:513-534

Yousef, M.I., K. Bertheussen, H.Z. Ibrahim, S. Helmi, M.A. Seehy and M.H. Salem. 1996. A sensitive sperm-motility test for the assessment of cytotoxic effect of pesticides. *J. Environ. Sci. Health* **B31**:99-115

Yu, C-C., G.M. Booth, D.J. Hansen and J.R. Larsen. 1974. Fate of carbofuan in a model ecosystem. *J. Agr. Food Chem.* **22**:431-434

Attachment I. Benchmark dose calculations for chewing behavior incidence in pregnant females (WARF, 1978a)

Logistic, log transformed, slope parameter restricted as slope >1



5% response:

```
==============================================================================
     Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
     Input Data File: D:\BMDS\UNSAVED1.(d)
     Gnuplot Plotting File:  D:\BMDS\UNSAVED1.plt
                                                Fri Mar 28 09:38:12 2003
==============================================================================

BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

  P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


  Dependent variable = incidence
  Independent variable = dose
  Slope parameter is restricted as slope >= 1

  Total number of observations = 4
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008


  User has chosen the log transformed model
```

Default Initial Parameter Values
background = 0
intercept = 0.89589
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background -slope
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	intercept
intercept	1

Parameter Estimates

Variable	Estimate	Std. Err.
background	0	NA
intercept	0.968979	0.261128
slope	1	NA

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-44.1936			
Fitted model	-44.5552	0.723144	3	0.8677
Reduced model	-61.7752	35.1631	3	<.0001

AIC: 91.1104

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	24	0
0.1000	0.2086	5.006	5	24	-0.002776
0.3000	0.4415	10.596	12	24	0.5769
1.0000	0.7249	17.398	16	24	-0.639

Chi-square = 0.74 DF = 3 P-value = 0.8635

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0199721

BMDL = 0.0130103

Logistic, log transformed, slope parameter restricted as slope >1

10% response:

```
==========================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: D:\BMDS\UNSAVED1.(d)
        Gnuplot Plotting File:  D:\BMDS\UNSAVED1.plt
                                                  Fri Mar 28 13:56:06 2003
==========================================================================

BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

  P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


  Dependent variable = incidence
  Independent variable = dose
  Slope parameter is restricted as slope >= 1

  Total number of observations = 4
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008



  User has chosen the log transformed model


             Default Initial Parameter Values
               background =           0
                intercept =     0.89589
                    slope =           1


       Asymptotic Correlation Matrix of Parameter Estimates

       ( *** The model parameter(s)  -background    -slope
            have been estimated at a boundary point, or have been specified by the user,
            and do not appear in the correlation matrix )

         intercept

intercept          1


                   Parameter Estimates

    Variable         Estimate           Std. Err.
```

background	0	NA
intercept	0.968979	0.261128
slope	1	NA

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-44.1936			
Fitted model	-44.5552	0.723144	3	0.8677
Reduced model	-61.7752	35.1631	3	<.0001

AIC: 91.1104

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	24	0
0.1000	0.2086	5.006	5	24	-0.002776
0.3000	0.4415	10.596	12	24	0.5769
1.0000	0.7249	17.398	16	24	-0.639

Chi-square = 0.74 DF = 3 P-value = 0.8635

Benchmark Dose Computation

Specified effect = 0.1

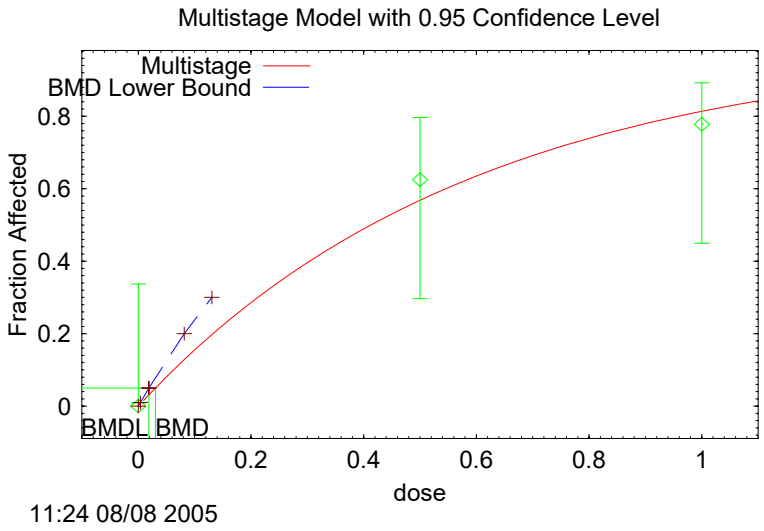
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0421634

BMDL = 0.0274663

Attachment II. Benchmark dose calculations for teeth grinding incidence in females (FMC, 2002)



5% response:

==========

Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
Input Data File: D:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: D:\BMDS\UNSAVED1.plt
Tue Jul 19 11:43:09 2005

==========

BMDS MODEL RUN

~~~~~~~~~~

The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

The parameter betas are restricted to be positive

Dependent variable = COLUMN2
Independent variable = COLUMN1

Total number of observations = 3
Total number of records with missing values = 0
Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
~~~~~~~~~~

Default Initial Parameter Values
Background = 0.073428
Beta(1) = 1.50408
Beta(2) = 0

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Beta(2)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0	NA
Beta(1)	1.68073	0.6261
Beta(2)	0	NA

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-10.0599			
Fitted model	-10.1494	0.17908	2	0.9144
Reduced model	-17.3087	14.4976	2	0.000711

AIC: 22.2988

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
i: 1					
0.0000	0.0000	0.000	0	8	0.000
i: 2					
0.5000	0.5684	4.548	5	8	0.231
i: 3					
1.0000	0.8138	7.324	7	9	-0.237

Chi-square = 0.18 DF = 2 P-value = 0.9134

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0305185

BMDL = 0.0187866

Attachment III. DEEM Acute Point Estimate Dietary Exposure Assessment

III.1. ACUTE RESIDUE DATA FILE - POINT ESTIMATE APPROACH

```
Filename: H:\ARubin\Corel\CARBOFURAN\Dietary Assessment\MC-22\PE22.RS7
Chemical: carbofuran
RfD(Chronic): 1 mg/kg bw/day  NOEL(Chronic): .1 mg/kg bw/day
RfD(Acute): 1 mg/kg bw/day  NOEL(Acute):  1 mg/kg bw/day
Date created/last modified: 09-19-2005/16:49:41/14         Program ver. 7.87
Comment: Initial residue file
```

Food Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	Adj.Factors #2	RDL Pntr	Comment
181	O	Artichokes-globe	0.190000	1.000	1.000		FT (CA
		Full comment: FT (CA), 1982					
72	O	Bananas	0.052000	1.000	1.000	8	PDP, 1
		Full comment: PDP, 1995, 2001-2, ND					
73	O	Bananas-dried	0.052000	3.900	1.000	8	PDP, 1
		Full comment: PDP, 1995, 2001-2, ND					
378	O	Bananas-juice	0.052000	1.000	1.000	8	PDP, 1
		Full comment: PDP, 1995, 2001-2, ND					
265	15	Barley	0.025000	1.000	1.000		PDP, 2
		Full comment: PDP, 2002-3, ND					
152	9B	Bitter melon	0.026000	1.000	1.000		Cantal
		Full comment: Cantaloupe, CA-only, 2000, ND					
301	O	Canola oil (rape seed oil)	0.063000	1.000	1.000		FT fro
		Full comment: FT from USEPA (2000)					
143	9A	Casabas	0.026000	1.000	1.000		Cantal
		Full comment: Cantaloupe, CA-only, 2000, ND					
112	O	Coffee	0.020000	1.000	1.000		FT, pr
		Full comment: FT, processed to inst. coffee (1994-6, Brazil), ND					
267	15	Corn grain-bran	0.052000	1.000	1.000	4	PDP CA
		Full comment: PDP CA-only, 2002-3, sw. corn, 2 3-OH detects					
266	15	Corn grain-endosperm	0.052000	1.000	1.000	4	PDP CA
		Full comment: PDP CA-only, 2002-3, sw. corn, 2 3-OH detects					
289	15	Corn grain-oil	0.018000	1.000	1.000	5	PDP, 1
		Full comment: PDP, 1998-9, ND, corn syrup					
268	15	Corn grain/sugar/hfcs	0.018000	1.500	1.000	5	PDP, 1
		Full comment: PDP, 1998-9, ND, corn syrup					
388	15	Corn grain/sugar-molasses	0.018000	1.500	1.000	5	PDP, 1
		Full comment: PDP, 1998-9, ND, corn syrup					
237	15	Corn/pop	0.052000	1.000	1.000	4	PDP CA
		Full comment: PDP CA-only, 2002-3, sw. corn, 2 3-OH detects					
238	15	Corn/sweet	0.052000	1.000	1.000	4	PDP CA
		Full comment: PDP CA-only, 2002-3, sw. corn, 2 3-OH detects					
291	O	Cottonseed-meal	0.075000	1.000	1.000		FT, se
		Full comment: FT, seeds, 1973, ND					
290	O	Cottonseed-oil	0.075000	1.000	1.000		FT, se
		Full comment: FT, seeds, 1973, ND (no oil data)					
8	O	Cranberries	0.020000	1.000	1.000		FDA, 1
		Full comment: FDA, 1995-8 (from USEPA CF dietary)					
9	O	Cranberries-juice	0.020000	1.100	1.000		FDA, 1
		Full comment: FDA, 1995-8 (from USEPA CF dietary)					
389	O	Cranberries-juice-concentrate	0.020000	3.300	1.000		FDA, 1
		Full comment: FDA, 1995-8 (from USEPA CF dietary)					
144	9A	Crenshaws	0.026000	1.000	1.000		Cantal
		Full comment: Cantaloupe, CA-only, 2000, ND					
148	9B	Cucumbers	0.200000	1.000	1.000	1	CA-onl
		Full comment: CA-only, 2002-3, 7 CF detects, tolerance					
13	O	Grapes	0.026000	1.000	1.000	6	Califo
		Full comment: California only, 2000, ND					
15	O	Grapes-juice	0.026000	1.000	1.000	7	Califo
		Full comment: California only, 1998-9, ND					
392	O	Grapes-juice-concentrate	0.026000	3.600	1.000	7	Califo
		Full comment: California only, 1998-9, ND					
14	O	Grapes-raisins	0.026000	4.300	1.000	6	Califo
		Full comment: California only, 2000, ND					
315	O	Grapes-wine and sherry	0.026000	1.000	1.000	7	CA-onl

```
   Full comment: CA-only, 1998-9, ND
141 9A   Melons-cantaloupes-juice           0.026000   1.000  1.000      Cantal
   Full comment: Cantaloupe, CA-only, 2000, ND
142 9A   Melons-cantaloupes-pulp            0.026000   1.000  1.000      Cantal
   Full comment: Cantaloupe, CA-only, 2000, ND
145 9A   Melons-honeydew                   0.026000   1.000  1.000      Cantal
   Full comment: Cantaloupe, CA-only, 2000, ND
146 9A   Melons-persian                    0.026000   1.000  1.000      Cantal
   Full comment: Cantaloupe, CA-only, 2000, ND
399 15   Oats-bran                         0.010000   1.000  1.000      PDP, 1
   Full comment: PDP, 1999, ND
269 15   Oats                              0.010000   1.000  1.000      PDP, 1
   Full comment: PDP, 1999, ND
139 8    Paprika                           0.143000   1.000  1.000   2  Sweet
   Full comment: Sweet bell pep., PDP, 2002-3, 21 CF/3OH detects
156 8    Peppers-chilli incl jalapeno      0.143000   1.000  1.000   2  Sweet
   Full comment: Sweet bell pep., PDP, 2002-3, 21 CF/3OH detects
157 8    Peppers-other                     0.143000   1.000  1.000   2  Sweet
   Full comment: Sweet bell pep., PDP, 2002-3, 21 CF/3OH detects
155 8    Peppers-sweet(garden)             0.143000   1.000  1.000   2  Sweet
   Full comment: Sweet bell pep., PDP, 2002-3, 21 CF/3OH detects
158 8    Pimientos                         0.143000   1.000  1.000   2  Sweet
   Full comment: Sweet bell pep., PDP, 2002-3, 21 CF/3OH detects
210 1C   Potatoes/white-dry                0.026000   6.500  1.000   9  PDP, 2
   Full comment: PDP, 2000-2, ND
209 1C   Potatoes/white-peeled             0.026000   1.000  1.000   9  PDP, 2
   Full comment: PDP, 2000-2, ND
211 1C   Potatoes/white-peel only          0.026000   1.000  1.000   9  PDP, 2
   Full comment: PDP, 2000-2, ND
208 1C   Potatoes/white-unspecified        0.026000   1.000  1.000   9  PDP, 2
   Full comment: PDP, 2000-2, ND
207 1C   Potatoes/white-whole              0.026000   1.000  1.000   9  PDP, 2
   Full comment: PDP, 2000-2, ND
149 9B   Pumpkin                           0.026000   1.000  1.000      W. squ
   Full comment: W. squash, CA-only (1997-9), ND
408 15   Rice-bran                         0.025000   1.000  1.000      PDP, 2
   Full comment: PDP, 2000, ND
271 15   Rice-milled (white)               0.025000   1.000  1.000      PDP, 2
   Full comment: PDP, 2000, ND
270 15   Rice-rough (brown)                0.025000   1.000  1.000      PDP, 2
   Full comment: PDP, 2000, ND
409 15   Rice-wild                         0.025000   1.000  1.000      PDP, 2
   Full comment: PDP, 2000, ND
275 15   Sorghum (including milo)          0.020000   1.000  1.000      FT (in
   Full comment: FT (in EPA assessment, no year), ND
303 6A   Soybean-other                     0.013000   1.000  1.000      PDP, 1
   Full comment: PDP, 1997-8, beans, ND
307 6A   Soybeans-flour (defatted)         0.013000   1.000  1.000      PDP, 1
   Full comment: PDP, 1997-8, beans, ND
306 6A   Soybeans-flour (low fat)          0.013000   1.000  1.000      PDP, 1
   Full comment: PDP, 1997-8, beans, ND
305 6A   Soybeans-flour (full fat)         0.013000   1.000  1.000      PDP, 1
   Full comment: PDP, 1997-8, beans, ND
304 6A   Soybeans-mature seeds dry         0.013000   1.000  1.000      PDP, 1
   Full comment: PDP, 1997-8, beans, ND
297 6A   Soybeans-oil                      0.013000   1.000  1.000      PDP, 1
   Full comment: PDP, 1997-8, beans, ND
482 O    Soybeans-protein isolate          0.013000   1.000  1.000      PDP, 1
   Full comment: PDP, 1997-8, ND
255 6A   Soybeans-sprouted seeds           0.013000   0.330  1.000      PDP, 1
   Full comment: PDP, 1997-8, beans, ND
150 9B   Squash-summer                     0.026000   1.000  1.000      W. squ
   Full comment: W. squash, CA-only, 1997-9, ND
415 9B   Squash-spaghetti                  0.026000   1.000  1.000      W. squ
   Full comment: W. squash, CA-only, 1997-9, ND
151 9B   Squash-winter                     0.026000   1.000  1.000      W. squ
   Full comment: W. squash, CA-only, 1997-9, ND
 17 O    Strawberries                      0.037000   1.000  1.000      PDP, 1
   Full comment: PDP, 1998-2000, fresh&froz., ND
416 O    Strawberries-juice                0.037000   1.000  1.000      PDP, 1
   Full comment: PDP, 1998-2000, fresh&froz., ND
282 1A   Sugar-beet                        0.040000   1.000  1.000      FT, 19
```

```
   Full comment: FT, 1986 & 1992, sugar beet roots, 2 detects
379 1A   Sugar-beet-molasses               0.040000   1.000  1.000      FT, 19
   Full comment: FT, 1986 & 1992, sugar beet roots, 2 detects
283 O    Sugar-cane                        0.020000   1.000  1.000      FT, 19
   Full comment: FT, 1990-2, ND at sugar stage
284 O    Sugar-cane/molasses               0.020000   1.000  1.000      FT, 19
   Full comment: FT, 1990-2, ND at molasses stage
298 O    Sunflower-oil                     0.020000   1.000  1.000      FT, 19
   Full comment: FT, 1981, only 2 samples
417 O    Sunflower-seeds                   0.330000   1.000  1.000      FT, 19
   Full comment: FT, 1981, confectionary seeds, many detects
432 O    Water-bottled                     0.000197   1.000  1.000      Drinki
   Full comment: Drinking H20, PDP, 2001-3, 14 CF detects
434 O    Water-commercial processing       0.000197   1.000  1.000      Drinki
   Full comment: Drinking H20, PDP, 2001-3, 14 CF detects
435 O    Water-non-food based              0.000197   1.000  1.000      Drinki
   Full comment: Drinking H20, PDP, 2001-3, 14 CF detects
433 O    Water-tap                         0.000197   1.000  1.000      Drinki
   Full comment: Drinking H20, PDP, 2001-3, 14 CF detects
147 9A   Watermelon                        0.026000   1.000  1.000      Cantal
   Full comment: Cantaloupe, CA-only, 2000, ND
436 9A   Watermelon-juice                  0.026000   1.000  1.000      Cantal
   Full comment: Cantaloupe, CA-only, 2000, ND
278 15   Wheat-bran                        0.028000   1.000  1.000   3  Wheat,
   Full comment: Wheat, PDP, 1995-7, 2003, 6 CF-only detects
279 15   Wheat-flour                       0.028000   1.000  1.000   3  Wheat,
   Full comment: Wheat, PDP, 1995-7, 2003, 6 CF-only detects
277 15   Wheat-germ                        0.028000   1.000  1.000   3  Wheat,
   Full comment: Wheat, PDP, 1995-7, 2003, 6 CF-only detects
437 15   Wheat-germ oil                    0.028000   1.000  1.000   3  Wheat,
   Full comment: Wheat, PDP, 1995-7, 2003, 6 CF-only detects
276 15   Wheat-rough                       0.028000   1.000  1.000   3  Wheat,
   Full comment: Wheat, PDP, 1995-7, 2003, 6 CF-only detects
439 9B   Wintermelon                       0.026000   1.000  1.000      Cantal
   Full comment: Cantaloupe, CA-only, 2000, ND
```

III.2. ACUTE EXPOSURES AND RISK ESTIMATES - POINT ESTIMATE APPROACH

California Department of Pesticide Regulation Ver. 7.87
DEEM ACUTE Analysis for CARBOFURAN (1994-98 data)
Residue file: PE22.RS7 Adjustment factor #2 NOT used.
Analysis Date: 09-19-2005/16:52:52 Residue file dated: 09-19-2005/16:49:41/14
NOEL (Acute) = 0.010000 mg/kg body-wt/day
Acute Reference Dose (aRfD) = 0.000100 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "PE-22, including new water, wheat, rice & barley data"
==========

U.S. Population Daily Exposure Analysis /a
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000238	0.000238
Standard Deviation	0.000215	0.000215
Standard Error of mean	0.000001	0.000001
Margin of Exposure 2/	42	41
Percent of aRfD	238.05	238.41

Percent of Person-Days that are User-Days = 99.85%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000069	69.09	144	90.00	0.000464	463.55	21
20.00	0.000098	98.48	101	95.00	0.000617	616.77	16
30.00	0.000125	124.51	80	97.50	0.000804	803.65	12
40.00	0.000150	150.04	66	99.00	0.001073	1073.27	9
50.00	0.000180	180.43	55	99.50	0.001318	1318.39	7
60.00	0.000216	216.22	46	99.75	0.001630	1629.75	6
70.00	0.000262	261.96	38	99.90	0.002062	2062.14	4
80.00	0.000330	329.55	30				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000069	68.61	145	90.00	0.000463	463.24	21
20.00	0.000098	98.17	101	95.00	0.000616	616.45	16
30.00	0.000124	124.22	80	97.50	0.000803	803.30	12
40.00	0.000150	149.82	66	99.00	0.001073	1072.68	9
50.00	0.000180	180.13	55	99.50	0.001318	1317.85	7
60.00	0.000216	216.00	46	99.75	0.001629	1629.46	6
70.00	0.000262	261.72	38	99.90	0.002062	2061.78	4
80.00	0.000329	329.28	30				

---
a/ Analysis based on all two-day participant records in CSFII 1994-98 survey.
2/ Margin of Exposure = NOEL/ Dietary Exposure.

Western region Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000256	0.000256
Standard Deviation	0.000236	0.000236
Standard Error of mean	0.000002	0.000002
Margin of Exposure	39	39
Percent of aRfD	255.59	256.21

Percent of Person-Days that are User-Days = 99.76%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000074	73.51	136	90.00	0.000490	489.72	20
20.00	0.000104	104.21	95	95.00	0.000651	651.09	15
30.00	0.000133	132.89	75	97.50	0.000859	858.61	11
40.00	0.000164	163.56	61	99.00	0.001198	1198.49	8
50.00	0.000197	196.73	50	99.50	0.001594	1593.70	6
60.00	0.000232	232.36	43	99.75	0.001906	1905.59	5
70.00	0.000280	280.13	35	99.90	0.002382	2381.74	4
80.00	0.000351	350.97	28				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000073	72.69	137	90.00	0.000489	489.09	20
20.00	0.000104	103.71	96	95.00	0.000651	650.88	15
30.00	0.000132	132.31	75	97.50	0.000858	858.11	11
40.00	0.000163	163.20	61	99.00	0.001198	1197.62	8
50.00	0.000196	196.29	50	99.50	0.001593	1593.07	6
60.00	0.000232	231.91	43	99.75	0.001905	1905.24	5
70.00	0.000280	279.78	35	99.90	0.002381	2381.23	4
80.00	0.000350	350.31	28				

Hispanics

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000260	0.000261
Standard Deviation	0.000229	0.000229
Standard Error of mean	0.000003	0.000003
Margin of Exposure	38	38
Percent of aRfD	260.28	260.62

Percent of Person-Days that are User-Days = 99.87%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000069	69.08	144	90.00	0.000535	535.42	18
20.00	0.000102	102.35	97	95.00	0.000688	687.59	14
30.00	0.000133	133.34	74	97.50	0.000879	879.00	11
40.00	0.000160	160.04	62	99.00	0.001157	1157.07	8
50.00	0.000198	198.33	50	99.50	0.001376	1376.02	7
60.00	0.000235	234.75	42	99.75	0.001645	1644.66	6
70.00	0.000285	284.81	35	99.90	0.001787	1787.41	5
80.00	0.000369	369.17	27				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000069	68.61	145	90.00	0.000534	534.47	18
20.00	0.000102	102.01	98	95.00	0.000687	687.20	14
30.00	0.000133	133.13	75	97.50	0.000878	878.44	11
40.00	0.000160	159.75	62	99.00	0.001157	1156.65	8
50.00	0.000198	198.12	50	99.50	0.001376	1375.86	7
60.00	0.000235	234.54	42	99.75	0.001645	1644.58	6
70.00	0.000285	284.64	35	99.90	0.001787	1787.00	5
80.00	0.000369	368.80	27				

Non-hispanic whites Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000236	0.000236
Standard Deviation	0.000207	0.000207
Standard Error of mean	0.000001	0.000001
Margin of Exposure	42	42
Percent of aRfD	236.02	236.36

Percent of Person-Days that are User-Days = 99.85%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000073	72.98	137	90.00	0.000454	453.75	22
20.00	0.000102	101.74	98	95.00	0.000598	597.98	16
30.00	0.000127	126.97	78	97.50	0.000780	780.38	12
40.00	0.000152	152.22	65	99.00	0.001032	1031.66	9
50.00	0.000182	181.75	55	99.50	0.001263	1262.72	7
60.00	0.000216	215.84	46	99.75	0.001521	1520.55	6
70.00	0.000260	259.54	38	99.90	0.001915	1914.98	5
80.00	0.000325	324.66	30				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000072	72.49	137	90.00	0.000453	453.49	22
20.00	0.000101	101.41	98	95.00	0.000598	597.62	16
30.00	0.000127	126.72	78	97.50	0.000780	779.94	12
40.00	0.000152	151.98	65	99.00	0.001031	1031.28	9
50.00	0.000182	181.51	55	99.50	0.001262	1262.37	7
60.00	0.000216	215.64	46	99.75	0.001520	1519.99	6
70.00	0.000259	259.28	38	99.90	0.001914	1914.19	5
80.00	0.000324	324.37	30				

Non-hispanic blacks Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000215	0.000216
Standard Deviation	0.000213	0.000213
Standard Error of mean	0.000003	0.000003
Margin of Exposure	46	46
Percent of aRfD	215.46	215.84

Percent of Person-Days that are User-Days = 99.83%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000053	52.83	189	90.00	0.000442	442.45	22
20.00	0.000077	77.06	129	95.00	0.000609	608.94	16
30.00	0.000099	98.60	101	97.50	0.000801	801.21	12
40.00	0.000125	125.10	79	99.00	0.001060	1059.82	9
50.00	0.000150	150.23	66	99.50	0.001235	1234.79	8
60.00	0.000189	188.78	52	99.75	0.001516	1516.33	6
70.00	0.000236	235.71	42	99.90	0.001794	1794.42	5
80.00	0.000305	304.56	32				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000052	52.39	190	90.00	0.000442	442.09	22
20.00	0.000077	76.60	130	95.00	0.000609	608.65	16
30.00	0.000098	98.39	101	97.50	0.000800	800.49	12
40.00	0.000125	124.77	80	99.00	0.001059	1059.18	9
50.00	0.000150	150.03	66	99.50	0.001234	1234.44	8
60.00	0.000188	188.42	53	99.75	0.001516	1516.19	6
70.00	0.000235	235.42	42	99.90	0.001794	1794.12	5
80.00	0.000304	304.26	32				

Non-hisp/non-white/non-black Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000283	0.000284
Standard Deviation	0.000297	0.000297
Standard Error of mean	0.000007	0.000007
Margin of Exposure	35	35
Percent of aRfD	283.14	283.66

Percent of Person-Days that are User-Days = 99.82%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000077	76.93	129	90.00	0.000522	521.98	19
20.00	0.000110	110.01	90	95.00	0.000734	734.31	13
30.00	0.000136	136.03	73	97.50	0.001080	1079.55	9
40.00	0.000169	169.37	59	99.00	0.001679	1678.91	5
50.00	0.000203	203.18	49	99.50	0.002168	2168.36	4
60.00	0.000256	256.35	39	99.75	0.002382	2382.34	4
70.00	0.000295	294.77	33	99.90	0.002553	2553.41	3
80.00	0.000391	390.59	25				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000076	76.21	131	90.00	0.000522	521.75	19
20.00	0.000109	109.34	91	95.00	0.000734	733.96	13
30.00	0.000136	135.68	73	97.50	0.001076	1076.14	9
40.00	0.000169	168.97	59	99.00	0.001678	1678.00	5
50.00	0.000203	202.81	49	99.50	0.002168	2168.00	4
60.00	0.000256	256.11	39	99.75	0.002382	2382.16	4
70.00	0.000295	294.63	33	99.90	0.002553	2553.38	3
80.00	0.000390	390.27	25				

All infants

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000352	0.000387
Standard Deviation	0.000346	0.000343
Standard Error of mean	0.000006	0.000007
Margin of Exposure	28	25
Percent of aRfD	352.04	386.59

Percent of Person-Days that are User-Days = 91.06%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000057	56.68	176	90.00	0.000845	844.86	11
20.00	0.000091	91.05	109	95.00	0.001019	1018.56	9
30.00	0.000143	142.56	70	97.50	0.001236	1235.89	8
40.00	0.000224	223.75	44	99.00	0.001519	1519.46	6
50.00	0.000316	316.50	31	99.50	0.002007	2006.60	4
60.00	0.000396	396.27	25	99.75	0.002163	2162.88	4
70.00	0.000480	479.91	20	99.90	0.002315	2315.42	4
80.00	0.000609	609.32	16				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000003	3.05	3,275	90.00	0.000813	813.44	12
20.00	0.000063	63.41	157	95.00	0.000995	994.56	10
30.00	0.000105	105.33	94	97.50	0.001202	1202.25	8
40.00	0.000183	182.89	54	99.00	0.001505	1505.43	6
50.00	0.000274	274.13	36	99.50	0.001955	1955.42	5
60.00	0.000370	369.61	27	99.75	0.002152	2151.82	4
70.00	0.000448	448.14	22	99.90	0.002311	2310.88	4
80.00	0.000584	584.45	17				

Nursing infants (<1 yr old) Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000174	0.000258
Standard Deviation	0.000293	0.000326
Standard Error of mean	0.000010	0.000013
Margin of Exposure	57	38
Percent of aRfD	173.65	257.79

Percent of Person-Days that are User-Days = 67.36%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000008	7.94	1,259	90.00	0.000658	657.69	15
20.00	0.000025	24.58	406	95.00	0.000963	962.83	10
30.00	0.000054	54.34	184	97.50	0.001147	1147.42	8
40.00	0.000085	84.94	117	99.00	0.001486	1486.15	6
50.00	0.000129	129.30	77	99.50	0.002113	2112.65	4
60.00	0.000219	219.48	45	99.75	0.002168	2168.04	4
70.00	0.000311	310.68	32	99.90	0.002168	2168.18	4
80.00	0.000413	413.13	24				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000000	0.00	>1,000,000	90.00	0.000491	491.17	20
20.00	0.000000	0.00	>1,000,000	95.00	0.000851	851.09	11
30.00	0.000000	0.00	>1,000,000	97.50	0.001001	1001.50	9
40.00	0.000009	8.93	1,119	99.00	0.001294	1294.22	7
50.00	0.000036	35.79	279	99.50	0.001497	1496.67	6
60.00	0.000086	86.00	116	99.75	0.002125	2124.55	4
70.00	0.000183	183.06	54	99.90	0.002168	2168.13	4
80.00	0.000312	311.59	32				

Non-nursing infants (<1 yr old) Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000419	0.000419
Standard Deviation	0.000340	0.000340
Standard Error of mean	0.000007	0.000007
Margin of Exposure	23	23
Percent of aRfD	419.30	419.30

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000076	75.96	131	90.00	0.000862	861.96	11
20.00	0.000117	116.76	85	95.00	0.001055	1054.78	9
30.00	0.000192	192.21	52	97.50	0.001247	1246.68	8
40.00	0.000275	275.31	36	99.00	0.001536	1535.62	6
50.00	0.000363	362.70	27	99.50	0.001978	1978.10	5
60.00	0.000426	426.43	23	99.75	0.002156	2156.08	4
70.00	0.000521	521.23	19	99.90	0.002355	2355.37	4
80.00	0.000645	644.79	15				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000076	75.96	131	90.00	0.000862	861.96	11
20.00	0.000117	116.76	85	95.00	0.001055	1054.78	9
30.00	0.000192	192.21	52	97.50	0.001247	1246.68	8
40.00	0.000275	275.31	36	99.00	0.001536	1535.62	6
50.00	0.000363	362.70	27	99.50	0.001978	1978.10	5
60.00	0.000426	426.43	23	99.75	0.002156	2156.08	4
70.00	0.000521	521.23	19	99.90	0.002355	2355.37	4
80.00	0.000645	644.79	15				

Females 13+ (preg/not lactating) Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000201	0.000202
Standard Deviation	0.000118	0.000117
Standard Error of mean	0.000010	0.000010
Margin of Exposure	49	49
Percent of aRfD	200.91	201.90

Percent of Person-Days that are User-Days = 99.51%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000078	78.45	127	90.00	0.000363	362.62	27
20.00	0.000106	106.04	94	95.00	0.000437	436.74	22
30.00	0.000126	126.25	79	97.50	0.000447	447.08	22
40.00	0.000149	149.40	66	99.00	0.000610	610.44	16
50.00	0.000176	175.97	56	99.50	0.000613	612.85	16
60.00	0.000200	200.14	49	99.75	0.000614	614.05	16
70.00	0.000243	242.60	41	99.90	0.000615	614.77	16
80.00	0.000293	292.80	34				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000074	74.32	134	90.00	0.000362	362.49	27
20.00	0.000106	105.78	94	95.00	0.000437	436.69	22
30.00	0.000126	126.08	79	97.50	0.000447	447.03	22
40.00	0.000149	148.75	67	99.00	0.000610	610.41	16
50.00	0.000176	175.72	56	99.50	0.000613	612.83	16
60.00	0.000200	199.98	50	99.75	0.000614	614.04	16
70.00	0.000242	242.41	41	99.90	0.000615	614.77	16
80.00	0.000293	292.52	34				

Females 13+ (lactating) Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000229	0.000229
Standard Deviation	0.000157	0.000157
Standard Error of mean	0.000018	0.000018
Margin of Exposure	43	43
Percent of aRfD	228.67	228.67

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000075	75.30	132	90.00	0.000394	393.68	25
20.00	0.000118	117.87	84	95.00	0.000519	518.70	19
30.00	0.000140	139.82	71	97.50	0.000597	597.01	16
40.00	0.000168	168.48	59	99.00	0.000955	955.31	10
50.00	0.000195	194.82	51	99.50	0.001030	1029.75	9
60.00	0.000225	225.19	44	99.75	0.001032	1032.00	9
70.00	0.000277	277.37	36	99.90	0.001033	1033.35	9
80.00	0.000325	325.20	30				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000075	75.30	132	90.00	0.000394	393.68	25
20.00	0.000118	117.87	84	95.00	0.000519	518.70	19
30.00	0.000140	139.82	71	97.50	0.000597	597.01	16
40.00	0.000168	168.48	59	99.00	0.000955	955.31	10
50.00	0.000195	194.82	51	99.50	0.001030	1029.75	9
60.00	0.000225	225.19	44	99.75	0.001032	1032.00	9
70.00	0.000277	277.37	36	99.90	0.001033	1033.35	9
80.00	0.000325	325.20	30				

Children 1-2 yrs Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000595	0.000595
Standard Deviation	0.000418	0.000418
Standard Error of mean	0.000007	0.000007
Margin of Exposure	16	16
Percent of aRfD	595.04	595.47

Percent of Person-Days that are User-Days = 99.93%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000201	200.72	49	90.00	0.001094	1093.99	9
20.00	0.000282	281.66	35	95.00	0.001349	1349.27	7
30.00	0.000349	348.88	28	97.50	0.001624	1624.36	6
40.00	0.000422	421.80	23	99.00	0.002115	2115.22	4
50.00	0.000499	499.26	20	99.50	0.002513	2513.08	3
60.00	0.000588	587.70	17	99.75	0.002781	2781.24	3
70.00	0.000694	693.54	14	99.90	0.003558	3558.32	2
80.00	0.000854	853.97	11				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000200	200.20	49	90.00	0.001094	1093.70	9
20.00	0.000281	281.30	35	95.00	0.001349	1349.03	7
30.00	0.000348	348.37	28	97.50	0.001624	1623.88	6
40.00	0.000421	421.47	23	99.00	0.002115	2114.73	4
50.00	0.000499	498.92	20	99.50	0.002513	2512.95	3
60.00	0.000587	587.44	17	99.75	0.002781	2780.82	3
70.00	0.000693	693.21	14	99.90	0.003558	3558.29	2
80.00	0.000854	853.66	11				

Children 3-5 yrs Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000536	0.000536
Standard Deviation	0.000349	0.000349
Standard Error of mean	0.000004	0.000004
Margin of Exposure	18	18
Percent of aRfD	536.33	536.33

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000221	221.09	45	90.00	0.000915	914.69	10
20.00	0.000286	285.83	34	95.00	0.001127	1126.73	8
30.00	0.000341	340.73	29	97.50	0.001371	1371.24	7
40.00	0.000397	397.30	25	99.00	0.001842	1842.02	5
50.00	0.000461	460.67	21	99.50	0.002221	2221.24	4
60.00	0.000530	530.30	18	99.75	0.002590	2590.07	3
70.00	0.000609	609.09	16	99.90	0.003346	3345.69	2
80.00	0.000729	729.10	13				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000221	221.09	45	90.00	0.000915	914.69	10
20.00	0.000286	285.83	34	95.00	0.001127	1126.73	8
30.00	0.000341	340.73	29	97.50	0.001371	1371.24	7
40.00	0.000397	397.30	25	99.00	0.001842	1842.02	5
50.00	0.000461	460.67	21	99.50	0.002221	2221.24	4
60.00	0.000530	530.30	18	99.75	0.002590	2590.07	3
70.00	0.000609	609.09	16	99.90	0.003346	3345.69	2
80.00	0.000729	729.10	13				

Children 6-12 yrs Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000357	0.000357
Standard Deviation	0.000248	0.000248
Standard Error of mean	0.000004	0.000004
Margin of Exposure	28	28
Percent of aRfD	356.50	356.50

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000139	139.31	71	90.00	0.000627	627.37	15
20.00	0.000183	183.16	54	95.00	0.000778	777.71	12
30.00	0.000221	221.43	45	97.50	0.000944	944.11	10
40.00	0.000262	261.83	38	99.00	0.001222	1221.86	8
50.00	0.000297	297.41	33	99.50	0.001606	1606.41	6
60.00	0.000342	342.15	29	99.75	0.002046	2045.66	4
70.00	0.000405	405.08	24	99.90	0.002556	2555.58	3
80.00	0.000488	487.61	20				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000139	139.31	71	90.00	0.000627	627.37	15
20.00	0.000183	183.16	54	95.00	0.000778	777.71	12
30.00	0.000221	221.43	45	97.50	0.000944	944.11	10
40.00	0.000262	261.83	38	99.00	0.001222	1221.86	8
50.00	0.000297	297.41	33	99.50	0.001606	1606.41	6
60.00	0.000342	342.15	29	99.75	0.002046	2045.66	4
70.00	0.000405	405.08	24	99.90	0.002556	2555.58	3
80.00	0.000488	487.61	20				

Youth 13-19 yrs Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000222	0.000222
Standard Deviation	0.000182	0.000182
Standard Error of mean	0.000004	0.000004
Margin of Exposure	44	44
Percent of aRfD	222.44	222.44

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000078	78.30	127	90.00	0.000393	392.92	25
20.00	0.000104	104.13	96	95.00	0.000491	490.93	20
30.00	0.000128	128.49	77	97.50	0.000605	605.49	16
40.00	0.000152	152.16	65	99.00	0.000882	882.48	11
50.00	0.000182	182.12	54	99.50	0.001507	1506.68	6
60.00	0.000215	214.84	46	99.75	0.001651	1650.80	6
70.00	0.000252	251.93	39	99.90	0.001899	1898.96	5
80.00	0.000304	303.97	32				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000078	78.30	127	90.00	0.000393	392.92	25
20.00	0.000104	104.13	96	95.00	0.000491	490.93	20
30.00	0.000128	128.49	77	97.50	0.000605	605.49	16
40.00	0.000152	152.16	65	99.00	0.000882	882.48	11
50.00	0.000182	182.12	54	99.50	0.001507	1506.68	6
60.00	0.000215	214.84	46	99.75	0.001651	1650.80	6
70.00	0.000252	251.93	39	99.90	0.001899	1898.96	5
80.00	0.000304	303.97	32				

Adults 20-49 yrs

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000193	0.000193
Standard Deviation	0.000135	0.000135
Standard Error of mean	0.000001	0.000001
Margin of Exposure	51	51
Percent of aRfD	193.35	193.41

Percent of Person-Days that are User-Days = 99.97%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000065	64.78	154	90.00	0.000353	353.31	28
20.00	0.000093	92.93	107	95.00	0.000441	440.60	22
30.00	0.000116	115.86	86	97.50	0.000536	536.07	18
40.00	0.000138	138.03	72	99.00	0.000683	682.54	14
50.00	0.000162	161.58	61	99.50	0.000783	783.36	12
60.00	0.000190	190.47	52	99.75	0.000893	893.36	11
70.00	0.000225	224.95	44	99.90	0.001210	1210.32	8
80.00	0.000271	270.73	36				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000065	64.70	154	90.00	0.000353	353.27	28
20.00	0.000093	92.87	107	95.00	0.000441	440.56	22
30.00	0.000116	115.82	86	97.50	0.000536	536.05	18
40.00	0.000138	138.00	72	99.00	0.000682	682.49	14
50.00	0.000162	161.54	61	99.50	0.000783	783.25	12
60.00	0.000190	190.43	52	99.75	0.000893	893.34	11
70.00	0.000225	224.92	44	99.90	0.001210	1210.29	8
80.00	0.000271	270.70	36				

Adults 50+ yrs

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000172	0.000172
Standard Deviation	0.000126	0.000126
Standard Error of mean	0.000001	0.000001
Margin of Exposure	58	58
Percent of aRfD	172.23	172.26

Percent of Person-Days that are User-Days = 99.98%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000058	57.75	173	90.00	0.000315	315.03	31
20.00	0.000080	80.37	124	95.00	0.000401	400.79	24
30.00	0.000102	101.52	98	97.50	0.000488	488.26	20
40.00	0.000122	121.98	81	99.00	0.000643	643.42	15
50.00	0.000143	142.63	70	99.50	0.000793	793.19	12
60.00	0.000167	167.27	59	99.75	0.000928	928.43	10
70.00	0.000198	197.88	50	99.90	0.001171	1171.23	8
80.00	0.000238	238.06	42				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000058	57.72	173	90.00	0.000315	315.01	31
20.00	0.000080	80.34	124	95.00	0.000401	400.76	24
30.00	0.000101	101.50	98	97.50	0.000488	488.24	20
40.00	0.000122	121.95	81	99.00	0.000643	643.39	15
50.00	0.000143	142.61	70	99.50	0.000793	793.16	12
60.00	0.000167	167.25	59	99.75	0.000928	928.40	10
70.00	0.000198	197.87	50	99.90	0.001171	1171.21	8
80.00	0.000238	238.04	42				

Females 13-49 yrs Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000184	0.000185
Standard Deviation	0.000132	0.000132
Standard Error of mean	0.000002	0.000002
Margin of Exposure	54	54
Percent of aRfD	184.49	184.51

Percent of Person-Days that are User-Days = 99.99%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000061	61.31	163	90.00	0.000342	341.62	29
20.00	0.000088	88.13	113	95.00	0.000419	418.79	23
30.00	0.000109	109.46	91	97.50	0.000508	507.97	19
40.00	0.000131	130.89	76	99.00	0.000641	640.57	15
50.00	0.000153	152.65	65	99.50	0.000770	770.17	12
60.00	0.000180	179.54	55	99.75	0.000912	911.62	10
70.00	0.000216	216.09	46	99.90	0.001252	1252.22	7
80.00	0.000261	260.52	38				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000061	61.29	163	90.00	0.000342	341.61	29
20.00	0.000088	88.10	113	95.00	0.000419	418.77	23
30.00	0.000109	109.44	91	97.50	0.000508	507.96	19
40.00	0.000131	130.88	76	99.00	0.000641	640.55	15
50.00	0.000153	152.63	65	99.50	0.000770	770.14	12
60.00	0.000180	179.52	55	99.75	0.000912	911.61	10
70.00	0.000216	216.08	46	99.90	0.001252	1252.21	7
80.00	0.000261	260.51	38				

Custom demographics 1: M/F 16-70 yr
All Seasons
All Regions
Sex: M/F-all/
All Races
Age-Low: 16 yrs High: 70 yrs

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000190	0.000190
Standard Deviation	0.000138	0.000138
Standard Error of mean	0.000001	0.000001
Margin of Exposure	52	52
Percent of aRfD	190.13	190.17

Percent of Person-Days that are User-Days = 99.98%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000063	63.22	158	90.00	0.000349	349.41	28
20.00	0.000090	90.41	110	95.00	0.000437	437.26	22
30.00	0.000113	113.35	88	97.50	0.000532	531.59	18
40.00	0.000135	134.79	74	99.00	0.000681	681.38	14
50.00	0.000158	157.88	63	99.50	0.000823	822.88	12
60.00	0.000186	186.19	53	99.75	0.000987	986.75	10
70.00	0.000219	219.37	45	99.90	0.001281	1280.91	7
80.00	0.000266	265.54	37				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000063	63.16	158	90.00	0.000349	349.39	28
20.00	0.000090	90.37	110	95.00	0.000437	437.24	22
30.00	0.000113	113.31	88	97.50	0.000532	531.57	18
40.00	0.000135	134.75	74	99.00	0.000681	681.34	14
50.00	0.000158	157.85	63	99.50	0.000823	822.84	12
60.00	0.000186	186.16	53	99.75	0.000987	986.65	10
70.00	0.000219	219.34	45	99.90	0.001281	1280.85	7
80.00	0.000266	265.52	37				

Attachment IV. DEEM Acute Distributional (Monte Carlo) Dietary Exposure Assessment

IV.1 ACUTE RESIDUE DATA - DISTRIBUTIONAL APPROACH

```
Filename: H:\ARubin\Corel\CARBOFURAN\Dietary Assessment\MC-22\MC22.RS7
Chemical: carbofuran
RfD(Chronic): 1 mg/kg bw/day  NOEL(Chronic): .1 mg/kg bw/day
RfD(Acute): 1 mg/kg bw/day  NOEL(Acute):  1 mg/kg bw/day
Date created/last modified: 09-20-2005/15:23:04/14         Program ver. 7.87
Comment: Initial residue file
```

RDL indices and parameters for Monte Carlo Analysis:

Index #	Dist Code	Parameter #1	Param #2	Param #3	Comment
1	6	RDF1-cucumber-halfLOD.rdf			
2	6	RDF2-peppers-halfLOD.rdf			
3	6	RDF3-wheat-halfLOD.rdf			
4	6	RDF4-swcorn-halfLOD.rdf			
5	6	RDF5-corngrainhfcs-halfLOD.rdf			
6	6	RDF6-grapes.halfLOD.rdf			
7	6	RDF7-grapes.juice.halfLOD.rdf			
8	6	RDF8-bananas-halfLOD.rdf			
9	6	RDF9-potatoes-halfLOD.rdf			
10	6	RDF10-wmelon-halfLOD.rdf			

Food Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	#2	RDL Pntr	Comment
181	O	Artichokes-globe	0.190000	1.000	1.000		FT (CA
		Full comment: FT (CA), 1982					
72	O	Bananas	0.052000	1.000	1.000	8	PDP, 1
		Full comment: PDP, 1995, 2001-2, ND					
73	O	Bananas-dried	0.052000	3.900	1.000	8	PDP, 1
		Full comment: PDP, 1995, 2001-2, ND					
378	O	Bananas-juice	0.052000	1.000	1.000	8	PDP, 1
		Full comment: PDP, 1995, 2001-2, ND					
265	15	Barley	0.025000	1.000	1.000		PDP, 2
		Full comment: PDP, 2002-3, ND					
152	9B	Bitter melon	0.026000	1.000	1.000		Cantal
		Full comment: Cantaloupe, CA-only, 2000, ND					
301	O	Canola oil (rape seed oil)	0.063000	1.000	1.000		FT fro
		Full comment: FT from USEPA (2000)					
143	9A	Casabas	0.026000	1.000	1.000		Cantal
		Full comment: Cantaloupe, CA-only, 2000, ND					
112	O	Coffee	0.020000	1.000	1.000		FT, pr
		Full comment: FT, processed to inst. coffee (1994-6, Brazil), ND					
267	15	Corn grain-bran	0.052000	1.000	1.000	4	PDP CA
		Full comment: PDP CA-only, 2002-3, sw. corn, 2 3-OH detects					
266	15	Corn grain-endosperm	0.052000	1.000	1.000	4	PDP CA
		Full comment: PDP CA-only, 2002-3, sw. corn, 2 3-OH detects					
289	15	Corn grain-oil	0.018000	1.000	1.000	5	PDP, 1
		Full comment: PDP, 1998-9, ND, corn syrup					
268	15	Corn grain/sugar/hfcs	0.018000	1.500	1.000	5	PDP, 1
		Full comment: PDP, 1998-9, ND, corn syrup					
388	15	Corn grain/sugar-molasses	0.018000	1.500	1.000	5	PDP, 1
		Full comment: PDP, 1998-9, ND, corn syrup					
237	15	Corn/pop	0.052000	1.000	1.000	4	PDP CA
		Full comment: PDP CA-only, 2002-3, sw. corn, 2 3-OH detects					
238	15	Corn/sweet	0.052000	1.000	1.000	4	PDP CA
		Full comment: PDP CA-only, 2002-3, sw. corn, 2 3-OH detects					
291	O	Cottonseed-meal	0.075000	1.000	1.000		FT, se
		Full comment: FT, seeds, 1973, ND					
290	O	Cottonseed-oil	0.075000	1.000	1.000		FT, se
		Full comment: FT, seeds, 1973, ND (no oil data)					
8	O	Cranberries	0.020000	1.000	1.000		FDA, 1
		Full comment: FDA, 1995-8 (from USEPA CF dietary)					
9	O	Cranberries-juice	0.020000	1.100	1.000		FDA, 1
		Full comment: FDA, 1995-8 (from USEPA CF dietary)					
389	O	Cranberries-juice-concentrate	0.020000	3.300	1.000		FDA, 1
		Full comment: FDA, 1995-8 (from USEPA CF dietary)					

144	9A	Crenshaws	0.026000	1.000	1.000		Cantal
	Full comment: Cantaloupe, CA-only, 2000, ND						
148	9B	Cucumbers	0.200000	1.000	1.000	1	CA-onl
	Full comment: CA-only, 2002-3, 7 CF detects, tolerance						
13	O	Grapes	0.026000	1.000	1.000	6	Califo
	Full comment: California only, 2000, ND						
15	O	Grapes-juice	0.026000	1.000	1.000	7	Califo
	Full comment: California only, 1998-9, ND						
392	O	Grapes-juice-concentrate	0.026000	3.600	1.000	7	Califo
	Full comment: California only, 1998-9, ND						
14	O	Grapes-raisins	0.026000	4.300	1.000	6	Califo
	Full comment: California only, 2000, ND						
315	O	Grapes-wine and sherry	0.026000	1.000	1.000	7	CA-onl
	Full comment: CA-only, 1998-9, ND						
141	9A	Melons-cantaloupes-juice	0.026000	1.000	1.000		Cantal
	Full comment: Cantaloupe, CA-only, 2000, ND						
142	9A	Melons-cantaloupes-pulp	0.026000	1.000	1.000		Cantal
	Full comment: Cantaloupe, CA-only, 2000, ND						
145	9A	Melons-honeydew	0.026000	1.000	1.000		Cantal
	Full comment: Cantaloupe, CA-only, 2000, ND						
146	9A	Melons-persian	0.026000	1.000	1.000		Cantal
	Full comment: Cantaloupe, CA-only, 2000, ND						
399	15	Oats-bran	0.010000	1.000	1.000		PDP, 1
	Full comment: PDP, 1999, ND						
269	15	Oats	0.010000	1.000	1.000		PDP, 1
	Full comment: PDP, 1999, ND						
139	8	Paprika	0.143000	1.000	1.000	2	Sweet
	Full comment: Sweet bell pep., PDP, 2002-3, 21 CF/3OH detects						
156	8	Peppers-chilli incl jalapeno	0.143000	1.000	1.000	2	Sweet
	Full comment: Sweet bell pep., PDP, 2002-3, 21 CF/3OH detects						
157	8	Peppers-other	0.143000	1.000	1.000	2	Sweet
	Full comment: Sweet bell pep., PDP, 2002-3, 21 CF/3OH detects						
155	8	Peppers-sweet(garden)	0.143000	1.000	1.000	2	Sweet
	Full comment: Sweet bell pep., PDP, 2002-3, 21 CF/3OH detects						
158	8	Pimientos	0.143000	1.000	1.000	2	Sweet
	Full comment: Sweet bell pep., PDP, 2002-3, 21 CF/3OH detects						
210	1C	Potatoes/white-dry	0.026000	6.500	1.000	9	PDP, 2
	Full comment: PDP, 2000-2, ND						
209	1C	Potatoes/white-peeled	0.026000	1.000	1.000	9	PDP, 2
	Full comment: PDP, 2000-2, ND						
211	1C	Potatoes/white-peel only	0.026000	1.000	1.000	9	PDP, 2
	Full comment: PDP, 2000-2, ND						
208	1C	Potatoes/white-unspecified	0.026000	1.000	1.000	9	PDP, 2
	Full comment: PDP, 2000-2, ND						
207	1C	Potatoes/white-whole	0.026000	1.000	1.000	9	PDP, 2
	Full comment: PDP, 2000-2, ND						
149	9B	Pumpkin	0.026000	1.000	1.000		W. squ
	Full comment: W. squash, CA-only (1997-9), ND						
408	15	Rice-bran	0.025000	1.000	1.000		PDP, 2
	Full comment: PDP, 2000, ND						
271	15	Rice-milled (white)	0.025000	1.000	1.000		PDP, 2
	Full comment: PDP, 2000, ND						
270	15	Rice-rough (brown)	0.025000	1.000	1.000		PDP, 2
	Full comment: PDP, 2000, ND						
409	15	Rice-wild	0.025000	1.000	1.000		PDP, 2
	Full comment: PDP, 2000, ND						
275	15	Sorghum (including milo)	0.020000	1.000	1.000		FT (in
	Full comment: FT (in EPA assessment, no year), ND						
303	6A	Soybean-other	0.013000	1.000	1.000		PDP, 1
	Full comment: PDP, 1997-8, beans, ND						
307	6A	Soybeans-flour (defatted)	0.013000	1.000	1.000		PDP, 1
	Full comment: PDP, 1997-8, beans, ND						
306	6A	Soybeans-flour (low fat)	0.013000	1.000	1.000		PDP, 1
	Full comment: PDP, 1997-8, beans, ND						
305	6A	Soybeans-flour (full fat)	0.013000	1.000	1.000		PDP, 1
	Full comment: PDP, 1997-8, beans, ND						
304	6A	Soybeans-mature seeds dry	0.013000	1.000	1.000		PDP, 1
	Full comment: PDP, 1997-8, beans, ND						
297	6A	Soybeans-oil	0.013000	1.000	1.000		PDP, 1
	Full comment: PDP, 1997-8, beans, ND						
482	O	Soybeans-protein isolate	0.013000	1.000	1.000		PDP, 1
	Full comment: PDP, 1997-8, ND						

```
255 6A   Soybeans-sprouted seeds            0.013000   0.330  1.000      PDP, 1
   Full comment: PDP, 1997-8, beans, ND
150 9B   Squash-summer                      0.026000   1.000  1.000      W. squ
   Full comment: W. squash, CA-only, 1997-9, ND
415 9B   Squash-spaghetti                   0.026000   1.000  1.000      W. squ
   Full comment: W. squash, CA-only, 1997-9, ND
151 9B   Squash-winter                      0.026000   1.000  1.000      W. squ
   Full comment: W. squash, CA-only, 1997-9, ND
 17 O    Strawberries                       0.037000   1.000  1.000      PDP, 1
   Full comment: PDP, 1998-2000, fresh&froz., ND
416 O    Strawberries-juice                 0.037000   1.000  1.000      PDP, 1
   Full comment: PDP, 1998-2000, fresh&froz., ND
282 1A   Sugar-beet                         0.040000   1.000  1.000      FT, 19
   Full comment: FT, 1986 & 1992, sugar beet roots, 2 detects
379 1A   Sugar-beet-molasses                0.040000   1.000  1.000      FT, 19
   Full comment: FT, 1986 & 1992, sugar beet roots, 2 detects
283 O    Sugar-cane                         0.020000   1.000  1.000      FT, 19
   Full comment: FT, 1990-2, ND at sugar stage
284 O    Sugar-cane/molasses                0.020000   1.000  1.000      FT, 19
   Full comment: FT, 1990-2, ND at molasses stage
298 O    Sunflower-oil                      0.020000   1.000  1.000      FT, 19
   Full comment: FT, 1981, only 2 samples
417 O    Sunflower-seeds                    0.330000   1.000  1.000      FT, 19
   Full comment: FT, 1981, confectionary seeds, many detects
432 O    Water-bottled                      0.000197   1.000  1.000      Drinki
   Full comment: Drinking H20, PDP, 2001-3, 14 CF detects
434 O    Water-commercial processing        0.000197   1.000  1.000      Drinki
   Full comment: Drinking H20, PDP, 2001-3, 14 CF detects
435 O    Water-non-food based               0.000197   1.000  1.000      Drinki
   Full comment: Drinking H20, PDP, 2001-3, 14 CF detects
433 O    Water-tap                          0.000197   1.000  1.000      Drinki
   Full comment: Drinking H20, PDP, 2001-3, 14 CF detects
147 9A   Watermelon                         0.026000   1.000  1.000  10  Cantal
   Full comment: Cantaloupe, CA-only, '98-00, PDP 03, ND
436 9A   Watermelon-juice                   0.026000   1.000  1.000  10  Cantal
   Full comment: Cantaloupe, CA-only, '98-00, PDP 03, ND
278 15   Wheat-bran                         0.028000   1.000  1.000   3  Wheat,
   Full comment: Wheat, PDP, 1995-7, 2003, 6 CF-only detects
279 15   Wheat-flour                        0.028000   1.000  1.000   3  Wheat,
   Full comment: Wheat, PDP, 1995-7, 2003, 6 CF-only detects
277 15   Wheat-germ                         0.028000   1.000  1.000   3  Wheat,
   Full comment: Wheat, PDP, 1995-7, 2003, 6 CF-only detects
437 15   Wheat-germ oil                     0.028000   1.000  1.000   3  Wheat,
   Full comment: Wheat, PDP, 1995-7, 2003, 6 CF-only detects
276 15   Wheat-rough                        0.028000   1.000  1.000   3  Wheat,
   Full comment: Wheat, PDP, 1995-7, 2003, 6 CF-only detects
439 9B   Wintermelon                        0.026000   1.000  1.000      Cantal
   Full comment: Cantaloupe, CA-only, 2000, ND
```

IV.1 EXPOSURES AND RISK ESTIMATES - DISTRIBUTIONAL APPROACH

California Department of Pesticide Regulation Ver. 7.87
DEEM ACUTE Analysis for CARBOFURAN (1994-98 data)
Residue file: MC22.RS7 Adjustment factor #2 NOT used.
Analysis Date: 09-21-2005/15:49:34 Residue file dated: 09-20-2005/15:23:04/14
NOEL (Acute) = 0.010000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500 MC list in residue file MC seed = 10
Run Comment: "MC-22, Monte Carlo, RDF10 w.melon + new wheat, barley, rice, H20 data"

U.S. Population	Daily Exposure Analysis /a (mg/kg body-weight/day)	
	per Capita	per User
Mean	0.000081	0.000081
Standard Deviation	0.000080	0.000080
Margin of Exposure 2/	122	122
Percent of aRfD	8.14	8.15

Percent of Person-Days that are User-Days = 99.85%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000022	2.21	452	90.00	0.000160	16.02	62
20.00	0.000031	3.15	317	95.00	0.000213	21.34	46
30.00	0.000040	3.99	250	97.50	0.000282	28.17	35
40.00	0.000049	4.94	202	99.00	0.000389	38.87	25
50.00	0.000060	5.98	167	99.50	0.000484	48.43	20
60.00	0.000072	7.23	138	99.75	0.000592	59.20	16
70.00	0.000090	8.96	111	99.90	0.000796	79.57	12
80.00	0.000114	11.44	87				

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000022	2.20	455	90.00	0.000160	16.01	62
20.00	0.000031	3.13	319	95.00	0.000213	21.32	46
30.00	0.000040	3.98	251	97.50	0.000282	28.16	35
40.00	0.000049	4.93	202	99.00	0.000389	38.85	25
50.00	0.000060	5.97	167	99.50	0.000484	48.40	20
60.00	0.000072	7.22	138	99.75	0.000592	59.18	16
70.00	0.000090	8.95	111	99.90	0.000795	79.54	12
80.00	0.000114	11.43	87				

Western region Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000088	0.000088
Standard Deviation	0.000084	0.000084
Margin of Exposure	114	113
Percent of aRfD	8.77	8.79

Percent of Person-Days that are User-Days = 99.76%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000024	2.40	416	90.00	0.000172	17.22	58
20.00	0.000034	3.41	293	95.00	0.000226	22.56	44
30.00	0.000043	4.29	233	97.50	0.000303	30.31	32
40.00	0.000054	5.37	186	99.00	0.000419	41.86	23
50.00	0.000064	6.44	155	99.50	0.000515	51.45	19
60.00	0.000080	7.95	125	99.75	0.000667	66.68	14
70.00	0.000098	9.84	101	99.90	0.000881	88.06	11
80.00	0.000124	12.35	80				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000024	2.37	421	90.00	0.000172	17.20	58
20.00	0.000034	3.39	295	95.00	0.000225	22.54	44
30.00	0.000043	4.27	233	97.50	0.000303	30.29	33
40.00	0.000054	5.35	186	99.00	0.000418	41.82	23
50.00	0.000064	6.43	155	99.50	0.000514	51.40	19
60.00	0.000079	7.94	125	99.75	0.000666	66.63	15
70.00	0.000098	9.82	101	99.90	0.000880	88.05	11
80.00	0.000123	12.32	81				

Hispanics

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000087	0.000087
Standard Deviation	0.000086	0.000086
Margin of Exposure	114	114
Percent of aRfD	8.71	8.72

Percent of Person-Days that are User-Days = 99.87%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000023	2.33	429	90.00	0.000173	17.35	57
20.00	0.000034	3.36	297	95.00	0.000238	23.76	42
30.00	0.000042	4.24	235	97.50	0.000311	31.06	32
40.00	0.000052	5.22	191	99.00	0.000460	46.05	21
50.00	0.000063	6.26	159	99.50	0.000546	54.62	18
60.00	0.000075	7.54	132	99.75	0.000656	65.59	15
70.00	0.000094	9.37	106	99.90	0.000744	74.41	13
80.00	0.000121	12.06	82				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000023	2.31	432	90.00	0.000173	17.34	57
20.00	0.000033	3.35	298	95.00	0.000237	23.74	42
30.00	0.000042	4.23	236	97.50	0.000311	31.05	32
40.00	0.000052	5.21	191	99.00	0.000460	46.03	21
50.00	0.000063	6.25	159	99.50	0.000546	54.60	18
60.00	0.000075	7.53	132	99.75	0.000656	65.58	15
70.00	0.000094	9.36	106	99.90	0.000744	74.40	13
80.00	0.000121	12.05	82				

Non-hispanic whites Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000080	0.000080
Standard Deviation	0.000079	0.000079
Margin of Exposure	124	124
Percent of aRfD	8.00	8.02

Percent of Person-Days that are User-Days = 99.85%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000022	2.24	446	90.00	0.000156	15.58	64
20.00	0.000032	3.15	317	95.00	0.000207	20.73	48
30.00	0.000040	3.98	251	97.50	0.000273	27.29	36
40.00	0.000049	4.90	204	99.00	0.000381	38.10	26
50.00	0.000059	5.91	169	99.50	0.000468	46.78	21
60.00	0.000071	7.10	140	99.75	0.000577	57.66	17
70.00	0.000088	8.81	113	99.90	0.000881	88.06	11
80.00	0.000112	11.21	89				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000022	2.22	449	90.00	0.000156	15.57	64
20.00	0.000031	3.14	318	95.00	0.000207	20.72	48
30.00	0.000040	3.97	251	97.50	0.000273	27.27	36
40.00	0.000049	4.89	204	99.00	0.000381	38.09	26
50.00	0.000059	5.90	169	99.50	0.000468	46.76	21
60.00	0.000071	7.09	141	99.75	0.000576	57.64	17
70.00	0.000088	8.80	113	99.90	0.000880	88.04	11
80.00	0.000112	11.21	89				

Non-hispanic blacks Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000077	0.000077
Standard Deviation	0.000076	0.000076
Margin of Exposure	130	130
Percent of aRfD	7.67	7.69

Percent of Person-Days that are User-Days = 99.83%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000019	1.88	532	90.00	0.000155	15.46	64
20.00	0.000028	2.78	359	95.00	0.000213	21.34	46
30.00	0.000036	3.61	276	97.50	0.000282	28.18	35
40.00	0.000044	4.37	228	99.00	0.000372	37.21	26
50.00	0.000055	5.46	182	99.50	0.000483	48.31	20
60.00	0.000068	6.81	146	99.75	0.000599	59.89	16
70.00	0.000085	8.50	117	99.90	0.000692	69.23	14
80.00	0.000111	11.06	90				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000019	1.86	536	90.00	0.000154	15.44	64
20.00	0.000028	2.77	360	95.00	0.000213	21.32	46
30.00	0.000036	3.60	277	97.50	0.000282	28.16	35
40.00	0.000044	4.36	229	99.00	0.000372	37.19	26
50.00	0.000055	5.46	183	99.50	0.000483	48.30	20
60.00	0.000068	6.81	146	99.75	0.000598	59.85	16
70.00	0.000085	8.49	117	99.90	0.000692	69.22	14
80.00	0.000110	11.04	90				

Non-hisp/non-white/non-black Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000103	0.000103
Standard Deviation	0.000088	0.000088
Margin of Exposure	97	96
Percent of aRfD	10.29	10.31

Percent of Person-Days that are User-Days = 99.82%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000029	2.91	343	90.00	0.000202	20.20	49
20.00	0.000043	4.31	231	95.00	0.000255	25.49	39
30.00	0.000056	5.60	178	97.50	0.000323	32.27	30
40.00	0.000068	6.78	147	99.00	0.000421	42.14	23
50.00	0.000082	8.21	121	99.50	0.000482	48.19	20
60.00	0.000098	9.81	101	99.75	0.000588	58.81	17
70.00	0.000119	11.95	83	99.90	0.000817	81.73	12
80.00	0.000145	14.48	69				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000029	2.88	347	90.00	0.000201	20.14	49
20.00	0.000043	4.29	232	95.00	0.000255	25.45	39
30.00	0.000056	5.58	179	97.50	0.000323	32.26	30
40.00	0.000068	6.77	147	99.00	0.000421	42.13	23
50.00	0.000082	8.20	121	99.50	0.000482	48.18	20
60.00	0.000098	9.80	102	99.75	0.000588	58.76	17
70.00	0.000119	11.93	83	99.90	0.000817	81.72	12
80.00	0.000145	14.46	69				

All infants

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000181	0.000199
Standard Deviation	0.000166	0.000164
Margin of Exposure	55	50
Percent of aRfD	18.09	19.87

Percent of Person-Days that are User-Days = 91.06%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000044	4.44	225	90.00	0.000418	41.81	23
20.00	0.000066	6.55	152	95.00	0.000513	51.25	19
30.00	0.000088	8.77	113	97.50	0.000603	60.35	16
40.00	0.000115	11.53	86	99.00	0.000717	71.69	13
50.00	0.000144	14.41	69	99.50	0.000838	83.82	11
60.00	0.000196	19.64	50	99.75	0.001004	100.40	9
70.00	0.000259	25.89	38	99.90	0.001156	115.55	8
80.00	0.000324	32.42	30				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000002	0.17	5,977	90.00	0.000403	40.31	24
20.00	0.000050	4.95	202	95.00	0.000497	49.65	20
30.00	0.000072	7.16	139	97.50	0.000590	59.05	16
40.00	0.000099	9.86	101	99.00	0.000709	70.85	14
50.00	0.000129	12.90	77	99.50	0.000833	83.28	12
60.00	0.000172	17.22	58	99.75	0.000997	99.73	10
70.00	0.000241	24.07	41	99.90	0.001152	115.19	8
80.00	0.000310	31.04	32				

Nursing infants (<1 yr old) Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000079	0.000117
Standard Deviation	0.000125	0.000137
Margin of Exposure	126	85
Percent of aRfD	7.88	11.70

Percent of Person-Days that are User-Days = 67.36%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000006	0.64	1,552	90.00	0.000283	28.29	35
20.00	0.000019	1.85	539	95.00	0.000408	40.79	24
30.00	0.000031	3.13	319	97.50	0.000483	48.26	20
40.00	0.000051	5.05	197	99.00	0.000669	66.86	14
50.00	0.000068	6.78	147	99.50	0.000692	69.24	14
60.00	0.000098	9.83	101	99.75	0.000823	82.31	12
70.00	0.000131	13.09	76	99.90	0.000978	97.84	10
80.00	0.000191	19.08	52				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000000	0.00	>1,000,000	90.00	0.000233	23.25	43
20.00	0.000000	0.00	>1,000,000	95.00	0.000345	34.55	28
30.00	0.000000	0.00	>1,000,000	97.50	0.000428	42.76	23
40.00	0.000007	0.74	1,356	99.00	0.000660	66.03	15
50.00	0.000025	2.48	403	99.50	0.000673	67.32	14
60.00	0.000051	5.15	194	99.75	0.000817	81.73	12
70.00	0.000084	8.36	119	99.90	0.000865	86.53	11
80.00	0.000133	13.33	75				

Non-nursing infants (<1 yr old) Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000219	0.000219
Standard Deviation	0.000164	0.000164
Margin of Exposure	45	45
Percent of aRfD	21.94	21.94

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000060	6.01	166	90.00	0.000433	43.34	23
20.00	0.000081	8.09	123	95.00	0.000529	52.86	18
30.00	0.000105	10.45	95	97.50	0.000616	61.63	16
40.00	0.000132	13.17	75	99.00	0.000739	73.85	13
50.00	0.000169	16.92	59	99.50	0.000888	88.80	11
60.00	0.000229	22.88	43	99.75	0.001057	105.67	9
70.00	0.000281	28.07	35	99.90	0.001160	115.95	8
80.00	0.000343	34.27	29				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000060	6.01	166	90.00	0.000433	43.34	23
20.00	0.000081	8.09	123	95.00	0.000529	52.86	18
30.00	0.000105	10.45	95	97.50	0.000616	61.63	16
40.00	0.000132	13.17	75	99.00	0.000739	73.85	13
50.00	0.000169	16.92	59	99.50	0.000888	88.80	11
60.00	0.000229	22.88	43	99.75	0.001057	105.67	9
70.00	0.000281	28.07	35	99.90	0.001160	115.95	8
80.00	0.000343	34.27	29				

Females 13+ (preg/not lactating) Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000071	0.000071
Standard Deviation	0.000052	0.000052
Margin of Exposure	140	139
Percent of aRfD	7.11	7.15

Percent of Person-Days that are User-Days = 99.51%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000022	2.18	457	90.00	0.000152	15.20	65
20.00	0.000036	3.62	276	95.00	0.000187	18.74	53
30.00	0.000040	4.00	249	97.50	0.000210	20.97	47
40.00	0.000050	4.95	201	99.00	0.000263	26.26	38
50.00	0.000056	5.61	178	99.50	0.000264	26.38	37
60.00	0.000066	6.55	152	99.75	0.000264	26.44	37
70.00	0.000075	7.53	132	99.90	0.000281	28.14	35
80.00	0.000099	9.94	100				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000021	2.13	469	90.00	0.000150	15.00	66
20.00	0.000036	3.60	277	95.00	0.000187	18.74	53
30.00	0.000040	3.99	250	97.50	0.000210	20.97	47
40.00	0.000049	4.93	202	99.00	0.000263	26.26	38
50.00	0.000056	5.57	179	99.50	0.000264	26.38	37
60.00	0.000065	6.54	152	99.75	0.000264	26.44	37
70.00	0.000075	7.52	133	99.90	0.000281	28.13	35
80.00	0.000099	9.92	100				

Females 13+ (lactating) Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000087	0.000087
Standard Deviation	0.000116	0.000116
Margin of Exposure	115	115
Percent of aRfD	8.65	8.65

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000020	1.97	507	90.00	0.000171	17.10	58
20.00	0.000034	3.38	296	95.00	0.000207	20.70	48
30.00	0.000042	4.16	240	97.50	0.000301	30.11	33
40.00	0.000054	5.36	186	99.00	0.000905	90.52	11
50.00	0.000063	6.25	159	99.50	0.000911	91.13	10
60.00	0.000067	6.74	148	99.75	0.000914	91.45	10
70.00	0.000079	7.93	126	99.90	0.000916	91.63	10
80.00	0.000104	10.35	96				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000020	1.97	507	90.00	0.000171	17.10	58
20.00	0.000034	3.38	296	95.00	0.000207	20.70	48
30.00	0.000042	4.16	240	97.50	0.000301	30.11	33
40.00	0.000054	5.36	186	99.00	0.000905	90.52	11
50.00	0.000063	6.25	159	99.50	0.000911	91.13	10
60.00	0.000067	6.74	148	99.75	0.000914	91.45	10
70.00	0.000079	7.93	126	99.90	0.000916	91.63	10
80.00	0.000104	10.35	96				

Children 1-2 yrs Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000189	0.000189
Standard Deviation	0.000158	0.000158
Margin of Exposure	52	52
Percent of aRfD	18.88	18.89

Percent of Person-Days that are User-Days = 99.93%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000060	5.99	166	90.00	0.000360	35.99	27
20.00	0.000083	8.31	120	95.00	0.000462	46.23	21
30.00	0.000104	10.42	95	97.50	0.000565	56.50	17
40.00	0.000126	12.58	79	99.00	0.000771	77.09	12
50.00	0.000149	14.89	67	99.50	0.000972	97.22	10
60.00	0.000175	17.51	57	99.75	0.001157	115.67	8
70.00	0.000212	21.21	47	99.90	0.001778	177.77	5
80.00	0.000263	26.31	38				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000060	5.97	167	90.00	0.000360	35.99	27
20.00	0.000083	8.30	120	95.00	0.000462	46.22	21
30.00	0.000104	10.41	96	97.50	0.000565	56.47	17
40.00	0.000126	12.57	79	99.00	0.000771	77.07	12
50.00	0.000149	14.88	67	99.50	0.000972	97.19	10
60.00	0.000175	17.50	57	99.75	0.001157	115.66	8
70.00	0.000212	21.20	47	99.90	0.001778	177.77	5
80.00	0.000263	26.30	38				

Children 3-5 yrs Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000176	0.000176
Standard Deviation	0.000117	0.000117
Margin of Exposure	56	56
Percent of aRfD	17.61	17.61

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000071	7.12	140	90.00	0.000307	30.71	32
20.00	0.000092	9.24	108	95.00	0.000382	38.20	26
30.00	0.000112	11.21	89	97.50	0.000473	47.28	21
40.00	0.000130	13.00	76	99.00	0.000608	60.82	16
50.00	0.000149	14.92	67	99.50	0.000692	69.23	14
60.00	0.000172	17.18	58	99.75	0.000823	82.32	12
70.00	0.000200	19.97	50	99.90	0.001009	100.90	9
80.00	0.000237	23.74	42				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000071	7.12	140	90.00	0.000307	30.71	32
20.00	0.000092	9.24	108	95.00	0.000382	38.20	26
30.00	0.000112	11.21	89	97.50	0.000473	47.28	21
40.00	0.000130	13.00	76	99.00	0.000608	60.82	16
50.00	0.000149	14.92	67	99.50	0.000692	69.23	14
60.00	0.000172	17.18	58	99.75	0.000823	82.32	12
70.00	0.000200	19.97	50	99.90	0.001009	100.90	9
80.00	0.000237	23.74	42				

Children 6-12 yrs Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000122	0.000122
Standard Deviation	0.000092	0.000092
Margin of Exposure	81	81
Percent of aRfD	12.21	12.21

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000046	4.60	217	90.00	0.000209	20.95	47
20.00	0.000063	6.31	158	95.00	0.000265	26.52	37
30.00	0.000077	7.68	130	97.50	0.000329	32.86	30
40.00	0.000090	9.04	110	99.00	0.000417	41.72	23
50.00	0.000104	10.38	96	99.50	0.000526	52.61	19
60.00	0.000119	11.92	83	99.75	0.000719	71.93	13
70.00	0.000137	13.73	72	99.90	0.001066	106.64	9
80.00	0.000163	16.31	61				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000046	4.60	217	90.00	0.000209	20.95	47
20.00	0.000063	6.31	158	95.00	0.000265	26.52	37
30.00	0.000077	7.68	130	97.50	0.000329	32.86	30
40.00	0.000090	9.04	110	99.00	0.000417	41.72	23
50.00	0.000104	10.38	96	99.50	0.000526	52.61	19
60.00	0.000119	11.92	83	99.75	0.000719	71.93	13
70.00	0.000137	13.73	72	99.90	0.001066	106.64	9
80.00	0.000163	16.31	61				

Youth 13-19 yrs Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000080	0.000080
Standard Deviation	0.000069	0.000069
Margin of Exposure	124	124
Percent of aRfD	8.03	8.03

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000028	2.78	360	90.00	0.000144	14.44	69
20.00	0.000037	3.72	269	95.00	0.000185	18.52	54
30.00	0.000047	4.65	214	97.50	0.000230	23.01	43
40.00	0.000056	5.59	178	99.00	0.000295	29.54	33
50.00	0.000065	6.49	154	99.50	0.000432	43.22	23
60.00	0.000076	7.63	130	99.75	0.000472	47.23	21
70.00	0.000090	9.00	111	99.90	0.001062	106.21	9
80.00	0.000111	11.08	90				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000028	2.78	360	90.00	0.000144	14.44	69
20.00	0.000037	3.72	269	95.00	0.000185	18.52	54
30.00	0.000047	4.65	214	97.50	0.000230	23.01	43
40.00	0.000056	5.59	178	99.00	0.000295	29.54	33
50.00	0.000065	6.49	154	99.50	0.000432	43.22	23
60.00	0.000076	7.63	130	99.75	0.000472	47.23	21
70.00	0.000090	9.00	111	99.90	0.001062	106.21	9
80.00	0.000111	11.08	90				

Adults 20-49 yrs Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000068	0.000068
Standard Deviation	0.000056	0.000056
Margin of Exposure	147	147
Percent of aRfD	6.78	6.78

Percent of Person-Days that are User-Days = 99.97%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000022	2.16	463	90.00	0.000126	12.56	79
20.00	0.000031	3.06	327	95.00	0.000161	16.14	61
30.00	0.000038	3.81	262	97.50	0.000199	19.89	50
40.00	0.000046	4.56	219	99.00	0.000265	26.47	37
50.00	0.000054	5.44	183	99.50	0.000340	33.97	29
60.00	0.000064	6.40	156	99.75	0.000427	42.67	23
70.00	0.000077	7.67	130	99.90	0.000563	56.31	17
80.00	0.000095	9.55	104				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000022	2.15	464	90.00	0.000126	12.56	79
20.00	0.000031	3.06	327	95.00	0.000161	16.13	61
30.00	0.000038	3.81	262	97.50	0.000199	19.88	50
40.00	0.000046	4.56	219	99.00	0.000265	26.47	37
50.00	0.000054	5.43	184	99.50	0.000340	33.96	29
60.00	0.000064	6.40	156	99.75	0.000427	42.67	23
70.00	0.000077	7.67	130	99.90	0.000563	56.31	17
80.00	0.000095	9.55	104				

Adults 50+ yrs Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000054	0.000054
Standard Deviation	0.000044	0.000044
Margin of Exposure	185	185
Percent of aRfD	5.38	5.38

Percent of Person-Days that are User-Days = 99.98%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000017	1.72	580	90.00	0.000103	10.31	96
20.00	0.000024	2.39	418	95.00	0.000132	13.24	75
30.00	0.000029	2.94	340	97.50	0.000164	16.42	60
40.00	0.000035	3.54	282	99.00	0.000212	21.19	47
50.00	0.000042	4.20	238	99.50	0.000260	26.05	38
60.00	0.000051	5.07	197	99.75	0.000320	32.03	31
70.00	0.000060	6.04	165	99.90	0.000416	41.58	24
80.00	0.000075	7.50	133				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000017	1.72	580	90.00	0.000103	10.31	96
20.00	0.000024	2.39	418	95.00	0.000132	13.24	75
30.00	0.000029	2.94	340	97.50	0.000164	16.42	60
40.00	0.000035	3.54	282	99.00	0.000212	21.19	47
50.00	0.000042	4.19	238	99.50	0.000260	26.05	38
60.00	0.000051	5.07	197	99.75	0.000320	32.03	31
70.00	0.000060	6.04	165	99.90	0.000416	41.58	24
80.00	0.000075	7.49	133				

Females 13-49 yrs Daily Exposure Analysis
---------- (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000065	0.000065
Standard Deviation	0.000054	0.000054
Margin of Exposure	154	154
Percent of aRfD	6.46	6.47

Percent of Person-Days that are User-Days = 99.99%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000021	2.05	487	90.00	0.000120	12.00	83
20.00	0.000029	2.92	342	95.00	0.000156	15.57	64
30.00	0.000036	3.65	274	97.50	0.000195	19.54	51
40.00	0.000043	4.34	230	99.00	0.000262	26.24	38
50.00	0.000052	5.15	194	99.50	0.000312	31.18	32
60.00	0.000061	6.09	164	99.75	0.000428	42.79	23
70.00	0.000073	7.28	137	99.90	0.000546	54.61	18
80.00	0.000090	9.03	110				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000021	2.05	487	90.00	0.000120	12.00	83
20.00	0.000029	2.92	342	95.00	0.000156	15.57	64
30.00	0.000036	3.64	274	97.50	0.000195	19.54	51
40.00	0.000043	4.34	230	99.00	0.000262	26.23	38
50.00	0.000052	5.15	194	99.50	0.000312	31.18	32
60.00	0.000061	6.09	164	99.75	0.000428	42.79	23
70.00	0.000073	7.28	137	99.90	0.000546	54.61	18
80.00	0.000090	9.03	110				

Custom demographics 1: m/f 16-70 yr
All Seasons
All Regions
Sex: M/F-all/
All Races
Age-Low: 16 yrs High: 70 yrs

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000065	0.000065
Standard Deviation	0.000054	0.000054
Margin of Exposure	153	153
Percent of aRfD	6.53	6.53

Percent of Person-Days that are User-Days = 99.98%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000020	2.04	489	90.00	0.000122	12.21	81
20.00	0.000029	2.89	346	95.00	0.000157	15.72	63
30.00	0.000036	3.63	275	97.50	0.000196	19.60	51
40.00	0.000044	4.38	228	99.00	0.000259	25.89	38
50.00	0.000052	5.22	191	99.50	0.000318	31.84	31
60.00	0.000062	6.17	162	99.75	0.000400	40.04	24
70.00	0.000074	7.36	135	99.90	0.000537	53.71	18
80.00	0.000092	9.22	108				

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000020	2.04	489	90.00	0.000122	12.21	81
20.00	0.000029	2.89	346	95.00	0.000157	15.72	63
30.00	0.000036	3.63	275	97.50	0.000196	19.60	51
40.00	0.000044	4.38	228	99.00	0.000259	25.89	38
50.00	0.000052	5.22	191	99.50	0.000318	31.84	31
60.00	0.000062	6.17	162	99.75	0.000400	40.04	24
70.00	0.000074	7.36	135	99.90	0.000537	53.71	18
80.00	0.000092	9.22	108				

IV.3. MONTE CARLO RESIDUE DATA FILES

RDF1
CUCUMBERS PCT=7%
TOTALNZ=7
TOTALZ=857
TOTALLOD=58 LODRES=0.021
0.55
0.45
0.16
0.15
0.13
0.043
0.043

RDF2
SWEETBELLPEPPERS PCT=4%
TOTALNZ=21
TOTALZ=874
TOTALLOD=16 LODRES=0.003
0.090
0.059
0.028
0.028
0.025
0.024
0.023
0.023
0.017
0.012
0.011
0.011
0.009
0.008
0.007
0.005
0.005
0.005
0.005
0.005
0.005

RDF3
WHEATGRAIN-UNCOOKED PCT=100% (i.e., BLENDED)
TOTALNZ=6
TOTALZ=0
TOTALLOD=1557 LODRES=0.005
0.027
0.013
0.013
0.013
0.013
0.013

RDF4
SWEETCORN-FRESH PCT=4%
TOTALNZ=2
TOTALZ=1223
TOTALLOD=49 LODRES=0.013
0.052
0.033

RDF5
CORNGRAIN-HFCS PCT=100% (i.e., BLENDED)
TOTALNZ=0
TOTALZ=0
TOTALLOD=454 LODRES=0.009

RDF6
GRAPES-UNCOOKED PCT=1%
TOTALNZ=0
TOTALZ=126
TOTALLOD=16 LODRES=0.013

RDF7
GRAPES-JUICE-UNCOOKED PCT=100% (i.e., BLENDED)
TOTALNZ=0
TOTALZ=0
TOTALLOD=348 LODRES=0.013

RDF8
BANANAS PCT=7%
TOTALNZ=0
TOTALZ=1780
TOTALLOD=135 LODRES=0.026

RDF9
POTATOES PCT=13%
TOTALNZ=0
TOTALZ=1280
TOTALLOD=192 LODRES=0.013

RDF10
WATERMELONS PCT=7%
TOTALNZ=0
TOTALZ=607
TOTALLOD=46 LODRES=0.013

Attachment V. Chronic Dietary Exposure Estimate

V.1. CHRONIC DIETARY RESIDUE DATA

Filename: H:\ARubin\Corel\CARBOFURAN\Dietary Assessment\MC-22\Chronic-22.RS7
Chemical:
RfD(Chronic): 0 mg/kg bw/day NOEL(Chronic): 0 mg/kg bw/day
RfD(Acute): 0 mg/kg bw/day NOEL(Acute): 0 mg/kg bw/day
Date created/last modified: 09-22-2005/14:10:58/14 Program ver. 7.87

Food Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
181	O	Artichokes-globe	0.057500	1.000	1.000	
72	O	Bananas	0.026000	1.000	1.000	
73	O	Bananas-dried	0.026000	3.900	1.000	
378	O	Bananas-juice	0.026000	1.000	1.000	
265	15	Barley	0.012500	1.000	1.000	
152	9B	Bitter melon	0.013000	1.000	1.000	cantal
		Full comment: cantaloupe data				
301	O	Canola oil (rape seed oil)	0.040500	1.000	1.000	
143	9A	Casabas	0.013000	1.000	1.000	cantal
		Full comment: cantaloupe data				
112	O	Coffee	0.010000	1.000	1.000	
267	15	Corn grain-bran	0.013000	1.000	1.000	sweet
		Full comment: sweet corn data				
266	15	Corn grain-endosperm	0.013000	1.000	1.000	sweet
		Full comment: sweet corn data				
289	15	Corn grain-oil	0.009000	1.000	1.000	corn g
		Full comment: corn grain - sugar - hfcs data				
268	15	Corn grain/sugar/hfcs	0.009000	1.500	1.000	corn g
		Full comment: corn grain - sugar - hfcs data				
388	15	Corn grain/sugar-molasses	0.009000	1.500	1.000	corn g
		Full comment: corn grain - sugar - hfcs data				
237	15	Corn/pop	0.013000	1.000	1.000	sweet
		Full comment: sweet corn data				
238	15	Corn/sweet	0.013000	1.000	1.000	sweet
		Full comment: sweet corn data				
291	O	Cottonseed-meal	0.037500	1.000	1.000	
290	O	Cottonseed-oil	0.037500	1.000	1.000	
8	O	Cranberries	0.010000	1.000	1.000	
9	O	Cranberries-juice	0.010000	1.100	1.000	
389	O	Cranberries-juice-concentrate	0.010000	3.300	1.000	
144	9A	Crenshaws	0.013000	1.000	1.000	cantal
		Full comment: cantaloupe data				
148	9B	Cucumbers	0.022300	1.000	1.000	
13	O	Grapes	0.013000	1.000	1.000	
15	O	Grapes-juice	0.013000	1.200	1.000	
392	O	Grapes-juice-concentrate	0.013000	3.600	1.000	
14	O	Grapes-raisins	0.013000	4.300	1.000	grape
		Full comment: grape data				
315	O	Grapes-wine and sherry	0.013000	1.000	1.000	grape
		Full comment: grape data				
141	9A	Melons-cantaloupes-juice	0.013000	1.000	1.000	cantal
		Full comment: cantaloupe data				
142	9A	Melons-cantaloupes-pulp	0.013000	1.000	1.000	cantal
		Full comment: cantaloupe data				
145	9A	Melons-honeydew	0.013000	1.000	1.000	cantal
		Full comment: cantaloupe data				
146	9A	Melons-persian	0.013000	1.000	1.000	cantal
		Full comment: cantaloupe data				
399	15	Oats-bran	0.005000	1.000	1.000	
269	15	Oats	0.005000	1.000	1.000	
139	8	Paprika	0.033000	1.000	1.000	sweet
		Full comment: sweet bell pepper data				
156	8	Peppers-chilli incl jalapeno	0.033000	1.000	1.000	sweet
		Full comment: sweet bell pepper data				
157	8	Peppers-other	0.033000	1.000	1.000	sweet
		Full comment: sweet bell pepper data				
155	8	Peppers-sweet(garden)	0.033000	1.000	1.000	sweet

		Full comment: sweet bell pepper data				
158	8	Pimientos Full comment: sweet bell pepper data	0.033000	1.000	1.000	sweet
210	1C	Potatoes/white-dry	0.013000	6.500	1.000	
209	1C	Potatoes/white-peeled	0.013000	1.000	1.000	
211	1C	Potatoes/white-peel only	0.013000	1.000	1.000	
208	1C	Potatoes/white-unspecified	0.013000	1.000	1.000	
207	1C	Potatoes/white-whole	0.013000	1.000	1.000	
149	9B	Pumpkin Full comment: winter squash data	0.013000	1.000	1.000	winter
408	15	Rice-bran	0.012500	1.000	1.000	
271	15	Rice-milled (white)	0.012500	1.000	1.000	
270	15	Rice-rough (brown)	0.012500	1.000	1.000	
409	15	Rice-wild	0.012500	1.000	1.000	
275	15	Sorghum (including milo)	0.010000	1.000	1.000	
303	6A	Soybean-other	0.006500	1.000	1.000	
307	6A	Soybeans-flour (defatted)	0.006500	1.000	1.000	
306	6A	Soybeans-flour (low fat)	0.006500	1.000	1.000	
305	6A	Soybeans-flour (full fat)	0.006500	1.000	1.000	
304	6A	Soybeans-mature seeds dry	0.006500	1.000	1.000	
297	6A	Soybeans-oil	0.006500	1.000	1.000	
482	O	Soybeans-protein isolate	0.006500	1.000	1.000	
255	6A	Soybeans-sprouted seeds	0.006500	0.330	1.000	
150	9B	Squash-summer	0.013000	1.000	1.000	
415	9B	Squash-spaghetti	0.013000	1.000	1.000	
151	9B	Squash-winter	0.013000	1.000	1.000	
17	O	Strawberries	0.018500	1.000	1.000	
416	O	Strawberries-juice	0.018500	1.000	1.000	
282	1A	Sugar-beet	0.020200	1.000	1.000	
379	1A	Sugar-beet-molasses	0.020200	1.000	1.000	
283	O	Sugar-cane	0.010000	1.000	1.000	
284	O	Sugar-cane/molasses	0.010000	1.000	1.000	
298	O	Sunflower-oil	0.015000	1.000	1.000	
417	O	Sunflower-seeds	0.084700	1.000	1.000	
432	O	Water-bottled	0.000127	1.000	1.000	
434	O	Water-commercial processing	0.000127	1.000	1.000	
435	O	Water-non-food based	0.000127	1.000	1.000	
433	O	Water-tap	0.000127	1.000	1.000	
147	9A	Watermelon Full comment: cantaloupe data	0.013000	1.000	1.000	cantal
436	9A	Watermelon-juice Full comment: cantaloupe data	0.013000	1.000	1.000	cantal
278	15	Wheat-bran	0.002500	1.000	1.000	
279	15	Wheat-flour	0.002500	1.000	1.000	
277	15	Wheat-germ	0.002500	1.000	1.000	
437	15	Wheat-germ oil	0.002500	1.000	1.000	
276	15	Wheat-rough	0.002500	1.000	1.000	
439	9B	Wintermelon Full comment: cantaloupe data	0.013000	1.000	1.000	cantal

V.2. CHRONIC DIETARY EXPOSURES AND RISK ESTIMATES

California Department of Pesticide Regulation Ver. 7.87
DEEM Chronic analysis for (1994-98 data)
Residue file name: H:\ARubin\Corel\CARBOFURAN\Dietary Assessment\MC-22\Chronic-22.RS7
Adjustment factor #2 NOT used.
Analysis Date 09-22-2005/14:16:42 Residue file dated: 09-22-2005/14:10:58/14
Reference dose (RfD, Chronic) = .001 mg/kg bw/day
NOEL (Chronic) = .1 mg/kg bw/day

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Margin of Exposure 1/	Percent of RfD
U.S. Population (total)	0.000085	1,172	8.5%
U.S. Population (spring season)	0.000087	1,145	8.7%
U.S. Population (summer season)	0.000092	1,092	9.2%
U.S. Population (autumn season)	0.000081	1,234	8.1%
U.S. Population (winter season)	0.000081	1,228	8.1%
Northeast region	0.000084	1,184	8.4%
Midwest region	0.000089	1,126	8.9%
Southern region	0.000079	1,259	7.9%
Western region	0.000092	1,089	9.2%
Hispanics	0.000095	1,054	9.5%
Non-hispanic whites	0.000084	1,189	8.4%
Non-hispanic blacks	0.000079	1,262	7.9%
Non-hisp/non-white/non-black	0.000101	992	10.1%
All infants (< 1 year)	0.000166	601	16.6%
Nursing infants	0.000081	1,235	8.1%
Non-nursing infants	0.000199	503	19.9%
Children 1-6 yrs	0.000202	495	20.2%
Children 7-12 yrs	0.000119	844	11.9%
Females 13-19 (not preg or nursing)	0.000068	1,467	6.8%
Females 20+ (not preg or nursing)	0.000062	1,616	6.2%
Females 13-50 yrs	0.000064	1,554	6.4%
Females 13+ (preg/not nursing)	0.000070	1,419	7.0%
Females 13+ (nursing)	0.000083	1,207	8.3%
Males 13-19 yrs	0.000085	1,180	8.5%
Males 20+ yrs	0.000068	1,465	6.8%
Seniors 55+	0.000061	1,627	6.1%
Children 1-2 yrs	0.000234	427	23.4%
Children 3-5 yrs	0.000196	510	19.6%
Children 6-12 yrs	0.000124	805	12.4%
Youth 13-19 yrs	0.000077	1,307	7.7%
Adults 20-49 yrs	0.000067	1,489	6.7%
Adults 50+ yrs	0.000062	1,623	6.2%
Females 13-49 yrs	0.000064	1,550	6.4%

APPENDIX I. Estimation of exposure of persons in California to pesticide products that contain carbofuran (HS-1803)

(Appendix I can be found on the following pages.)

ESTIMATION OF EXPOSURE OF PERSONS IN CALIFORNIA TO PESTICIDE PRODUCTS THAT CONTAIN CARBOFURAN

HS-1803

By

Sheryl Beauvais, Staff Toxicologist (Specialist)

Josh Johnson, Associate Environmental Research Scientist

California Environmental Protection Agency

Department of Pesticide Regulation

Worker Health and Safety Branch

1001 I Street, Box 4015

Sacramento, California 95812

January 6, 2006

TABLE OF CONTENTS

ABSTRACT 3

INTRODUCTION 4

U.S. EPA STATUS 5

FORMULATIONS AND USES 6

REPORTED ILLNESSES 7

LABEL PRECAUTIONS AND CALIFORNIA REQUIREMENTS 8

PHARMACOKINETICS 9

Dermal and Inhalation Absorption 9

Metabolism 13

ENVIRONMENTAL CONCENTRATIONS 13

Dislodgeable Foliar Residues 13

Ground and Surface Water 16

Air 17

EXPOSURE ASSESSMENT 20

Handlers 21

Reentry Workers 30

Ambient Air and Bystander Exposures 34

EXPOSURE APPRAISAL 38

Handler Exposure Estimates 38

Reentry Worker Exposure Estimates 43

Ambient Air and Bystander Exposure Estimates 44

REFERENCES 45

APPENDICES 58

ABSTRACT

Carbofuran is a carbamate insecticide/miticide that has been registered in California since 1974, exclusively for agricultural uses. One formulation is currently registered in California, a liquid flowable formulation containing 44% active ingredient that is a Restricted Use Pesticide. Carbofuran may be applied to foliage by ground or air methods, to soil during planting, by chemigation, as a dip/slurry, or by drenching. This exposure assessment was performed in response to adverse reproductive, chronic, and genotoxic effects observed in animal model studies. Metabolic and toxicity studies using laboratory animals suggest that the principle metabolite, 3-hydroxy carbofuran, has a similar toxicity to the parent compound.

Significant exposure scenarios were identified based on uses listed on product labels. A total of nine handler and three reentry scenarios were identified. As acceptable exposure data were lacking, handler exposures were estimated using surrogate data from the Pesticide Handler Exposure Database and two models from the U.S. Environmental Protection Agency; reentry exposures were estimated using dislodgeable foliar residue data for carbofuran from several studies and transfer coefficients from surrogate chemicals. Acute Absorbed Daily Dosage (Acute ADD) estimates for handlers ranged from 0.002 mg/kg/day to 6.40 mg/kg/day. Seasonal, Annual and Lifetime ADD estimates for handlers ranged 0.0006 – 2.14 mg/kg/day; 0.0001 – 0.357 mg/kg/day; and 0.0001 – 0.190 mg/kg/day, respectively. Acute ADD estimates for fieldworkers in potentially significant exposure scenarios were 0.007 mg/kg/day for cotton scouts, 0.099 mg/kg/day for alfalfa scouts and 0.016 mg/kg/day for potato scouts. Seasonal, Annual and Lifetime ADD estimates for cotton scouts were 0.0009, 0.0001 and 0.00008 mg/kg/day. Seasonal, Annual and Lifetime ADD estimates for alfalfa scouts were 0.070, 0.012, and 0.006 mg/kg/day. Seasonal, Annual and Lifetime ADD estimates for potato scouts were 0.010, 0.002, and 0.001 mg/kg/day.

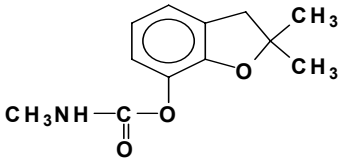
Ambient air exposures and bystander exposures during applications were estimated as well. Acute ADD for ambient air exposures in Imperial County ranged 0.000004 – 0.000070 mg/kg/day for infants and 0.000002 – 0.000034 mg/kg/day for adults. Acute ADD for ambient air exposures in Sacramento County ranged 0.0000014 – 0.0000016 mg/kg/day for infants and 0.0000007 – 0.0000008 mg/kg/day for adults. Seasonal ADD ranged 0.000004 – 0.000020 mg/kg/day for Imperial County and 0.0000002 – 0.0000005 mg/kg/day for Sacramento County. Annual ADD ranged 0.000001 – 0.000003 mg/kg/day for Imperial County and 0.00000007 – 0.0000002 mg/kg/day for Sacramento County.

Bystander exposure estimates were based on air monitoring done 20 meters from the edge of an Imperial County alfalfa field. Acute ADD for bystanders was 0.000454 mg/kg/day for infants and 0.000216 mg/kg/day for adults. These estimates were based on a 24-hour time-weighted average concentration and an assumption of typical activity levels. As available information suggests that exposures of less than 24 hours can result in toxicity, 1-hour absorbed dose estimates were calculated as well, based on the highest measured concentration during a one-hour measuring period and an assumption of heavy activity. These 1-hour absorbed dose estimates were 0.000550 mg/kg/hr for infants and 0.000099 mg/kg/hr for adults. Seasonal and annual exposures for bystanders were not estimated separately, because airborne concentrations are anticipated to reach ambient levels within a few days after each application.

INTRODUCTION

Carbofuran (2,2-dimethyl-2,3-dihydro-7-benzofuranyl-N-methylcarbamate or 2,3-dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate) is sold under the trade name Furadan® (FMC Corporation). As a carbamate, it is a cholinesterase inhibitor (Gupta, 1994). It is a broad-spectrum insecticide, acaricide, and nematicide, and has been shown to be absorbed and translocated by certain plants (Arunachalam and Lakshmanan, 1982; Buyanovsky *et al*., 1995).

Technical carbofuran is a white crystalline solid whose empirical formula is $C_{12}H_{15}NO_3$. It has the following chemical structure:



The molecular weight of carbofuran is 221.26. Selected physicochemical properties include water solubility of 351 ppm @ 25° (Evert, 2002); melting point of 153-154 °C (Alvarez, 1987); and vapor pressure of 6×10^{-7} mm Hg @ 25°C (Alvarez, 1989).

The octanol/water partition coefficients (K_{ow}) for carbofuran were measured as 17 and 26 in 1 and 10 µg/L solutions, respectively (Brandau, 1975). The log K_{ow} for carbofuran would be 1.23 – 1.42. The K_{ow} differed only slightly between solutions with different carbofuran concentrations, and was not considered to be affected by concentration (Brandau, 1975). The vapor pressure and water solubility reported above were used to calculate a Henry's Law constant of 5×10^{-10} atm-m^3/mole (Ferraro, 1989). Airborne carbofuran is reported to be photooxidized by reacting with hydroxyl radicals; the half-life of this reaction is estimated at 4.6 hours (Evert, 2002).

Carbofuran is stable under neutral or acid conditions and readily hydrolyses in basic solution (McCarthy, 1975). The rate of base-catalyzed hydrolysis increases with increasing pH (McCarthy, 1975; Gupta, 1994; Mohapatra and Awasthi, 1997; Evert, 2002). The half-life of carbofuran varies from 1 – 2 days in rice paddy water, and 2 – 5 weeks in soils during the growing season, to 3 – 5 months during the winter (McCarthy, 1975). It does not bioaccumulate (McCarthy, 1975; Evert, 2002), and its degradation can be both chemical and microbial (Kross *et al.*, 1992; Mohapatra and Awasthi, 1997). In water and soils, it decomposes to carbon dioxide, methylamine, and carbofuran phenol (McCarthy, 1975).

Carbofuran has been assigned to Toxicity Category I by the U.S. Environmental Protection Agency (U.S. EPA), based on responses to exposure via the oral, inhalation and dermal routes (U.S. EPA, 1984). As a carbamate, it is a reversible cholinesterase inhibitor, with recovery of inhibited enzyme occurring in as little as a few hours (Gupta, 1994). All carbofuran products are classified by U.S. EPA as restricted-use pesticides due to concern about inhalation toxicity (Title 40 Code of Federal Regulations (CFR), Section 152.175), and are listed as restricted-use pesticides under California regulations as well (Title 3 Code of California Regulations (3 CCR), Section 6400).

The Department of Pesticide Regulation (DPR) is charged with protecting individuals and the environment from potential adverse effects that may result from the use of pesticides in the State (California Food and Agriculture Code (CFAC), Sections 11501, 12824, 12825, 12826, 13121-13135, 14102, and 14103). As part of DPR's effort to meet this mandate, pesticide active ingredients (AIs) are prioritized for assessment of exposure and risk potential (DPR, 2004). Following this prioritization process, AIs are evaluated in accordance with California regulation (3 CCR 6158). Carbofuran is being evaluated based on adverse reproductive, chronic, and genotoxic effects observed in laboratory studies. This Exposure Assessment Document (EAD) is the first prepared by DPR for carbofuran.

U.S. EPA STATUS

U.S. EPA issued a reregistration guidance document for carbofuran (U.S. EPA, 1984), which outlined their regulatory position on the use of carbofuran products. Subsequently, based on acute adverse effects on avian species, six positional documents were issued in the Federal Register (FR) restricting carbofuran uses, application methods, and formulations (50 FR 41938, 16 October 1985; 54 FR 3744, 25 January 1989; 55 FR 42266, 18 October 1990; 56 FR 33286, 19 July 1991; 56 FR 64621, 11 December 1991; 60 FR 11090, 1 March 1995). Use on rice, which was one of the uses voluntarily cancelled, was conditionally extended through 2000 (60 FR 11090, 1 March 1995). Carbofuran use on rice was discontinued after the 2000 growing season (66 FR 39709, 1 August 2001).

Because of the acute avian risk posed by the use of flowable carbofuran products (Furadan® 4F Insecticide-Nematicide, EPA Reg. No. 279-2876), the U.S. EPA cancelled uses on grapes and strawberries in 1997 (62 FR 6775, 13 February 1997). As of October 2001, three Special Local Need (SLN, Section 24c of the Federal Insecticide, Fungicide, and Rodenticide Act, or FIFRA) uses were registered in California to control specific pests on grapes; applications are allowed via drip irrigation only (CA SLN No. 940005, CA SLN No. 980011, and CA SLN No. 980012). Two other SLN uses were registered as well, to control specific pests on ornamental plants (CA SLN No. 830058) and artichokes (CA SLN No. 860037). Emergency exemptions (FIFRA Section 18) issued in 1999 – 2003 allowed foliar uses on cotton to control cotton aphids in California. No emergency exemption was issued in 2004, nor has one been issued or requested as of July 2005. However, foliar applications to cotton are considered in this EAD, in case emergency exemptions are issued in the future.

Dietary risks are being evaluated by the U.S. EPA as required under the Food Quality Protection Act. One food tolerance, for carbofuran residues on rice, has already been revoked and will not be evaluated (66 FR 39709,1 August 2001). This tolerance was revoked because use of granular carbofuran on rice is no longer allowed, in response to concern about avian toxicity. As part of its pesticide Reregistration Eligibility Decision process required by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), U.S. EPA recently released human occupational exposure and preliminary risk assessments for carbofuran (Drew *et al.*, 2005; Weiss, 2005).

FORMULATIONS AND USES

Just one carbofuran formulation is registered in California, a 44% AI flowable liquid concentrate, Furadan® 4F Insecticide-Nematicide (EPA Reg. No. 279-2876). A 5% AI granular formulation, Furadan® 5G Insecticide-Nematicide (EPA Reg. No. 279-50634), was registered until 2001 as a SLN registration (CA SLN No. 970005) for use on rice. The registration for a granular formulation was withdrawn by U.S. EPA and was not considered in this exposure assessment. Carbofuran may be applied as a foliar spray by aerial or ground equipment, as a soil application, by irrigation (SLN No. CA-980012 for winegrapes), as a dip, or by drenching (SLN No. CA-830058 for container grown ornamental plants in nurseries or greenhouses). Maximum application rates for Furadan® 4F range from 0.5 pints/acre (0.25 lbs AI/acre, or 0.28 kg AI/hectare (ha)) applied as a foliar application (e.g., on cotton) to 2.5 gallons/acre (10 lbs AI/acre, or 11 kg AI/ha) applied as a soil drench (e.g., on field-grown ornamentals).

Table 1 summarizes carbofuran use in California in the years 1999 through 2003, the most recent five years for which data are available (DPR, 2000, 2001, 2002, 2003, 2005a). The three crops receiving most of the carbofuran applications were alfalfa (forage, fodder/hay), grapes (table and wine), and cotton. Annual use on these three crops in the years 1999 through 2003 accounted for greater than 70% of all carbofuran uses (mean: 90%, range: 74 – 98%). Use on rice has not been allowed since 2000. Although dip/slurry use on pine seedlings is allowed in California, a review of the 1991 – 2003 PUR shows no reported uses on pine seedlings (DPR, 2005b).

Table 1. Carbofuran Use in California Between 1999 and 2003 [a]

	Pounds applied (% total in state)				
Crop	1999	2000	2001	2002	2003
Alfalfa [b]	64,442 (46.6)	65,333 (49.3)	39,316 (41.0)	41,920 (53.3)	37,182 (45.5)
Grapes	26,225 (19.0)	21,709 (16.8)	15,394 (16.1)	14,876 (18.2)	7,921 (9.7)
Cotton [c]	12,848 (9.3)	26,359 (19.9)	38,829 (40.5)	21,938 (26.9)	1,832 (2.2)
Nursery	1,629 (1.2)	1,044 (0.8)	1,524 (1.6)	1,528 (1.9)	1,072 (1.3)
Artichokes [b]	2,289 (1.7)	1,067 (0.8)	715 (0.7)	527 (0.6)	882 (1.1)
Bermudagrass	1,006 (0.7)	0 (0.0)	15 (0.0)	75 (0.1)	0 (0.0)
Rice	29,014 (21.0)	14,547 (11.3)	0 (0.0)	3 (0.0)	0 (0.0)
Other crops [d]	759 (0.5)	314 (0.2)	70 (0.1)	783 (1.0)	385 (0.5)
Total	138,212	128,618	95,863	81,650	49,275

[a] DPR (2000, 2001, 2002, 2003, 2005a). Crops arranged in descending order by use in 2003.
[b] Foliar applications of carbofuran are allowed on this crop.
[c] The product label allows applications at planting only. Section 18 emergency exemptions issued each year between 1999 and 2003 allowed foliar use to control cotton aphids (exemption has not been issued since 2003).
[d] Includes the following crops on which foliar applications of carbofuran are allowed: potatoes, barley, oats, wheat, soybeans and sugarcane. Foliar applications are allowed on sweet corn that is mechanically harvested, and on field corn that has not received post-plant soil applications.

Total carbofuran use declined between 1999 and 2003, as did use on alfalfa, grapes and cotton (Table 1). Annual use on cotton was greater in 2000 – 2002 than in 1999 or 2003. Insecticide use in general increased in cotton between 2002 and 2003, but most of the increase was of newer, "low risk" insecticides rather than insecticides such as carbofuran (DPR, 2005a).

Worker exposure to carbofuran may be anticipated to occur during handling (mixing, loading, flagging, and application), and during reentry activities, such as scouting, thinning and harvesting of crops that have received foliar applications of carbofuran (these crops have been indicated in Table 1). Additionally, carbofuran was detected in monitoring of ambient air in some urban and rural areas and in air near application sites, suggesting that public exposure to airborne carbofuran might occur.

REPORTED ILLNESSES

Reports of illness and injury associated with definite, probable, or possible exposure to pesticide products are recorded in a database maintained by the Pesticide Illness Surveillance Program (PISP) at DPR. The PISP database contains information about the nature of the pesticide exposure and the subsequent illness or injury. "Definite" means that both physical and medical evidence document exposure and consequent health effects, "probable" means that circumstantial evidence supports a relationship to pesticide exposure, and "possible" means that evidence neither supports nor contradicts a relationship (DPR, 2005c).

Between 1992 and 2003, a total of 77 reports of illnesses, injuries, or death associated with exposure to carbofuran, alone or in combination with other pesticides, were received by PISP (Verder-Carlos, 2005). Most of the illnesses were systemic in nature (69 of 77, about 90% of the total cases), with complaints of nausea, vomiting, abdominal cramps, headache, and dizziness (Verder-Carlos, 2005). The other eight incidents consisted of injuries or irritation to eyes, skin or throat. There were two reported cases of hospitalization, one in 1994 and one in 1998, and 37 cases involving disability that ranged from one to twenty-eight days. A single reported death in 1999 followed ingestion of carbofuran; no other deaths have been associated with carbofuran exposures in California.

Of the 77 total illness reports received by PISP, 56 came from occupational exposures, in which the subjects were working with or near carbofuran (or multiple pesticides that included carbofuran), or were working in treated areas. Of the individuals reporting illness following occupational exposures, three were mixer/loaders and five were applicators. Thirty-six workers reported illness after entering a field treated with carbofuran. Most of the other exposures occurred when carbofuran drifted from a nearby application.

Two incidents resulted in multiple illness reports to PISP. Following a drift incident in 1993, 19 residents from a single neighborhood reported symptoms including headache, dizziness, nausea, and irritated throat and eyes (Verder-Carlos, 2005). In 1998, 34 field workers began weeding a treated cotton field two hours after an application of carbofuran, mepiquat chloride, and abamectin (Das *et al*., 1999; Edmiston *et al*., 1999). The exposure duration was approximately 3.5 hours; shortly afterward, the workers developed symptoms including headache, nausea,

vomiting, diarrhea, eye irritation, respiratory problems, salivation, and muscle weakness. Carbofuran and 3-hydroxycarbofuran residues were detected in foliage samples collected from the field, as well as in clothing and urine samples taken from the affected workers. Additionally, red cell cholinesterase activity was below the normal range for all ten workers from whom blood samples were drawn (Edmiston *et al*., 1999).

LABEL PRECAUTIONS AND CALIFORNIA REQUIREMENTS

Furadan® 4F (44% AI) has been assigned Toxicity Category I due to oral and inhalation toxicity. The signal word on the label is DANGER. Due to its acute oral and inhalation toxicity, carbofuran is classified as a Restricted Use Pesticide according to U.S. EPA (40 CFR 152.175) and under California regulation (3 CCR 6400). As a Toxicity Category I pesticide, carbofuran has additional requirements under the California Worker Safety Regulations. A closed system is required during mixing and loading, unless one gallon or less is handled per day from the original one gallon container (3 CCR 6746). Pilots are required to use a closed system during handling if the pesticide is an organophosphate or a carbamate and is Toxicity Category I (3 CCR 6544).

With regard to protective clothing, the label states that applicators and other handlers must wear long-sleeved shirt, long pants, shoes, and socks. Required personal protective equipment (PPE) for handlers includes chemical resistant gloves for all handling tasks, and protective eyewear when mixing or loading, cleaning out or repairing contaminated equipment. In enclosed areas, a Mine Safety and Health Administration/National Institute of Occupational Safety and Health (MSHA/NIOSH) approved vapor barrier pesticide mask is required. For outdoor use, a MSHA/NIOSH approved pesticide dust/mist filtering respirator is required. Ground applicators and flaggers (unless flaggers work in enclosed cabs) are required by California regulation to wear protective eyewear (3 CCR 6738).

As carbofuran products are legally required in California to be mixed and loaded in closed systems, alternate PPE may be substituted for PPE listed on product labels. Under the federal Worker Protection Standard (40 CFR 170.240), "Persons using a closed system to mix or load pesticides with a signal word of DANGER or WARNING may substitute a long-sleeved shirt, long pants, shoes, socks, chemical-resistant apron, and any protective gloves specified on the labeling for handlers for the labeling-specified personal protective equipment." Additionally, under the Worker Protection Standard, "Persons using a closed system that operates under pressure shall wear protective eyewear."

The corresponding California regulations have more restrictive PPE requirements (3 CCR 6738): "Persons using a closed system to handle pesticide products with the signal word 'DANGER' or 'WARNING' may substitute coveralls, chemical resistant gloves, and a chemical resistant apron for personal protective equipment required by pesticide product labeling." Also, "Persons using a closed system that operates under positive pressure shall wear protective eyewear in addition to the personal protective equipment listed...Persons using any closed system shall have all personal protective equipment required by pesticide product labeling immediately available for use in an emergency."

Requirements for PPE that are unique to California were incorporated into worker exposure estimates in the following manner: closed systems were assumed for M/L, and PPE required on the label were assumed because both the Worker Protection Standard and the corresponding California regulation (3 CCR 6738) state that PPE *may* be substituted. That is, substitution of PPE during use of a closed system is optional, and the PPE stated on the label is less protective than the substitute PPE listed in the federal Worker Protection Standard (40 CFR 170.240), and in California regulations (3 CCR 6738), both of which require use of a chemical apron. Adjustments of dermal exposure estimates for use of substitute PPE would result in lower estimates than estimates that assume use of label-required protective clothing and PPE, which includes a respirator. As a result, the most health-protective, realistic exposure estimates use PPE listed on product labels (see below, in the Exposure Assessment section).

According to requirements listed on the label, the Restricted Entry Interval (REI) is 48 hours except for foliar application to cotton, corn, sunflowers, and sorghum, for which the REI is fourteen days. For these crops, early reentry on day 2 or later may be permitted, without time limit, for non-handler work tasks that may involve contact with treated surfaces/sites provided the following PPE is worn: coveralls, chemical-resistant gloves, shoes, and socks.

PHARMACOKINETICS

Dermal and Inhalation Absorption

For carbofuran, no *in vivo* human dermal absorption studies are available, although reports of two *in vivo* and two *in vitro* dermal absorption studies have been published in the scientific literature. The first *in vivo* study examined dermal penetration rates of several pesticides in mice (Shah *et al*., 1981). The second *in vivo* study compared dermal penetration of carbofuran in young and adult female rats (Shah *et al.*, 1987a; 1987b). The first *in vitro* study compared dermal penetration of several pesticides, including carbofuran, through human foreskin pieces mounted in a static diffusion chamber (Shehata-Karam *et al*., 1988). The second *in vitro* study compared dermal penetration of three pesticides, including carbofuran, through rat abdominal skin mounted in a static diffusion chamber (Liu and Kim, 2003).

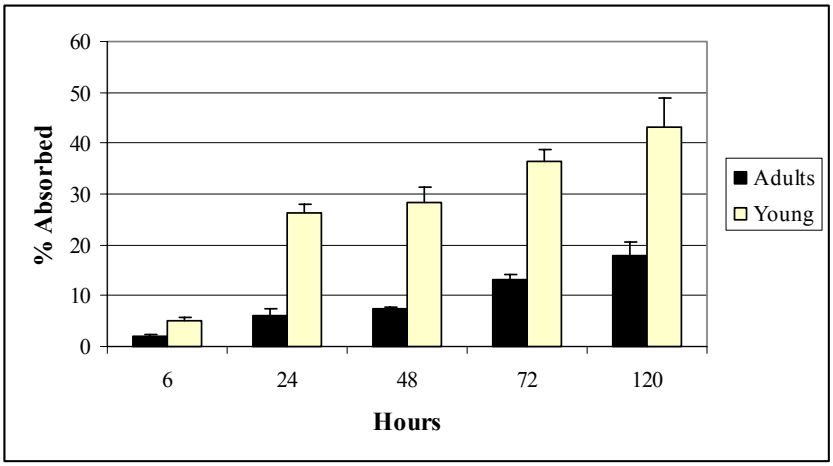
In Vivo Studies

In the first study (Shah *et al*., 1981), female mice aged seven to eight weeks were used. Radiolabeled pesticides dissolved in acetone were applied at a rate of 1 mg/kg to shaved skin areas of 1 cm^2. The carbofuran used in this study was ring-labeled (specific activity 2.85 mCi/mmol). Mice were kept in metabolism cages with CO_2-trapping devices after dosing. The dose site was unprotected, though mice were not observed to groom during the study. Groups of three mice were euthanized following intervals of 1, 5, 15, 60 and 480 min. Following euthanasia, 3- to 4-cm^2 patches of skin were excised (not washed first) to determine the amount of unabsorbed radioactivity. The percentage of radioactivity recovered from carcass, blood and urine was compared to that in skin from the dose site (total recovered radioactivity was > 90% for all compounds). Shah *et al.* (1981) concluded their data showed that carbofuran penetrated mouse skin rapidly. At 5 min post-dose, 32.6% of recovered radioactivity had been absorbed,

and at 15 min post-dose, 71.7% of recovered radioactivity had been absorbed. Shah *et al.* (1981) estimated the half-life for dermal penetration through mouse skin of carbofuran in an acetone vehicle to be 7.7 min; at 8 hours, 94.7% had penetrated (geometric mean of three animals).

The second study was reported in Shah *et al*. (1987a; 1987b). Briefly, young (33-day-old) and mature (82-day-old) female Fisher 344 rats were used, and dermal penetration was studied via both *in vivo* and *in vitro* methods. In the *in vivo* study, ring-labeled ^{14}C-carbofuran (specific activity 39.4 mCi/mmol), diluted with 100 µl and 200 µl of acetone for the young and adults respectively, was assayed at doses of 28, 285, 535, and 2680 nmol/cm^2 (equivalent to 6.2, 63, 118, and 593 µg/cm^2), following an exposure duration of 72 hours; also, the penetration of one dose (285 nmol/cm^2) was reported following multiple exposure durations (6, 24, 48, 72, and 120 hours). Treated areas were 2.8 cm^2 for young rats and 5.6 cm^2 for the adults. The dose site was protected by perforated plastic blister glued to the site. Following euthanasia, treated skin was excised (not washed first) to determine the amount of unabsorbed radioactivity. Dermal absorption was calculated by subtracting the radioactivity recovered from the application site from total radioactivity recovered from all tissues (i.e., bound skin residues were considered unabsorbed). Two major results reported in this study were that dermal penetration in young animals generally exceeded that in adults (see Figure 1), and that dermal penetration was inversely proportional to the applied dose, over the range of doses tested (see Figure 2). At 120 hours, the mean *in vivo* dermal penetration of a mid-level dose (285 nmol/cm^2) was 43% in young rats and 18% in adults (Figure 1). At 72 hours, mean dermal penetration in mature rats ranged from 6% of the high dose to 83% of the low dose, though the 83% was anomalously high compared to other results (Figure 2; also compare Figure 1). Dermal penetration in young rats at 72 hours ranged from 4% of the high dose to 36% of the next-to-lowest dose tested.

Figure 1. Dermal Absorption of Carbofuran at Multiple Exposure Durations [a]

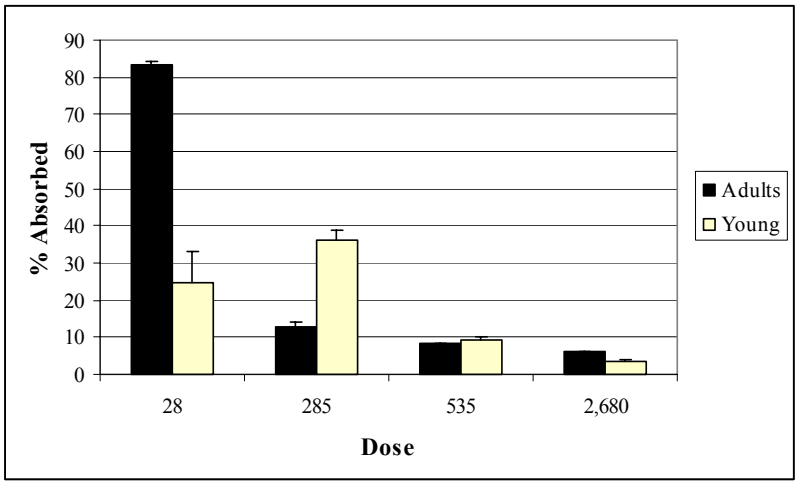


[a] Dermal absorption of carbofuran (285 nmol/cm^2) in acetone solution applied to skin of clipped mid-dorsal back of female adult (age 82 days) and female young (age 33 days) rats. Data from Table 1 of Shah *et al.* (1987b).

Both *in vivo* studies are anticipated to overestimate dermal absorption in humans. Both studies used acetone as a vehicle. Acetone has been shown to increase dermal absorption of several compounds, including pesticides (Moody *et al*., 1992; Baynes *et al*., 1997; Baynes and Riviere, 1998; Tsai *et al.*, 2001). Organic solvents can damage the skin barrier properties, artificially

increasing dermal penetration (Scheuplein and Ross, 1970; Fartasch, 1997; Williams and Barry, 2004). For this reason, U.S. EPA (1998a) recommends that the vehicle used in dermal penetration studies should be the same as that "under which field exposure occurs," and states that organic solvents "must not be used."

Figure 2. Dermal Absorption of Carbofuran (Multiple Doses) at 72 Hours [a]



[a] Dermal absorption of carbofuran in acetone solution applied to skin of clipped mid-dorsal back of female adult (age 82 days) and female young (age 33 days) rats. Doses in nmol/cm^2. Lowest dose was 28 nmol/cm^2 (or 6.2 μg/cm^2) for young rats, but 23 nmol/cm^2 (or 5.1 μg/cm^2) for adults. Data from Table 3 of Shah *et al.* (1987b).

The highest dermal absorption of carbofuran, 94.7%, was reported in mice (Shah *et al.*, 1981). Comparison of the four other pesticides tested at comparably low doses in these two studies in both mice (at a dose of 20 μg/cm^2) and rats (at doses ranging 2 – 37 μg/cm^2) showed that in each case absorption was lower in rats following 72 hours of exposure than in mice following 8 – 48 hours exposure (Shah *et al*., 1981; Shah *et al*., 1987a). Furthermore, dermal absorption of all fourteen pesticides tested in mice by Shah *et al*. (1981) exceeded 65% at 8 hours, suggesting that all of these results were higher than would normally be anticipated. For four of the pesticides tested by Shah *et al*. (1981) in mice, Ross *et al.* (2001) reported human dermal absorption of 10% or less. In other studies involving pesticides, mice also showed higher dermal absorption than rats or humans (U.S. EPA, 1992; Baynes *et al.*, 1997). Because of the use of mice, but mainly due to the use of acetone as a vehicle, the study by Shah *et al.* (1981) was considered unacceptable.

The highest mean dermal absorption of carbofuran reported in rats was 83% (Shah *et al*., 1987b). Figure 1 and Figure 2 show this result to be more than double any other result in the study, and in contrast to the pattern seen with other doses it occurred in adults rather than young rats. Because results were presented on a wet-weight basis, and no organ wet weights were given, these discrepancies could not be investigated, nor were they explained by Shah *et al*. (1987b). With the exception of this one result, all dermal absorption results for all dose levels and exposure intervals were less than 40%. U.S. EPA used this study to estimate a dermal absorption of 6%, based on the 24-hour absorption of 285 nmol/cm^2 doses in adults (Drew *et al.*, 2005).

In addition to the use of acetone as a vehicle, there were other ways in which the study conducted by Shah *et al*. (1987b) did not conform to accepted methods (Thongsinthusak, 1994; U.S. EPA, 1998a). The treated skin was covered with a perforated plastic blister, which is possibly an occlusive cover. The treated skin was not washed off after the exposure period. Doses tested for durations approximating a workday (8 hours) were too high (Thongsinthusak *et al*., 1999). Treated areas measured 2.8 cm^2 for the juveniles and 5.6 cm^2 for the adults, rather than the recommended 10 cm^2. The first two of these factors might be expected to result in overestimation of dermal absorption, and the latter two might result in underestimation. Along with the use of acetone as a vehicle, all of these factors undermine use of these data to reliably predict dermal absorption of carbofuran and this study was considered unacceptable.

In Vitro Studies

In the first study, *in vitro* dermal penetration was studied using foreskin segments from newborn humans (Shehata-Karam *et al*., 1988). Briefly, the tissue was obtained immediately after circumcision, kept moist on ice until used, and then mounted in a modified static diffusion chamber with nutrient media. Tests were run at 37°C. Pesticides were applied at a dose of 38 $\mu g/cm^2$, dissolved in 1 µl of acetone. Samples were collected from the media at intervals of 1, 6, 24, and 48 hours. The dermal penetration of carbofuran at 48 hours was 82%, a value which agrees with the 72-hr low-dose *in vivo* absorption result of Shah *et al*. (1987b). As both studies used acetone as a vehicle, the similarity in results is perhaps not surprising.

In the second study, *in vitro* dermal penetration was studied using strips of abdominal skin obtained from male Sprague-Dawley rats that were 5-6 weeks old (Liu and Kim, 2003). Skin membranes (3.14 cm^2) were placed into diffusion chambers with physiological saline media immediately after they were obtained. Technical grade pesticides were applied in varying amounts ranging from 2 mg to 150 mg, dissolved in 100 µL of acetone. Tests were run at 32°C, with continuous shaking at 600 rpm for 48 hours. Samples were collected from the media at intervals of 6, 12, 24, 36, and 48 hours. The limit of detection was 0.1 ppm for all pesticides. The dermal penetration rate was estimated by plotting percent absorbed by time, and fitting a least-squares regression to the steady-state linear portion of the curve. For carbofuran, the steady-state linear equation was 1.05 $\mu g/cm^2$ per hour (Liu and Kim, 2003).

Both *in vitro* studies used acetone as a vehicle, and are considered unacceptable. Furthermore, the use of *in vitro* studies to determine dermal absorption is problematic because the extent of compound solubility in receptor solutions may affect results and because relationships between *in vivo* and *in vitro* test results have not been reliably established for many classes of compounds, and have been shown to vary for compounds that have been tested (Franklin *et al*., 1989; Wester and Maibach, 2000; Zendzian and Dellarco, 2003). Therefore, DPR does not, by standard practice, rely on *in vitro* studies to determine dermal absorption.

Dermal Absorption Estimate Used in Exposure Assessment

When no acceptable data are available for dermal absorption, DPR policy is to use a default value of 50% (Donahue, 1996). This default value is based on a review of data from forty pesticides, twenty-six of which were documented in Thongsinthusak *et al*. (1993b).

Inhalation Absorption Estimate Used in Exposure Assessment

No inhalation absorption data are available for carbofuran, although the disposition of inhaled aerosolized carbonyl-^{14}C-carbofuran was investigated in rats by Ferguson *et al*. (1982). Male Sprague-Dawley rats were exposed in nose-only chambers to either 4.1 or 1.5 µM aerosols for 50 and 70 minutes, respectively. Exposed rats were immediately exsanguinated by cardiac puncture after exposure and dissected. Tissues were frozen until analysis. Relative disposition was reported by Ferguson *et al*. (1982), rather than absorption data, although based on the theoretical estimate of inhaled dose the deposition was estimated to be 89% of the 4.1 µM and 77% of the 1.5 µM aerosol. In the absence of absorption data, a default inhalation absorption value of 100% was used for calculations of doses absorbed via inhalation.

Metabolism

In a series of *in vivo* and *in vitro* studies, Dorough (1968), Metcalf *et al*. (1968), Marshall and Dorough (1979), and Ferguson *et al.* (1984) found that the most common major metabolite of carbofuran is 3-hydroxycarbofuran, free or conjugated (Table 2). Oral toxicity tests using rats suggest that carbofuran and 3-hydroxycarbofuran are toxicologically similar (McCarthy, 1975; Ferguson *et al*., 1984). The oral LD_{50} in rats of carbofuran is in the range 8-14 mg/kg, and that of 3-hydroxycarbofuran is 18 mg/kg (McCarthy, 1975). Other major metabolites of carbofuran are less toxic to mammals, with oral rat LD_{50} values in the range of 69 mg/kg to 2200 mg/kg (McCarthy, 1975).

ENVIRONMENTAL CONCENTRATIONS

Dislodgeable Foliar Residues

Dislodgeable foliar residue (DFR) is defined as the pesticide residue that can be removed from both sides of treated leaf surfaces using an aqueous surfactant. DFR is assumed to be the portion of an applied pesticide available for transfer to humans from leaf and other vegetative surfaces. Measurements of DFR can be used, along with an appropriate transfer coefficient (TC), to estimate the amount of pesticide adhering to clothing and skin surfaces following entry into a previously treated field. The DFR is reported as residue per leaf area (µg/cm^2).

DFR data from studies involving crops where carbofuran is likely to be used in California are summarized in Table 3. In most studies, 3-hydroxycarbofuran residues were analyzed along with carbofuran; the "Total DFR" column in Table 3 includes carbofuran and 3-hydroxycarbofuran. In general, 3-hydroxycarbofuran residues were small compared to carbofuran, but were included in the total DFR estimate because toxicity of the two compounds is similar (Gupta, 1994), which suggests they are of equal concern.

Table 2. Major Metabolites of Carbofuran (^{14}C Label on Aromatic Ring)

Metabolites	Percentage of Dose Recovered					
	Bile Duct	Urine				
	(a)	*(b)*	*(c)*	*(d)*	*(e)*	*(f)*
3-Hydroxycarbofuran	60	15.8	14.8	45	27.7	27.9
3-Ketocarbofuran phenol	5.2	40.8	50.5	1.3		
Carbofuran phenol	3	15.2	21.1	17.7		
3-Hydroxycarbofuran phenol	1.1	14.7	1.4			
3-Ketocarbofuran	0.0	1.2		3.4		
Unknown	29	5.9	8.1		62.2	63.8

[a] Marshall and Dorough (1979): single oral dose of 0.1 mg/kg (1 x 10^6 disintegrations per minute; dpm); within 24 hours, 28.1% of dose was detected via cannulation of bile duct. Of the bile fraction detected via cannulation, 98.3% was recovered as H_2O soluble and 1.7% was recovered as organosoluble.

[b] Marshall and Dorough (1979): single oral dose of 0.1 mg/kg (1 x 10^6 dpm); within 48 hours, 65.4% of dose was detected in the urine. Of the urine-collected fraction, respectively, 93.6% and 6.4% were recovered as H_2O soluble and as organosoluble.

[c] Dorough (1968): single oral dose of 4 mg/kg (0.07 µg/mmole, 200 counts per minute (cpm)/µg); urine collected over 72 hours. Unknown is sum of water solubles (remaining ^{14}C materials from H_2O fraction after acid treatment and extraction with chloroform) + Unknown III.

[d] Metcalf *et al*. (1968): Two 1-hr fasted male mice, each treated with single oral dose of 2 mg/kg [0.1% (w/v) 4,5,6-^{3}H-labeled carbofuran]. Percentage calculated using cpm for each metabolite divided by total cpm. Within 24 hours, one mouse had excreted 37% whereas the other mouse had excreted 67% of the administered radiolabeled dose in the urine.

[e] Ferguson *et al*. (1984): single oral dose of 50 µg/kg [carbonyl-^{14}C (23.7 mCi/mmole)]. The values represent the sum of the H_2O + organic soluble fractions. Of the fraction collected from the urine, 67% was recovered as H_2O soluble and 25% was recovered as organosoluble. The sum of the unidentified and unextractable residues is unknown.

[f] Ferguson *et al*. (1984): single intravenous (lateral tail vein) dose of 50 µg/kg [carbonyl-^{14}C (23.7 mCi/mmole)]. The values represent the sum of the H_2O + organic soluble fractions. Of the urine collected fraction, 69% recovered as H_2O soluble and 25% recovered as organosoluble. Unknown is the sum of the unidentified and unextractable residues.

DFR values shown in Table 3 and used in exposure estimates were back-calculated from equations using study data, as explained in Andrews (2000). Values shown in the "Total DFR" column of Table 3 were calculated at the REI for each crop (the crops listed in Table 3, except corn and cotton receiving foliar applications under Section 18 emergency exemptions, all have an REI of 48 hours); the DFR for potatoes was used for the acute exposure estimates of potato scouts, and the DFR for field corn was used for the acute exposure estimates of scouting in corn (see Exposure Assessment section). In Table 3 and in subsequent discussion, Day 0 refers to the day of application, Day 1 is the first post-application day, and subsequent post-application days are similarly identified. The log-linear regression model was used fit the data (Andrews, 2000), using the following equation: $\ln DFR_t = \ln (DFR_0) - kt$. In this equation, k is the slope of the log-linear, first-order dissipation curve and t represents the time interval (days). As shown in Table 3, the half-life of carbofuran residues on foliage (along with its major metabolite, 3-hydroxycarbofuran) ranged from approximately 2.1 to 11.5 days.

Table 3. Dissipation of Carbofuran on Selected Crops [a]

Crop	Location	Initial DFR [b] (μg/cm^2)	Total DFR at REI [c] (μg/cm^2)	Half-Life (Days) [d]
Cotton [e]	Arizona	5.76	0.057	2.1
Field Corn [f]	Minnesota [g]	0.181	0.000	2.4
Field Corn [f]	Missouri	0.101	0.003	3.0
Field Corn [h]	Contra Costa County, California	0.691	0.330	11.5
Grapes [i]	Madera County, California	0.87	0.58 [j]	3.2
Grapes [i]	Napa County, California	1.17	0.88 [j]	5.2
Grapes [i]	Fresno County, California	1.15	0.85 [j]	4.0
Potato [k]	Idaho	0.994	0.186	4.0

[a] Carbofuran applied as Furadan® 4F liquid formulation, mixed with water. Application rate was 1.0 lb AI/acre (1.1 kg AI/ha) in all studies shown. Studies meet acceptability criteria described in Iwata *et al*. (1977) and U.S. EPA (1996a). Residues dislodged with surfactant solution, unless otherwise stated.

[b] Measured on Day 0 (day of application). Includes carbofuran residues alone.

[c] Calculated DFR at expiration of restricted entry interval (REI; 48 hours for most crops, 14 days for corn and cotton receiving foliar applications). Includes summed carbofuran and 3-hydroxycarbofuran residues, which are anticipated to contribute about equally to toxicity. Values calculated using ln DFR_t equation shown in footnote [d].

[d] Half-life calculated from the following equation: $T_{1/2} = (\ln 0.5)/k$, where k is the slope of the linear regression generated from study data (t is the sample time in days): $\ln DFR_t = \ln (DFR_0) - kt$ (Andrews, 2000).

[e] Ware *et al.* (1978); application with tractor-driven groundboom sprayer. Residues dislodged with water.

[f] Liu (1987); aerial application (data followed two applications, four weeks apart).

[g] Rain occurred daily from Day 6 through Day 12.

[h] Leppert (1986); aerial application (data followed two applications, two weeks apart).

[i] Serat (1978); application method not specified (data followed three applications, 26 to 33 days apart).

[j] Includes carbofuran residues alone (3-hydroxycarbofuran not tested).

[k] Barros and Dow (1998); application with groundboom sprayer (data followed three applications, one week apart). Rain occurred during the study, but days with rain events were not specified.

Of the crops listed in Table 3, foliar applications are allowed in California only on potatoes and on field corn that has not received post-plant soil applications, and cotton under Section 18 emergency exemptions. Barros and Dow (1998) reported DFR results following three groundboom applications made at weekly intervals to a potato field, each at 1.0 lbs AI/acre (1.1 kg AI/ha). Although this study was generally well-conducted, because of rainfall occurring during the study, residues were potentially washed from foliage between application and completion of sampling. However, as most California potatoes are grown in winter (Mayberry, 2000), conditions during the study are similar to those that would be anticipated for this crop in California. DFR data from this study were used to estimate exposure of workers scouting potatoes (see Exposure Assessment section). But other crops that might receive foliar applications, such as corn and alfalfa, can be grown in summer, when rain events are rare. Another scenario is needed for these crops. Examination of Table 1 shows that the crop receiving the most carbofuran use is alfalfa (in contrast, carbofuran is rarely used on field corn or sweet corn, suggesting that seasonal and annual exposures would be unlikely in these crops). Although a DFR dissipation study has not been done for carbofuran in alfalfa, other data are available that can be used to estimate exposure to workers reentering treated alfalfa fields.

As part of a large study of pesticide residues encountered by reentering fieldworkers on several crops, Hernandez *et al.* (2002) collected and analyzed 1,003 foliar samples in fifteen counties in

California's Central Valley and coastal regions. DFR samples were collected at the expiration of the REI following known pesticide applications. Carbofuran was detected in 21 out of 27 samples of alfalfa and in 57 out of 74 samples of cotton. Alfalfa leaves were sampled 48 to 60 hours (i.e., within 12 hours of the expiration of the 48-hour REI) following carbofuran applications of 0.25 – 0.5 lbs AI/acre (0.28 – 0.56 kg AI/ha) to fields in Imperial County in March 2001. The overall mean DFR on alfalfa reported by Hernandez *et al.* (2002) was 0.510 $\mu g/cm^2$. This DFR was used in calculating acute exposure of alfalfa scouts, after first adjusting it because none of the fields sampled by Hernandez *et al.* (2002) had received the maximum application rate allowed on alfalfa (Hernandez, 2001). The DFR was multiplied by the ratio of this rate (1.0 lb AI/acre) to the weighted average rate (0.44 lb AI/acre) used, to get an adjusted DFR of 1.16 $\mu g/cm^2$. Dissipation of the DFR was estimated using the mean dissipation of carbofuran in all studies done in California, which is 6.0 days (range 3.2 to 11.5). The adjusted DFR at Day 2 and the estimated half-life can be used to solve for the remaining variables in the equations given in Footnote d of Table 3. Doing so gives a DFR equation of $\ln DFR_t = 0.928 – 0.116t$, which can be used to calculate DFR for long-term exposure estimates for alfalfa scouts (see Exposure Assessment section).

Although foliar applications of carbofuran are not currently allowed on cotton (the most recent Section 18 emergency exemption was issued in 2003), reentry exposure into cotton was considered in this EAD as emergency exemptions could be issued in the future. DFR data from Ware *et al*. (1978) were used in exposure estimates. These data were collected in Arizona; cotton in California is grown under similar conditions. Data collected in California are available to compare with DFR results reported by Ware *et al*. (1978). To supplement the DFR sampling at the expiration of the REI, DPR collected additional cotton foliage samples 3 to 14 days following carbofuran applications of 0.25 lbs AI/acre (0.28 kg AI/ha) to 35 fields in Fresno, Madera, Colusa and Yolo Counties in July-September 2001 (Curtis, 2002). The study was not designed to measure carbofuran dissipation; initial DFR samples were not collected, and just eight of the 35 fields were repeatedly sampled. In Fresno and Madera counties, which are adjacent to one another, the mean DFR at Day 2 was 0.218 $\mu g/cm^2$; the mean DFR at Day 7 was 0.087 $\mu g/cm^2$; and the mean DFR at Day 14 was 0.078 $\mu g/cm^2$ (Curtis, 2002). Comparison of the Day 14 value from Curtis (2002) to the value estimated from data shown in Ware *et al.* (1978)—in which DFR at Day 14 was 0.057 $\mu g/cm^2$—suggests that the Day 14 DFR value based on Ware *et al.* (1978) is in the range of residues to which workers might be exposed.

Carbofuran total (not dislodgeable) foliar residues were determined following applications to strawberries (Archer *et al*., 1977) and alfalfa (Shaw *et al*., 1969; Archer, 1976; Draper *et al.*, 1981). Three studies were available in which carbofuran residues were monitored as breakdown products following carbosulfan application (Markle, 1982; Iwata *et al.*, 1983; Nigg *et al.*, 1984); none of these studies was used to estimate exposure following applications of carbofuran.

Ground and Surface Water

A Public Health Goal of 1.7 µg/L was developed for carbofuran in drinking water by the Office of Environmental Health Hazard Assessment (Jowa, 2000). California has set a Maximum

Contaminant Level (MCL) of 18 µg/L (22 CCR 64444). The federal MCL is 40 µg/L (U.S. EPA, 2002)

Carbofuran has been detected only occasionally in routine surface and ground water monitoring. Wangsness (1997) reported in a United States Geological Survey (U.S.G.S.) draft document that in the U.S. surface water concentrations of carbofuran ranged from less than 0.003 to 9.0 µg/L; ground water carbofuran concentrations ranged from less than 0.003 to 2.8 µg/L. The highest carbofuran concentration found in either surface or ground water in California was 0.149 µg/L at a site in the lower Colorado River basin. DPR's Surface Water Database contains records of detections every year between 1991 and 1998, with a total of 279 detections in 3007 samples collected as of December 2002 (Evert, 2002).

Ganapathy *et al.* (1997) reported no detections of carbofuran in 224 surface water samples taken in the watersheds of the Merced, Sacramento, Salinas, and Russian rivers between 1993 and 1995 (detection limit: 0.05 µg/L); one sample, from the Merced watershed, was positive for the carbofuran metabolite, 3-hydroxy carbofuran (0.18 µg/L). Nordmark (1998) sampled the Sacramento River watershed from December 1996 through March 1997 without detecting carbofuran or its metabolites (detection limit: 0.05 µg/L). Jones *et al.* (2000) sampled several rivers in northern California in 1998 and 1999 without detecting carbofuran (detection limit: 0.05 µg/L; metabolites were not monitored).

Carbofuran was detected in three studies designed to measure concentrations in runoff from rice fields and receiving water bodies. Nicosia *et al*. (1990) sampled runoff water from three rice and three sugar beet fields in 1988. In rice field runoff, maximum carbofuran concentrations occurred within the first 26 days following flooding and ranged 21 – 33 µg/L. In 1995, Bennet *et al*. (1998) measured carbofuran concentrations in irrigation drain and slough water receiving runoff from rice fields, as well as in the Sacramento River. Carbofuran was detected in several irrigation drain samples collected in May through July, with concentrations ranging 0.12 – 0.70 µg/L, and in four slough water samples with concentrations ranging 0.37 – 0.57 µg/L (Bennet *et al*., 1998). Newhart and Bennett (1999) reported on a rice pesticide monitoring study at the same locations in April - June 1999, with sampling timed to coincide with anticipated peak pesticide concentrations. Carbofuran was detected in four irrigation drain samples and one slough water sample, with peak concentrations of 3.6 and 0.77 µg/L, respectively. Carbofuran was not detected in any Sacramento River sample in either of the latter two studies; both had detection limits of 0.10 µg/L (Bennett *et al*., 1998; Newhart and Bennett, 1999).

Air

California has laws that limit ambient air concentrations of pesticides, including the Toxic Air Contaminants Act (California Health and Safety Code, Sections 39650-39761), which codified the state program to evaluate and control toxic air contaminants (TAC). A pesticide is placed on the TAC list if its concentrations in ambient air have been determined to be within an order of magnitude of the concentration determined to cause human health effects (3 CCR 6890). Carbofuran is a TAC candidate (Shibamoto *et al*., 1993). Carbofuran concentrations have been monitored in the ambient air during peak application season and in the air surrounding application sites.

Ambient Air

In 1995, the Air Resources Board (ARB) of the California Environmental Protection Agency did ambient air monitoring in Imperial County in southern California (ARB, 1995). The ARB collected air samples during a four-week interval, from February 14 through March 10, at four sites near anticipated carbofuran applications (although whether applications actually occurred near all sampling locations during the sampling interval was not reported) and an urban (background) site. The ambient sites were rural areas in the following locations: one in Calipatria (Site C; duplicate samples collected at this site); one at the Meadows Union School between El Centro and Holtville (Site M); one in Heber (Site H); and one northeast of El Centro at an Air Pollution Control District monitoring station (Site PM). The background site was in El Centro (Site EC). Except for one site that was at ground level (Site PM; 1.5 m above ground), all samples were taken on roof tops approximately 5 m above ground. Sample devices consisted of 30 ml XAD-4 resin in Teflon holders, connected to air pumps with Teflon tubing; air pumps were calibrated to 14.7 L/min (ARB, 1995). Quality assurance included the use of laboratory spikes, field spikes (recovery 106% $\pm$ 7%), one method blank, one field blank, collocated samples at one site, and background samples prior to the application; all were acceptable (ARB, 1995). Monitoring results are summarized in Appendix 1. Of the 82 samples, 55 were below the limit of detection (LOD) of 0.25 µg/sample (approximately 0.012 µg/m^3). No limit of quantification (LOQ) was reported by ARB (1995); concentrations were reported if greater than the LOD. The same practice is followed in this EAD. Concentrations in the remaining samples ranged from 0.014 to 0.11 µg/m^3 (ARB, 1995; Kollman, 1995).

In 1996 and 1997, the U.S.G.S. monitored atmospheric concentrations of several pesticides, including carbofuran, at three locations in Sacramento County (Majewski and Baston, 2002). Two of the sites were rural, at airports northwest and southeast of Sacramento (samplers were about 3 m above ground); the third site was in downtown Sacramento (about 10 m above ground). The rural sites were approximately 10 and 20 miles (16 and 32 km) northwest and southeast, respectively, of the downtown site. Sample devices consisted of 119-cm^3 polyurethane foam plugs (mean density = 0.043 g/m^3) in Teflon cartridges, connected to high-volume blowers flowing at approximately 100 L/min (Majewski and Baston, 2002). Weekly whole-air (particulates were not filtered out), composite samples were collected at each site throughout the study. Sampling was triggered when 15-min mean wind speeds were >1 m/sec in a northerly or southerly direction, and continued until the directional wind speed decreased below the trigger velocity; maximum sampling was 20 min/hr. Carbofuran was detected just once at each of the rural sites (concentrations: 0.00033 and 0.00338 µg/m^3); both samples were collected when the wind was from the south (detection limit 0.00015 µg/m^3). In contrast, carbofuran was detected several times in the downtown Sacramento site; it was detected in 32.4% of samples collected when the wind was blowing from the south, and in 19.7% of samples collected when the wind was out of the north. Concentrations of carbofuran in samples collected from the downtown site ranged 0.00008 – 0.013 µg/m^3, and are summarized in Appendix 1. Average detected carbofuran was 0.0017 and 0.0024 µg/m^3 for samples collected during south and north winds, respectively (Majewski and Baston, 2002). Because carbofuran has no registered use in urban settings, the pattern of detections is puzzling, and Majewski and Baston (2002) were unable to provide an explanation. The northern rural sampling site is surrounded by areas where rice is cultivated, and the southern rural site is in an area dominated by pastureland,

vineyards and native vegetation. There are some areas where grain and hay crops are grown both north and south of the downtown site; it's possible carbofuran applications to alfalfa occurred in these areas.

Ambient air concentrations of carbofuran were also greater at an urban than a rural site in a study done in the Rhine Valley in France in 1993 – 1994, probably because the urban site was located within a larger agricultural area (Sanusi *et al*., 2000). The rural site was southeast of the small city of Colmar, in a region where most crops were either corn or vine crops; the urban site was a "polluted city," Strasbourg, which was largely industrial but with a larger surrounding agricultural area (the valley is narrower at Colmar than at Strasbourg). A total of eight 24-hour samples were collected at Colmar; nine samples were collected at Strasbourg. Sample devices consisted of 20 ml XAD-4 resin in Teflon holders, connected to a high-volume sampler; particulates were collected on glass fiber filters (30 cm diameter). Sampler flow rates varied, but 140 – 700 m^3 air was collected. Carbofuran concentrations at Colmar ranged from < 0.000228 – 0.0081 $\mu g/m^3$, with a mean of 0.00285 $\mu g/m^3$. Concentrations at Strasbourg ranged from 0.00143 – 0.02897 $\mu g/m^3$, with a mean of 0.01259 $\mu g/m^3$ (Sanusi *et al*., 2000).

Application Site Air

Two studies are available of airborne carbofuran associated with applications. In 1993, the ARB measured carbofuran concentrations in air during a groundboom application of carbofuran in Imperial County in California (ARB, 1994). The air monitoring stations were located approximately 20 m from the N, E, W, and S, respectively, edges of a 70-acre (28-ha) alfalfa field receiving carbofuran applications at a rate of 0.3 lb AI/acre (0.34 kg AI/ha). Sample devices consisted of 30 ml XAD-4 resin in Teflon holders, connected to air pumps with Teflon tubing; air pumps were calibrated to 16.2 L/min. The application took place on March 31 between 10:00 and 11:00 AM. Samples were collected from the day of application (March 31) through April 2. Quality assurance included the use of laboratory spikes (recovery 96% $\pm$ 5%), one method blank, one field blank, and seven duplicate samples; all were acceptable (ARB, 1994). Of the 35 samples, eleven were below the LOQ of 0.3 µg/sample (approximately 0.014 $\mu g/m^3$ for a 24-hour sample). Concentrations in the remaining samples ranged from 0.15 to 0.66 $\mu g/m^3$ on March 31, and from 0.03 to 0.21 $\mu g/m^3$ on April 1-2 (ARB, 1994).

Table 4 summarizes air concentrations during the monitoring periods. A time-weighted average (TWA) concentration was calculated for the first day, starting with the hour during which the application occurred (21 hours of monitoring). This TWA value was used in estimating bystander exposures (see the Exposure Assessment section).

In a study conducted outside California, Draper *et al.* (1981) collected air samples during and 2 hours following aerial carbofuran applications to alfalfa fields in Utah. The two fields, 20 and 40 acres (8 and 16 ha) each, were treated with Furadan® 4F at a rate of 0.5 lbs AI/acre (0.56 kg AI/ha). Wind speeds during both applications were less than 5 mph (8 km/hr). A total of eleven air samples were collected from five locations, using high-volume air samplers. Samplers were located within the field, or up to 600 m away (sampler heights were not stated). Each sample device consisted of 120 ml XAD-4 resin in a 1.8-cm bed, connected to a high-volume sampler, and particulates were collected on a glass fiber filters. Sampler flow rates were 230 – 710 L/min. Both the air sampling locations and the aerial applications were oriented in an E-W direction,

and the wind direction was W-SW for both fields during sampling. No carbofuran was detected in samples collected 200 – 600 m from application sites. At a sampler located 25 m E of the 20-acre field, carbofuran concentrations ranged 0.7 – 3.3 μg/m^3. At a sampler located 42 m NE of the 40-acre field, carbofuran concentrations ranged 0.17 – 0.22 μg/m^3 (Draper *et al.*, 1981). These data were not used in estimating bystander exposure because of the inability reported by Draper *et al.* (1981) to distinguish between airborne concentrations and fallout from the aerial spray (i.e., air samplers might have been directly sprayed).

Table 4. Carbofuran Concentrations (μg/m^3) Twenty Meters from an Alfalfa Field Receiving an Application by Groundboom [a]

Date and time of monitoring	West	North [b]	East	South	Wind Speed [c]	Wind Direction
March 31, 1993, 0800-0930 [d]	ND [e]	ND	ND	ND	1	NE
March 31, 1993, 1000-1100 [f]	0.29	ND	0.66	ND	2	SE
March 31, 1993, 1100-1400	0.49	0.28	0.15	ND	3	SE/SW
March 31, 1993, 1400-1730	0.53	0.60	0.27	ND	5	SE
March 31, 1993, 1730-2100	0.26	0.21	0.15	ND	2	SE
March 31-April 1, 1993, 2100-0700	0.031	0.08	0.24	0.11	2	W/NW
24-hour Time-Weighted Average [g]	0.23	0.22	0.22	0.08	NA	NA
April 1-2, 1993, 0700-0600	0.035	0.06	0.12	0.05	8	W/N/S/E

[a] All stations were approximately 20 m from the edge of field (ARB, 1994). Concentrations calculated by dividing carbofuran measured in sample by sample volume. Sample pumps were calibrated to run 16.2 L/min.
[b] Mean of two stations.
[c] Wind speed in miles/hour. NA: not applicable.
[d] Background air monitoring before application.
[e] Not detected, below limit of quantification (LOQ) of 0.3 μg/sample.
[f] Air monitoring during application. Subsequent measures are post-application.
[g] Time-weighted average (TWA) concentration over first 24 hours, beginning with application at 10:00 AM and ending with sample completed 20 hours post-application. Samples taken during 21 hours were used as an approximation for the 24-hour TWA. For ND samples, ½ LOQ was used in calculations.

EXPOSURE ASSESSMENT

Handler and reentry exposure to carbofuran is anticipated to be limited to workers engaged in agricultural tasks. No residential, industrial or institutional use of carbofuran is permitted by its label. However, residents and bystanders may be exposed to airborne carbofuran, as suggested by results of air monitoring studies summarized in the Environmental Concentrations section. Significant exposure scenarios are discussed in the following sections.

For each scenario, estimates are provided for acute (defined in this EAD as exposures lasting from less than a day to short-term intervals up to one week) and intermediate to long-term (seasonal, annual, and lifetime) exposures. Seasonal exposure is defined as a period of frequent exposure lasting more than a week but substantially less than a year, whether the exposure is constant or intermittent during the period. Annual exposure integrates all exposure periods

during the year. Lifetime exposures integrate all exposure periods over several years. For occupational scenarios, two assumptions are used in calculating lifetime exposure, that the average life expectancy is 75 years (U.S. Bureau of the Census, 1995), and that a person does the same job for 40 years.

Surrogate data from the PUR were used to estimate intervals for seasonal and annual exposures. Carbofuran is registered for use on several different crops, and for some crops repeated use is allowed within a growing season, suggesting that handlers may potentially be exposed throughout the year. Repeated exposures are more likely for professional applicators and their employees, as these handlers can make the same treatment for several growers. However, PUR data show that for many crops carbofuran use does not occur throughout the year, and that for others relatively few applications are made. It is reasonable to assume that an individual handler is less likely to be exposed to carbofuran during these relatively low-use intervals. Thus, rather than assume that handlers are exposed throughout the year, annual use patterns are plotted based on monthly PUR data. Annual exposure to carbofuran is assumed to be limited to the months when use is relatively high (defined as 5% or more of annual use each month). Seasonal exposure intervals are assumed to be the longest contiguous period during which monthly use is at least 5% of annual total; seasonal use may involve fewer months than annual use.

Handlers

Exposure Monitoring

One study was available in which handler exposure to carbofuran was monitored. Hussain *et al*. (1990) monitored prairie grain farmers in southern Alberta, Canada, during groundboom applications of Furadan® 480F in wheat at application rates ranging 0.26 – 0.70 lb AI/acre (0.29 – 0.79 kg AI/ha). Four individuals were mixer/loader/applicators (M/L/As) and two were applicators, although results were not reported in an activity-specific way. Each participant in the study wore long pants, long-sleeve shirt, wool socks, a cap, and leather or rubber boots. During mixing, the M/L/As wore disposable Tyvek® coveralls, rubber gloves, and a MSMA approved respirator with dual organic vapor cartridges with dust filters. During spraying, M/L/As and applicators did not wear rubber gloves. Potential dermal exposure was measured using Tegaderm® patches (10 cm^2) placed both on the skin beneath the work clothing and outside of the coveralls, and isopropanol rinses of wrists and hands. Potential inhalation exposure was measured using polyurethane foam plugs inserted in Plexiglass columns connected to suction pumps. In addition to potential dermal and inhalation exposures, medical baseline data, including both blood and urine samples, were collected one week before the spraying season began. Subsequent 24-hour urine collections were done for 4 days after individuals began spraying, and blood samples were also taken every 24 hours for 4 days.

During the monitoring period, the amount of AI handled per participant ranged from 2.11 to 25.3 lbs (0.96 to 11.5 kg). The areas treated ranged 6 – 72 hectares (14.8 – 178 acres) and the application time ranged from 34 minutes to 5 hours. Samples were analyzed for carbofuran only, not for metabolites. The mean estimated total exposure to the volunteer handlers was 574.4 µg AI/lb handled (range, 33.8 – 2,585.6 µg AI/lb handled). Average inhalation exposure was 0.15% of total exposure, including samples from two participants in which carbofuran was nondetectable (detection limit = 0.01 ppm). Most of the dermal exposure (87%) occurred on

hands and wrists. The mean amount of carbofuran detected in the urine was 12.5 µg/lb AI handled, or 6.6% of the total exposure per volunteer. No cholinesterase inhibition was observed in whole blood or plasma. However, while samples were maintained on ice prior to analysis, they were analyzed 3 – 5 days after collection, and evidence from other studies suggests that the storage precaution may not have been sufficient to prevent reactivation of inhibited cholinesterase (Gupta, 1994). No changes were detected in any of the 30 other hematology and blood chemistry parameters measured (Hussain *et al*., 1990).

This study was unacceptable for estimating exposure because of the small sample size, and because exposure results were not related to activities. Data from this study were not used in estimating handler exposure, although in the Exposure Appraisal section these data were compared to exposure estimates from surrogate data.

Exposure Estimates Using Surrogate Exposure Monitoring Data

As no acceptable studies were available for assessment of handler exposure, estimates were based on surrogate data from the Pesticide Handler Exposure Database (PHED, 1995). PHED was developed by the U.S. EPA, Health Canada and the American Crop Protection Association to provide non-chemical-specific pesticide handler exposure estimates for specific handler scenarios. It combines exposure data from multiple field monitoring studies of different AIs. The user selects a subset of the data having the same or a similar application method and formulation type as the target scenario. The use of non-chemical-specific exposure estimates is based on two assumptions: (1) that exposure is primarily a function of the pesticide application method/equipment and formulation type and not of the physical-chemical properties of the specific AI; and (2) that exposure is proportional to the amount of AI handled.

PHED has limitations as a surrogate database (Powell, 2002). It combines measurements from diverse studies involving different protocols, analytical methods and residue detection limits. Most dermal exposure studies in PHED use the patch dosimetry method of Durham and Wolfe (1962); residues on patches placed on different parts of the body are multiplied by the surface area of the body part to estimate its exposure. These partial estimates are then summed to provide a total body exposure estimate. Some studies observed exposure to only selected body parts such as the hands, arms and face. As a consequence, dermal exposure estimates for different body parts may be based on a different set of observations. Further, for some handler scenarios, the number of matching observations in the PHED is so small that the possibility they do not represent the target scenario is substantial. Due to the degree of uncertainty introduced by using this surrogate data, DPR calculates upper confidence limits on the exposure statistics to increase the confidence in the estimates of exposure.

When using surrogate data from PHED to estimate acute exposure, DPR uses the 90% upper confidence limit (UCL) on the 95th percentile. The confidence limit is used to account for some of the uncertainty inherent in using surrogate data and to increase our confidence in the estimate. (Confidence limits on percentiles, also called tolerance limits, are described by Hahn and Meeker (1991).) Estimating the confidence limit requires knowing the mean and standard deviation. PHED reports the mean of total dermal exposure, but only the coefficients of variation for separate body regions. Because the sample sizes per body region differ and because the correlations among body regions are unknown, the standard deviation of total dermal

exposure cannot be calculated. In order to approximate the confidence limit for the 95th percentile, DPR makes the assumption that total exposure is lognormally distributed across persons and has a coefficient of variation of 100 percent. The method of approximation is described in Powell (2002), and uses the fact that in any lognormal distribution with a given coefficient of variation, the confidence limit for the 95th percentile is a constant multiple of the arithmetic mean. The value of the multiplier depends only on sample size. If the sample size is between 20 and 119, the multiplier is 4; if it is between 12 and 19, the multiplier is 5. Estimated exposures from PHED are summarized in Table 5, along with statements of assumptions used in exposure calculations and results of PHED subsets. Numbers of observations are given in the PHED reports (Appendices 2-6); for non-hand dermal exposure, the median number of observations over body regions is used as the sample size.

When using surrogate data to estimate intermediate or long-term exposure, DPR uses the 90% UCL on the arithmetic mean. The 90% UCL is used for the reasons listed in the previous paragraph. If the sample size is between 6 and 14, the multiplier is 2; if it is greater than 15, the multiplier is 1.

Groundboom Applications.

Significant exposure scenarios involving groundboom applications are M/L and applicator. For M/L, use of a closed system was assumed, based on California requirements, and M/L were assumed to wear the clothing and PPE listed on product labels. A 90% protection factor was applied to the inhalation PHED results for use of a respirator (Appendix 2). Applicators were assumed to use clothing and PPE required by product labels and California regulations. The groundboom applicator scenario included use of either truck or tractor, and an open cab was assumed as there is no requirement for a closed cab. Two 90% protection factors were applied to PHED results for applicators (Appendix 3): to hand exposure for use of gloves (Aprea *et al.*, 1994), and to inhalation exposure for use of a respirator (NIOSH, 1987). The protection factor for gloves was needed because the applicator PHED scenario with gloves gave results with insufficient numbers of high-quality observations, and the scenario used did not include gloves.

It was assumed that 40 acres/day (16 ha/day) would be treated (Haskell, 1998). The application rate, 10 lbs AI/acre (11 kg AI/ha), is the rate allowed for field-grown ornamentals to which carbofuran is applied as a high volume spray or drench, which is then irrigated immediately after treatment to move spray or drench into the root zone (Special Local Need registration, CA SLN No. 830058).

As shown in Table 5, the total Acute Absorbed Daily Dosage (Acute ADD) estimate for M/L was 0.224 mg/kg/day. For the applicator scenario, the Acute ADD estimate was 0.318 mg/kg/day. Assuming that a M/L/A spends part of a workday mixing/loading and part making the application, exposure of the M/L/A should be less than the applicator exposure and greater than that of the M/L.

Table 5. Data Used in Estimates of Exposure for Workers Handling Carbofuran and Acute Pesticide Handler Exposure Estimates

Scenario [a]	# [b]	Acute Exposure [c] (µg/lb AI handled)		Long-term Exposure [c] (µg/lb AI handled)		Acute ADD [d] (mg/kg/day)		
		Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Total
GB [e]								
M/L	2	77.3	0.512	19.3	0.128	0.221	0.003	0.224
A	3	102	4.72	25.5	1.18	0.291	0.027	0.318
Aerial [f]								
M/L	2	77.3	0.512	19.3	0.128	0.552	0.008	0.560
A	4	891	2.86	297	1.15	6.36	0.041	6.40
F	5	152	0.800	25.5	1.18	1.09	0.011	1.10
C [g]								
M/L	2	77.3	0.512	19.3	0.128	1.16	0.015	1.18
LPHW [h]								
M/L/A	6	9,480	137	3,160	45.6	0.002	0.00005	0.002
Dip [i]								
M/L	2	77.3	0.512	- -	- -	0.002	0.00003	0.002
A	7/8	- -	- -	- -	- -	1.29	0.001	1.29

[a] Abbreviations: A = Applicator. C = Chemigation F = Flagger GB = Groundboom. LPHW =Low pressure handwand. M/L = Mixer/loader. M/L/A = Mixer/loader/applicator.

[b] Appendix number. Handlers were assumed to wear gloves as specified on product labels, except aerial applicators (exempt from wearing gloves under California regulation). Mixing/loading assumed to require closed system, except small quantities that can be handled with low pressure handwand.

[c] Acute exposures last from less than a day to short-term intervals up to one week; long-term exposure estimates cover longer intervals, including seasonal, annual and lifetime. Dermal and inhalation exposure calculated from surrogate data using the Pesticide Handlers Exposure Database (PHED, 1995), except for dip/slurry applicator. Values from PHED were rounded to three significant figures.

[d] Acute Absorbed Daily Dosage (acute ADD) is an upper-bound estimate calculated from the acute exposure. Application rate is maximum rate on product labels, which varied for each scenario; acres treated per day varies by scenario. Estimates were rounded to three significant figures. Calculation:

Acute ADD = [(acute exposure) x (absorption) x (acres treated/day) x (application rate)]/(70 kg body weight).

Calculation assumptions include: dermal absorption = 50% (Donahue, 1996); body weight = 70 kg (Thongsinthusak, *et al*., 1993a); inhalation absorption = 100%.

[e] Acute ADD estimates assumed 40 acres (16 ha) treated/day (Haskell, 1998), and a maximum application rate of 10 lbs AI/acre (11 kg AI/ha), maximum rate on field-grown ornamentals.

[f] Acute ADD estimates assumed 1,000 acres (405 ha) treated/day (Haskell, 1998), and a maximum application rate of 1.0 lb AI/acre (1.1 kg AI/ha), maximum rate on alfalfa.

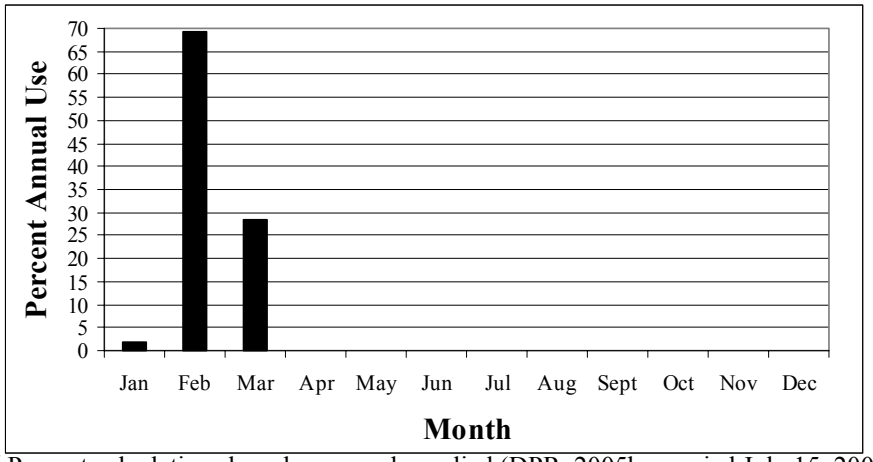
[g] Acute ADD estimates assumed 350 acres (142 ha) treated/day (U.S. EPA, 2001), and a maximum application rate of 6.0 lbs AI/acre (6.7 kg AI/ha), maximum rate on post-harvest grapes.

[h] Acute ADD estimates assumed handling of 40 gal/day, containing 0.062 lb AI/100 gal (U.S. EPA, 2001), for a total of 0.025 lb AI/day (0.011 kg AI/day).

[i] Acute ADD estimates assumed handling of 40 gal/day, containing 0.1 lb AI/100 gal (U.S. EPA, 2001), for a total of 4 lb AI/day (1.8 kg AI/day). M/L estimates from PHED. Applicator dermal exposure estimates based on RAGS-E equations (U.S. EPA, 2004a). Applicator inhalation exposure estimates based on SWIMODEL (U.S. EPA, 2003), assuming a saturated carbofuran vapor concentration. See Appendix 7 and Appendix 8 for calculations of applicator exposure estimates.

Groundboom applications are common in row and field crops, such as alfalfa, artichokes, bermudagrass, and cotton. Alfalfa was selected as a representative crop, and all ground applications to alfalfa were assumed to be groundboom applications. Figure 3 summarizes ground applications of carbofuran to alfalfa in Imperial County, based on pounds applied per month for the most recent five years for which data are available, 1999-2003 (DPR, 2005b; queried July 15, 2005). Most carbofuran use on alfalfa during the five-year period occurred in Imperial County.

Figure 3. Ground Applications of Carbofuran to Alfalfa in Imperial County, 1999 – 2003 [a]



[a] Percent calculations based on pounds applied (DPR, 2005b; queried July 15, 2005).

Nearly all applications occurred in the two-month period of February and March (Figure 3). Ground applications to other field crops also tended to occur during two months each year (data not shown), supporting a seasonal and annual estimate of two months. Both seasonal (the longest period of frequent exposure) and annual exposures were assumed to occur during these two months. Estimates of seasonal, annual and lifetime exposures are given in Table 6.

Aerial Applications

Significant exposure scenarios involving aerial applications are M/L, applicator, and flagger. All M/L exposure estimates (in support of groundboom, aerial, and chemigation applications) used the same surrogate PHED data, with the same clothing and PPE assumptions, and the same protection factors were applied to the PHED results. Applicators and flaggers were assumed to use clothing and PPE listed on product labels; this included long-sleeved shirt and pants, shoes plus socks, waterproof gloves, and a respirator. Open cockpits were assumed, as there is no requirement for closed cockpits during applications. A 90% protection factor was applied to inhalation data in PHED results for applicators and flaggers (Appendix 4 and Appendix 5), for use of a respirator (NIOSH, 1987). Also, a 90% protection factor was applied to hand exposure data in PHED results for flaggers for use of gloves (Aprea *et al*., 1994), because flagger PHED scenarios with gloves gave results with insufficient numbers of high-quality observations, and the scenario used did not include gloves. The application rate, 1.0 lb AI/acre (1.1 kg AI/ha), is the maximum rate allowed for alfalfa and foliar applications to field corn, and it was assumed that 1,000 acres/day (405 ha/day) would be treated (Haskell, 1998).

Table 6. Seasonal, Annual, and Lifetime Estimates of Pesticide Handler Exposure to Carbofuran

Scenario [a]	SADD [b] (mg/kg/day)			AADD [c] (mg/kg/day)			LADD [d] (mg/kg/day)		
	Dermal	Inhalation	Total	Dermal	Inhalation	Total	Dermal	Inhalation	Total
GB [e]									
M/L	0.055	0.001	0.056	0.009	0.0001	0.009	0.005	0.0001	0.005
A	0.073	0.007	0.080	0.012	0.001	0.013	0.006	0.001	0.007
Aerial [f]									
M/L	0.138	0.002	0.140	0.023	0.0003	0.023	0.012	0.0002	0.012
A	2.12	0.016	2.14	0.354	0.003	0.357	0.189	0.001	0.190
F	0.271	0.003	0.274	0.045	0.001	0.046	0.024	0.0003	0.024
C [g]									
M/L	0.290	0.004	0.294	0.072	0.001	0.073	0.039	0.001	0.040
LPHW [h]									
M/L/A	0.0006	0.00002	0.0006	0.0001	0.00001	0.0001	0.0001	0.000002	0.0001

[a] Abbreviations: A = Applicator. C = Chemigation F = Flagger GB = Groundboom. LPHW = Low pressure handwand. M/L = Mixer/loader. M/L/A = Mixer/loader/applicator.

[b] Seasonal Average Daily Dosage is a 90% upper confidence estimate calculated from the long-term exposure estimate given in Table 5. Application rate is maximum rate on product labels, which varied for each scenario; acres treated per day varies by scenario. Dermal absorption assumed to be 50% (Donahue, 1996). Inhalation absorption assumed to be 100%. Body weight assumed to be 70 kg (Thongsinthusak *et al*., 1993a). Calculation: SADD = [(long-term exposure) x (absorption) x (acres treated/day) x (application rate)]/(70 kg body weight).

[c] Annual Average Daily Dosage = SADD x (annual use months per year)/(12 months in a year). Annual use estimates vary for each scenario.

[d] Lifetime Average Daily Dosage = AADD x (40 years of work in a lifetime)/(75 years in a lifetime).

[e] Estimates assumed a maximum application rate of 10 lbs AI/acre (11 kg AI/ha), maximum rate on field-grown ornamentals. Assumed 40 acres (16 ha) treated/day (Haskell, 1998). Seasonal and annual exposures are estimated to occur over two months.

[f] Estimates assumed a maximum application rate of 1.0 lb AI/acre (1.1 kg AI/ha), maximum rate on alfalfa. Assumed 1,000 acres (405 ha) treated/day (Haskell, 1998). Seasonal and annual exposures are estimated to occur over two months.

[g] Estimates assumed a maximum application rate of 6.0 lb AI/acre (6.7 kg AI/ha), maximum rate on post-harvest grapes. Assumed 350 acres (142 ha) treated/day (U.S. EPA, 2001). Seasonal exposure is estimated to occur during a two-month period; annual exposure is estimated to occur over a total of three months.

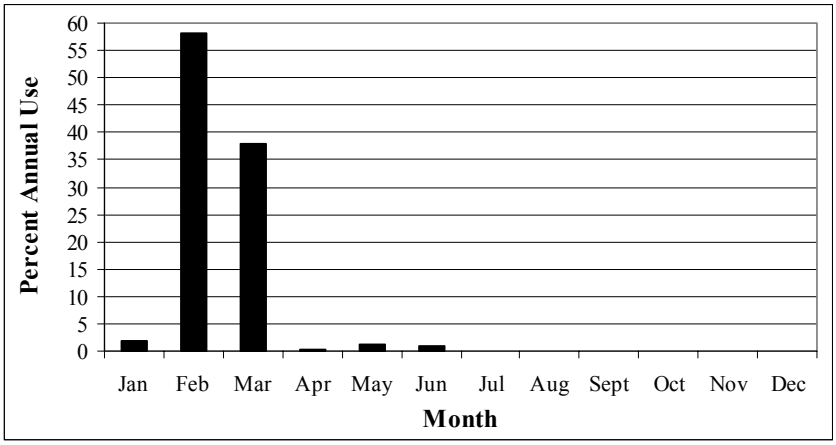
[h] Estimates assumed handling of 40 gal/day, containing 0.000625 lb AI/100 gal (U.S. EPA, 2001), for a total of 0.025 lb AI/day (0.011 kg AI/day). Seasonal and annual exposures are estimated to occur over three months.

The Acute ADD estimates were 0.560 mg/kg/day for M/L, 6.40 mg/kg/day for aerial applicators, and 1.10 mg/kg/day for flaggers (Table 5).

Figure 4 shows percent of annual use based on pounds applied per month for the most recent five years for which data are available, 1999-2003 (DPR, 2005b; queried July 15, 2005). Data from Imperial County, which has the most aerial applications of carbofuran, are summarized in Figure 4. Nearly all applications occurred in the two-month period of February and March. For seasonal and annual exposure estimates, it was assumed that workers were exposed on each

workday for these two months. Estimates of seasonal, annual and lifetime exposure are given in Table 6.

Figure 4. Aerial Applications of Carbofuran in Imperial County, 1999 – 2003 [a]



[a] Percent calculations based on pounds applied (DPR, 2005b; queried July 15, 2005).

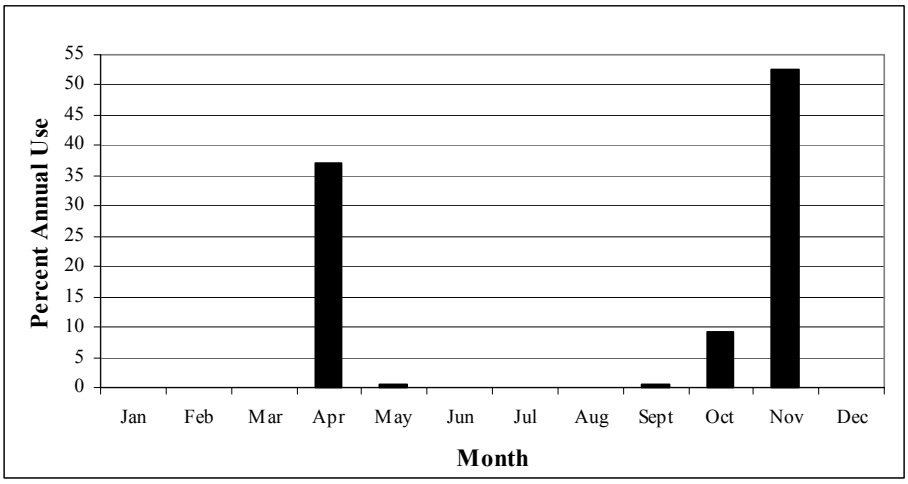
Chemigation (Drip Irrigation)

The significant exposure scenario for chemigation is M/L. No exposure to the applicator is expected during application via drip irrigation (Lavy and Mattice, 1985). For M/L, use of a closed system was assumed, in accordance with California regulations, and M/L were assumed to wear the clothing and PPE listed on product labels. A 90% protection factor was applied to the inhalation PHED results for use of a respirator (Appendix 2). The maximum application rate is 6.0 lbs AI/acre (6.7 kg AI/ha), on post-harvest grapes (Special Local Need registration, CA SLN No. 980012). A default of 350 acres/day (142 ha/day) was assumed (U.S. EPA, 2001). The Acute ADD estimate for M/L in support of chemigation was 1.18 mg/kg/day (Table 5).

Chemigation is used to apply carbofuran to grapes. Figure 5 shows percent of annual use based on pounds applied to grapes per month for the most recent five years for which data are available, 1999-2003 (DPR, 2005b; queried July 21, 2005). All applications were assumed to be made using chemigation, although Section 24(c) labels also allow soil applications using a sprayblade and soil drenching in container-grown grapevines. Data from Monterey County, which has the most applications of carbofuran to grapes, are summarized in Figure 5.

Nearly all applications occurred in April, October, or November (Figure 5). Seasonal exposure was estimated to occur during the two-month interval of October and November (the longest contiguous period during which monthly use was at least 5% of annual total). Annual exposure was estimated to occur during all three months. Estimates of seasonal, annual and lifetime exposure are given in Table 6.

Figure 5. Applications of Carbofuran to Grapes in Monterey County, 1999 – 2003 [a]



[a] Percent calculations based on pounds applied (DPR, 2005b; queried July 21, 2005).

Handwand Applications

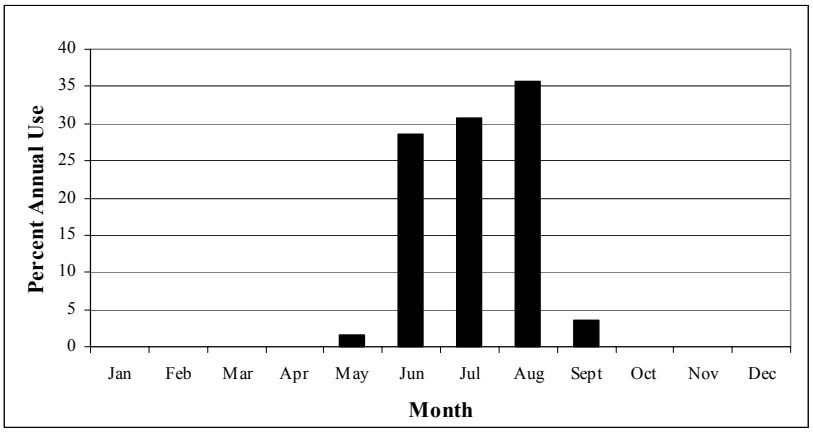
The significant exposure scenario is M/L/A. Workers were assumed to use clothing and PPE listed on product labels. A 90% protection factor was applied to inhalation exposure data for use of a respirator (NIOSH, 1987). The maximum application rate for container-grown ornamentals is 2 fluid ounces of Furadan® 4F per 100 gallons. Workers were assumed to handle 40 gal/day (U.S. EPA, 2001). The amount of carbofuran handled per day was calculated as follows:

(2 fl oz product/100 gal) x (1 gal/128 fl oz) x (4 lbs AI/gallon) = 0.000625 lb AI/gal.
(0.000625 lb AI/gal) x (40 gal/day) = 0.025 lb AI/day.

The estimated Acute ADD for M/L/A using low-pressure handwands was 0.002 mg/kg/day.

Figure 6 shows percent of annual use based on pounds applied to plants grown in containers in greenhouses and nurseries per month for the most recent five years for which data are available, 1999-2003 (DPR, 2005b; queried July 21, 2005). All applications were assumed to be made using handwands. Data from Del Norte County, which has the most applications of carbofuran to container-grown plants, are summarized in Figure 6.

Figure 6. Applications of Carbofuran in Nurseries and Greenhouses in Del Norte County, 1999 – 2003 [a]



[a] Percent calculations based on pounds applied to plants in containers (DPR, 2005b; queried July 21, 2005).

Dip/Slurry Applications

Product label directions for treating pine seedlings for pales weevils and pitch-eating weevils are as follows: "Apply a 1% (W/W) active Furadan clay slurry (see following for preparation) to the roots of pine seedlings prior to transplanting. Treat seedlings by dipping roots or use any other suitable means which allows thorough coating. Keep roots moist until transplanted. Prepare the slurry as follows: Add 1.6 ounces (2 ½ tablespoons) of Furadan® 4F to ½ gallon of water. Mix thoroughly. Add 2 pounds of pulverized kaolin clay (pH 4.5) to this suspension. Mix thoroughly. This is sufficient to treat the roots of 150 to 200 seedlings. Adequate ventilation is required for indoor treatment."

Furadan® 4F contains 4 lbs carbofuran per gallon. Thus, each gallon of slurry prepared according to the directions contains 0.1 lbs AI (1.6 ounces product per ½ gallon slurry = 3.2 ounces product per gallon slurry; 3.2 ounces product = 0.025 gallon product; 4 lbs AI/gallon product). Handlers were assumed to wear clothing and PPE listed on product labels.

The M/L exposure estimate is based on data from PHED. Because carbofuran is a Toxicity Category I pesticide, a closed system is required during mixing and loading, unless one gallon or less is handled per day from the original one gallon container (3 CCR 6746). For this scenario, there is no information available on amounts of AI handled daily, although it is possible that thousands of seedlings are treated daily (Beauvais, 2004). For exposure estimates, it was assumed that 40 gallons of solution would be handled daily (sufficient to treat up to 8,000 seedlings); thus a closed-system was assumed for M/L exposure estimates.

As details about pesticide root dipping are lacking, exposure estimates for this scenario are based on the assumption that root dips with pesticides are similar to root dips done to protect roots from desiccation, except that pesticidal root dips require workers to wear clothing and PPE specified on pesticide product labels. Workers are assumed to immerse seedling roots into a container such as a bucket or vat while holding seedlings above roots, and that hands are immersed in the pesticide slurry. Several models were evaluated to determine the best estimates of applicator exposure (Beauvais, 2004).

Applicator dermal exposure was estimated from equations in the Risk Assessment Guidance for Superfund, Part E (RAGS-E). The series of calculations is summarized in Appendix 7. The formula used to estimate dermal exposure requires AI concentration in mg/L units. To convert, 0.1 lbs AI = 45,360 mg AI and 1 gallon = 3.79 L. The AI concentration is about 12,000 mg/L (this concentration is greater than the water solubility of carbofuran; however, the product contains additives to increase AI solubility in water).

Most of the exposure is anticipated to be to hands. However, available information suggests that workers may also be exposed by splashes or drips on the forearms, torso, and legs (Beauvais, 2004). Although this exposure is not immersion in the same way as hands, in the absence of a better approach these exposed body surfaces were also considered in exposure estimates. Dermal exposure via hands and non-hand areas were corrected for 90% protection factors for gloves and clothing (Thongsinthusak *et al.*, 1993a; Aprea *et al.*, 1994). The surface area of both hands was assumed to be 904 cm^2, the value of combined male and female medians; the surface area of the other parts of a worker's body anticipated to be exposed was assumed to be 7,306 cm^2, the total surface area of chest/stomach, forearms, front of thighs and lower legs based on combined male and female medians (U.S. EPA, 1997).

As with dermal exposure, no inhalation exposure monitoring data are available for workers dipping pine seedlings. Inhalation exposure is anticipated to occur, assuming that dipping tanks have a free liquid surface from which chemicals can volatilize into the air. Several models have been proposed to estimate inhalation exposure resulting from volatilization of chemicals from aqueous solutions; three models used by U.S. EPA to estimate exposure to chemicals evaporated from containers or pools of liquid were evaluated in Beauvais (2004). Applicator inhalation exposure was estimated from equations in SWIMODEL (U.S. EPA, 2003), assuming a saturated carbofuran vapor concentration (the vapor concentration calculated by SWIMODEL exceeded this value, and was considered unrealistically high). The calculations are summarized in Appendix 8.

The Acute ADD estimates were 0.002 mg/kg/day for M/L and 1.29 mg/kg/day for applicators (Table 5). Although dip/slurry use on pine seedlings is allowed in California, a review of the 1991 – 2003 PUR shows no reported uses on pine seedlings (DPR, 2005b). Therefore, seasonal, annual and lifetime exposures to carbofuran are not anticipated to occur during activities in these crops, and only acute exposures are estimated.

Reentry Workers

Reentry workers are subject to occupational exposure primarily from contact with dislodgeable carbofuran residues that have accumulated on treated foliage. Potentially significant exposure scenarios for reentry workers were selected based on crop-activity groupings developed by U.S. EPA's Science Advisory Council for Exposure (U.S. EPA, 2000). Scenarios considered to have high exposure potential in U.S. EPA (2000) were assessed. For each of these scenarios, exposure of workers reentering fields following foliar applications of carbofuran was estimated from DFR. Crops on which foliar applications are allowed are listed in Table 1.

In the absence of chemical-specific exposure data for workers entering treated fields, residue decay data and default transfer coefficients (TCs) were used to estimate worker exposure; each TC estimate was based on the crop and the activity of the worker. The absorbed daily dosage (ADD) was calculated as shown in the equation below (Zweig *et al*., 1980; Zweig *et al*., 1985), using a dermal absorption rate (DA) of 50% (Donahue, 1996), a default exposure duration (ED) of 8 hours, and a default body weight (BW) of 70 kg (Thongsinthusak *et al*., 1993a). Acute exposure estimates are given in Table 7.

$$ADD\ (\mu g / kg / day) = \frac{DA \times DFR\ (\mu g / cm^2) \times TC\ (cm^2 / hr.) \times ED\ (hrs. / day)}{BW(kg)}$$

Exposures were estimated for three reentry scenarios. These are considered to be representative scenarios, and protection of workers in these scenarios would be anticipated to protect other reentry workers. Scouting cotton covers all activities in field corn, sweet corn, and sugarcane. Scouting alfalfa covers all activities in alfalfa, barley, wheat, oats, soybeans, and artichokes. Scouting potatoes covers all activities in potatoes.

Reentry workers are not required to wear protective clothing unless entering before expiration of the restricted entry interval (REI). As much reentry work occurs in hot weather and for several hours each day, protective clothing is often not worn by fieldworkers. Therefore, fieldworker exposure estimates were based on an assumption that no protective clothing or equipment was used. Acute exposures were estimated at the expiration of the REI for all activities (Table 7).

Table 7. Acute Exposures to Carbofuran Estimated for Reentry Workers

Exposure scenario	DFR (µg/cm^2) [a]	TC (cm^2/hr) [b]	Acute ADD (mg/kg/day) [c]
Scouting Cotton [d]	0.057	2,000	0.007
Scouting Alfalfa [e]	1.16	1,500	0.099
Scouting Potatoes [f]	0.186	1,500	0.016

[a] Dislodgeable foliar residue (DFR) estimated at expiration of restricted entry interval (REI).
[b] Transfer coefficient (TC) is an estimate of skin contact with treated foliage.
[c] Acute Absorbed Daily Dosage (Acute ADD) calculated as described in text. Assumptions include:
- Exposure duration = 8 hr
- Dermal Absorption = 50% (Donahue, 1996)
- Body weight = 70 kg (Thongsinthusak, *et al*., 1993a)

[d] REI = 14 days for foliar applications. DFR derived from Ware *et al.* (1978). TC from Dong (1990).
[e] REI = 48 hours. DFR derived from Hernandez *et al.* (2002). TC from U.S. EPA (2000).
[e] REI = 48 hours. DFR derived from Barros and Dow (1998). TC from U.S. EPA (2000).

For longer-term exposure estimates it was assumed that workers would not always enter fields at the expiration of the REI. Seasonal, annual and lifetime exposures were estimated at an assumed average reentry of REI + 6 days for cotton scouts and REI + 3 days for alfalfa scouts and potato scouts (Table 8). These assumed averages were not based on data; rather, they were based on the reasonable, health-protective assumption that workers may enter fields an average of 3 - 10 days after expiration of the REI.

Table 8. Exposures to Carbofuran Estimated for Reentry Workers

Exposure scenario	SADD (mg/kg/day) [a]	AADD (mg/kg/day) [b]	LADD (mg/kg/day) [c]
Scouting Cotton [d]	0.0009	0.0001	0.00008
Scouting Alfalfa [e]	0.070	0.012	0.006
Scouting Potatoes [f]	0.010	0.002	0.001

[a] Seasonal Average Daily Dosage is a mean estimate of absorbed dose, calculated as described in text. Dislodgeable foliar residue (DFR) estimates are given below for each scenario.
[b] Annual Average Daily Dosage = ADD x (annual use months per year)/(12 months in a year).
[c] Lifetime Average Daily Dosage = AADD x (40 years of work in a lifetime)/(75 years in a lifetime).
[d] DFR (Day 20) = 0.0076. Estimated seasonal and annual exposure is 2 months.
[e] DFR (Day 5) = 0.819. Estimated seasonal and annual exposure is 2 months.
[f] DFR (Day 5) = 0.111. Estimated seasonal and annual exposure is 3 months.

Scouting Cotton

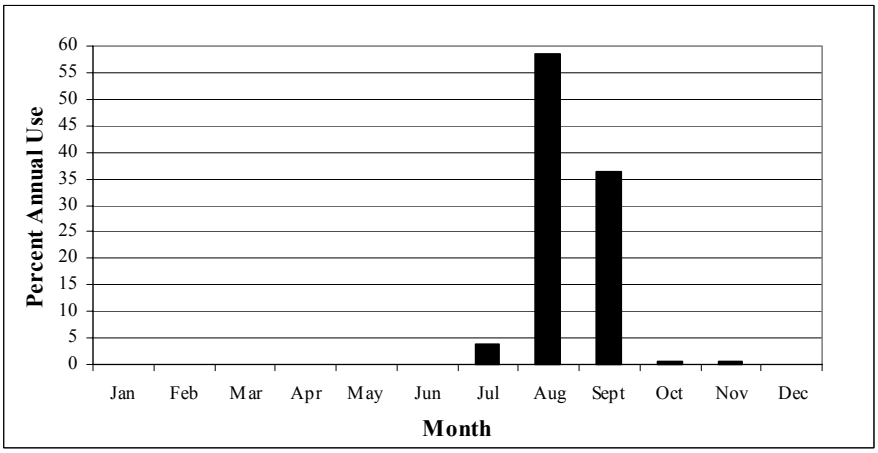
Under the Section 18 emergency exemption label, the maximum application rate is 0.5 lb AI/acre (0.56 kg AI/acre), with a limit of two applications per season. The REI is 14 days following foliar application. The DFR value used in exposure estimates was based on a study done in cotton in Arizona (Ware *et al*., 1978), as discussed in the Environmental Concentrations section. The equation is: ln DFR(t) = 1.86 - 0.337t; $r^2 = 0.92$. From this equation, the DFR on Day 14 was estimated to be 0.057 μg/cm^2.

A transfer factor (potential residue transferred to clothing) was derived from a series of studies in which several organophosphates were applied to cotton (Ware *et al.*, 1973, 1974, 1975). Geometric mean transfer factors were computed for bare hands (950 cm^2/hr), the clothed upper body (1,020 cm^2/hr), and the clothed lower body (9,640 cm^2/hr). The transfer factor for the whole body of cotton scouts (11,600 cm^2/hr) was calculated by summing these individual geometric mean transfer factors (Dong, 1990). Assuming a clothing penetration of 10%, the TC used to estimate exposure to cotton scouts was 2000. The Acute ADD for cotton scouts was estimated to be 0.007 mg/kg/day.

Figure 7 shows the relative numbers of cotton acres treated with carbofuran on a monthly basis for the most recent five years for which data are available, 1999-2003 (DPR, 2005b; queried July 28, 2005). In the high-use county of Fresno, most applications occurred in August and September. For seasonal and annual exposure estimates, all applications shown in Figure 7 were assumed to be foliar applications, and it was assumed that scouts were exposed on each workday for these two months. Estimates of seasonal, annual and lifetime exposure are given in Table 8.

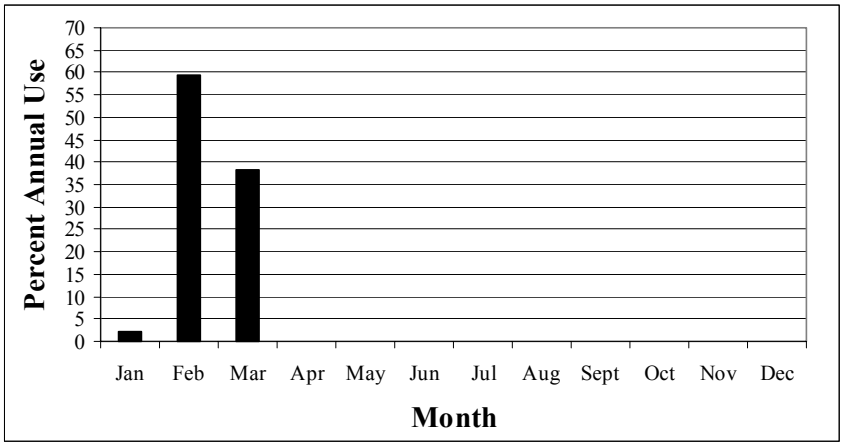
Scouting may occur at any time, and was assumed to potentially occur following pesticide use (e.g., to confirm efficacy of the application). Figure 8 summarizes applications of carbofuran to alfalfa in Imperial County, based on acres treated each month for the most recent five years for which data are available, 1999-2003 (DPR, 2005b; queried July 15, 2005). Most carbofuran use on alfalfa during the five-year period occurred in Imperial County. The majority of carbofuran use on alfalfa occurred in February and March (Figure 8). For seasonal and annual exposure estimates, it was assumed that workers were exposed on each workday for these two months. Estimates of seasonal, annual and lifetime exposure are given in Table 8.

Figure 7. Applications of Carbofuran to Cotton in Fresno County, 1999 – 2003 [a]



[a] Percent calculations based on acres of cotton treated (DPR, 2005b; queried July 28, 2005).

Figure 8. Applications of Carbofuran to Alfalfa in Imperial County, 1999 – 2003 [a]



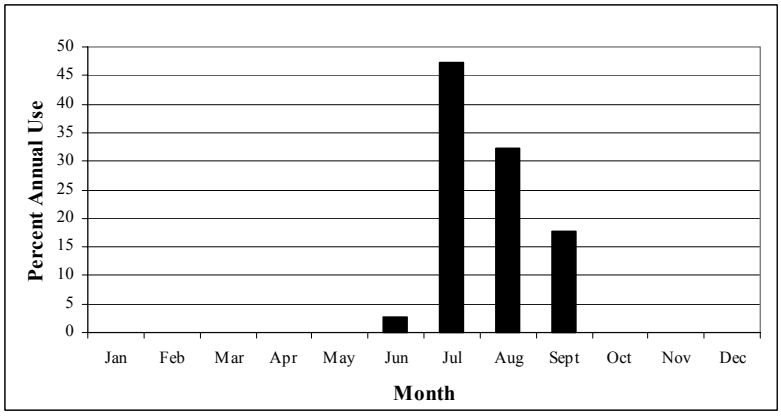
[a] Percent calculations based on acres of alfalfa treated (DPR, 2005b; queried July 21, 2005).

Scouting Potatoes

The maximum application rate allowed on potatoes is 1.0 lb AI/acre (1.1 kg AI/ha), and the REI following carbofuran applications is 48 hours. For exposure estimates, the estimated DFR 2 days post-application was used, based on data from Barros and Dow (1998), as well as a default TC of 1,500 cm^2/hr (U.S. EPA, 2000). The Acute ADD was estimated at 0.016 mg/kg/day (Table 7).

Scouting may occur at any time, and was assumed to potentially occur following pesticide use (e.g., to confirm efficacy of the application). Figure 9 summarizes applications of carbofuran to potatoes in San Joaquin County, based on acres treated each month for the most recent five years for which data are available, 1999-2003 (DPR, 2005b; queried July 15, 2005). Most carbofuran use on potatoes during the five-year period occurred in San Joaquin County. The majority of carbofuran use on potatoes occurred in July through September (Figure 9). For seasonal and annual exposure estimates, it was assumed that workers were exposed on each workday for these three months. Estimates of seasonal, annual and lifetime exposure are given in Table 8.

Figure 9. Applications of Carbofuran to Potatoes in San Joaquin County, 1999 – 2003 [a]



[a] Percent calculations based on acres of potatoes treated (DPR, 2005b; queried July 21, 2005).

Ambient Air and Bystander Exposures

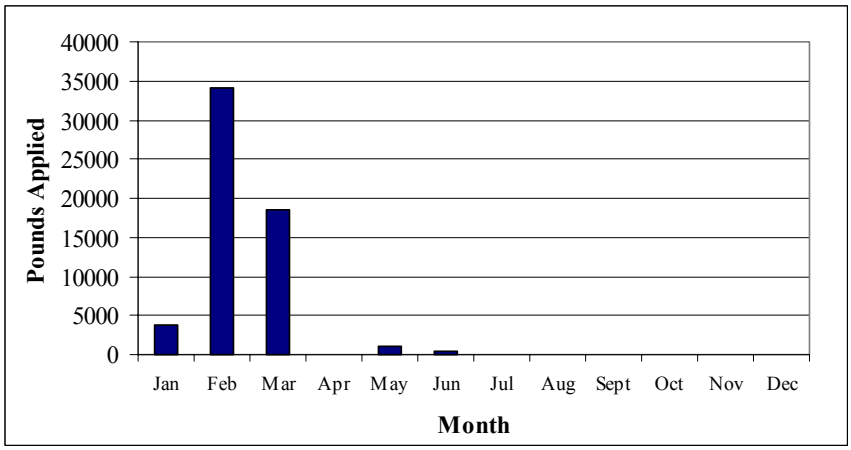
Ambient air and application site air monitoring detected carbofuran, suggesting that the public may be exposed to airborne carbofuran. Individuals might be exposed to carbofuran if they live, work, or perform other activities adjacent to fields that are being treated or have recently been treated (bystander exposure). Also, air monitoring studies in Imperial and Sacramento counties suggest that airborne carbofuran exposures are possible in urban areas, and in areas that are far from application sites (ambient air exposure). Ambient air and bystander exposures are perhaps more likely in California than in other parts of the U.S. because of the close proximity of urban and agricultural areas in parts of the state where the greatest carbofuran use occurs (CAST, 2002). Public exposure to airborne carbofuran was estimated, based on monitoring studies of carbofuran at application sites and in ambient air. See the Environmental Concentrations section for study details.

Ambient Air

Carbofuran concentrations in ambient air were higher in Imperial County than in Sacramento County (ARB, 1995; Majewski and Baston, 2002). This coincided with greater use in Imperial County than in Sacramento County (total annual use 58,200 and 2,750 pounds, respectively; see Figures 10 and 11).

Whereas ambient air monitoring was done year-round in Sacramento County (Majewski and Baston, 2002), it was only done for two months in Imperial County (ARB, 1995). Figure 10 shows the use of carbofuran in Imperial County in 1995, the year ambient air sampling was done in Imperial County. Figure 10 shows that the ambient air sampling, which was done in February and March, coincided with the greatest use of carbofuran in Imperial County in 1995. Examination of use in 1999 – 2003 (DPR, 2005b; data not shown) suggested that this pattern is consistent from year to year, and that exposures to carbofuran in ambient air are most likely to occur in February and March. Smaller amounts of carbofuran are used in January, May and June.

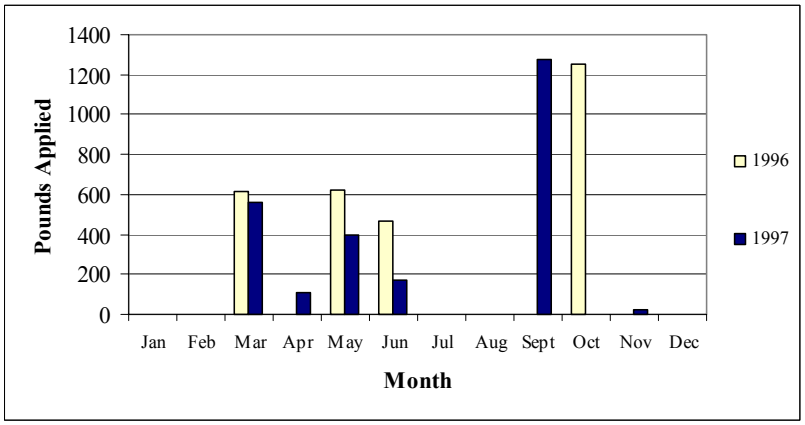
Figure 10. Pounds of Carbofuran Applied in Imperial County, 1995 [a]



[a] Based on pounds applied by all methods to all crops in Imperial County (DPR, 2005b; queried December 14, 2005).

In comparison, in Sacramento County during air monitoring in 1996 – 1997 the greatest use occurred in either September or October, with substantial use also occurring in March, May and June (Figure 11). Examination of use in 1999 – 2003 (DPR, 2005b; data not shown) suggested that use in March has increased, while use in other months has decreased, but most the use occurred in one to four months (specific months varied between years). Each year, exposures to carbofuran in ambient air are assumed most likely to occur during the months of greatest use, and exposure estimates were based on an assumption that greatest use will occur in four months each year.

Figure 11. Pounds of Carbofuran Applied in Sacramento County, 1996 and 1997 [a]



[a] Based on pounds applied by all methods to all crops in Sacramento County (DPR, 2005b; queried December 14, 2005).

Table 9 summarizes ambient air exposure estimates to carbofuran based on ambient air monitoring studies in Imperial and Sacramento counties. Following DPR practice, acute ADDs were calculated with 95% percentile concentrations estimated using lognormal methods. DPR's experience with many large environmental datasets has shown that they are usually well described by the lognormal distribution.

Acute ADD for ambient air exposures in Imperial County ranged 0.000004 – 0.000032 mg/kg/day for infants and 0.000002 – 0.000015 mg/kg/day for adults (Table 9). Acute ADD for ambient air exposures in Sacramento County ranged 0.0000010 – 0.0000012 mg/kg/day for infants and 0.0000005 – 0.0000006 mg/kg/day for adults.

Seasonal and annual exposure estimates shown in Table 9 were based on high-use months as shown in Figures 10 and 11. Seasonal and annual exposures were not estimated at sites where carbofuran was not detected (Site H) or detected once (Sites C and EC). Seasonal ADD ranged 0.000004 – 0.000019 mg/kg/day for Imperial County and 0.0000002 – 0.0000005 mg/kg/day for Sacramento County. Annual ADD ranged 0.000001 – 0.000003 mg/kg/day for Imperial County and 0.00000007 – 0.0000002 mg/kg/day for Sacramento County.

Table 9. Exposure Estimates for Persons Exposed to Carbofuran in Ambient Air [a]

	Air Concentration [b] ($\mu g/m^3$)		95th Percentile	Acute ADD [d] (mg/kg/day)		Seasonal ADD [e] (mg/kg/day)		Annual ADD [f] (mg/kg/day)	
Site	Mean	SD	Conc. [c]	Infants	Adults	Infants	Adults	Infants	Adults
Imperial County									
Site C [g]	0.007	0.003	0.012	0.000007	0.000003	NA [h]	NA	NA	NA
Site M	0.014	0.008	0.032	0.000019	0.000010	0.000008	0.000004	0.000001	0.000001
Site EC	0.007	0.002	0.010	0.000006	0.000003	NA	NA	NA	NA
Site H [i]	0.006	0.001	0.006	0.000004	0.000002	NA	NA	NA	NA
Site PM	0.033	0.037	0.118	0.000070	0.000034	0.000020	0.000010	0.000003	0.000002
Sacramento County Metro (Downtown)									
South	0.0007	0.0011	0.0024	0.0000014	0.0000007	0.0000004	0.0000002	0.0000001	0.00000007
North	0.0009	0.0020	0.0027	0.0000016	0.0000008	0.0000005	0.0000003	0.0000002	0.0000001

[a] Imperial County data from ARB (1995). Sacramento County data from Majewski and Baston (2002). The total number of observations in Imperial County data sets, including non-detects, was 14 except for site PM, which had 12; the total numbers of observations in the Sacramento County Metro site were 66 for south winds and 50 for north winds. Appendix 1 summarizes ambient air monitoring data on which exposure estimates are based.

[b] Calculated using ½ detection limit (reporting limit) for non-detects.

[c] Concentration (in $\mu g/m^3$) used for acute exposure estimates. Calculated using lognormal distribution methods.

[d] Acute Absorbed Daily Dosage ($\mu g/kg/day$) = (95th percentile upper bound air concentration) x (inhalation rate). Calculation assumptions include:

- Infant inhalation rate = 0.59 $m^3/kg/day$ (Layton, 1993; U.S. EPA, 1997)
- Adult inhalation rate = 0.28 $m^3/kg/day$ (Wiley *et al*., 1991; U.S. EPA, 1997; OEHHA, 2000)
- Inhalation absorption is assumed to be 100%

[e] Seasonal ADD = (mean air concentration) x (inhalation rate). Calculation assumptions as above.

[f] Annual ADD = (Seasonal ADD) x (number of high-use months/12). Imperial County: two high-use months. Sacramento County: four high-use months.

[g] Site C: Calipatria. Site M: Meadows Union School. Site H: Heber. Site EC: El Centro. Site PM: Air Pollution Control District monitoring station.

[h] NA: Not applicable. Seasonal and annual exposure estimates not done at sites with no detects or one detect (i.e., Site C, Site EC, and Site H).

[i] All samples at this site were non-detects. Calculated concentrations varied slightly due to different sample volumes.

Bystanders at Application Sites

To estimate bystander exposure to carbofuran in air, data were used from application site monitoring in a 1993 study in Imperial County (ARB, 1994). Stations (one each east, west and south, and two north) were located 20 m from the edge of the field. The application took place on March 31 between 10:00 and 11:00 AM. Table 4 summarizes air concentrations during several monitoring periods at each of these stations.

Table 10 summarizes the bystander exposure estimates. As available information suggests that exposures of less than 24 hours can result in toxicity, 1-hour exposure estimates were calculated based on the highest measured concentration during a one-hour measuring period. This maximum concentration measured by ARB occurred during the first hour of monitoring during the application at the east monitoring station (0.66 $\mu g/m^3$). However, in ARB (1994) carbofuran was applied at a rate (0.3 lb AI/acre) that was below the maximum application rate allowed on alfalfa (1.0 lb AI/acre). Bystanders near a field receiving the maximum application rate would be anticipated to be exposed to higher concentrations than measured by ARB (1994). The concentration used to estimate exposure was therefore adjusted (multiplied by 1.0/0.3 = 3.3) to 2.2 $\mu g/m^3$. The 1-hour absorbed dose was 0.000550 mg/kg/hr for infants and 0.000099 mg/kg/hr for adults.

Table 10. Bystander Exposure Estimates for Carbofuran [a]

	Adjusted Carbofuran Concentration ($\mu g/m^3$) [b]	Inhalation Rate [c]	Absorbed Dose [d]
1-Hour Absorbed Dose (during heavy activity for 1 hour) [e]			
Infant	2.2	0.16 m^3/kg/hr	0.000550 mg/kg/hr
Adult	2.2	0.022 m^3/kg/hr	0.000099 mg/kg/hr
Acute Absorbed Daily Dosage (Acute ADD) [f]			
Infant	0.77	0.59 m^3/kg/day	0.000454 mg/kg/day
Adult	0.77	0.28 m^3/kg/day	0.000216 mg/kg/day

[a] Based on air monitoring done 20 m from an Imperial County alfalfa field in 1993 (ARB, 1994).

[b] Carbofuran concentrations were multiplied by the ratio of maximum allowed application rate on alfalfa (1.0 lb AI/acre) to the 0.3 lb AI/acre rate used by ARB (1994), to get adjusted concentrations for exposure estimates.

[c] Different inhalation rates were used for the 1-hour and acute 24-hour absorbed doses. The inhalation rates for 1-hour absorbed dose estimates were calculated from values reported in Andrews and Patterson (2000), assuming heavy activity and dividing by the mean body weight for males and females (71.8 kg). Hourly inhalation rates for heavy activity are 1.9 m^3/hr for infants (Layton, 1993; U.S. EPA, 1997) and 3.2 m^3/hr for adults (Wiley *et al*., 1991; U.S. EPA, 1997; OEHHA, 2000). Daily inhalation rates are default values from Andrews and Patterson (2000).

[d] 1-hour absorbed doses assume 1-hour exposure during heavy activity, and are based on highest carbofuran concentration measured by ARB (1994). Absorbed daily doses assume a typical mixture of activity levels throughout the day and are based on the highest 24-hour time-weighted average (TWA) air concentrations from ARB (1994).

[e] 1-hour absorbed dose (mg/kg/hr) = (highest 1-hour air concentration) x (inhalation rate). The maximum 1-hour concentration from Table 4 (0.66 $\mu g/m^3$), from the East air monitoring station, was adjusted as described in Footnote [b].

[f] Acute ADD (mg/kg/day) = (TWA air concentration) x (inhalation rate). The 24-hour TWA concentration from Table 4 (TWA = 0.23 $\mu g/m^3$), from the West air monitoring station, was adjusted as described in Footnote [b].

The 24-hour time-weighted average (TWA) for the west monitoring station (TWA = 0.23 μg/m^3) was used to estimate daily exposure. This concentration was adjusted for the sub-maximum application rate used in the application monitored in ARB (1994), to 0.77 μg/m^3. Acute ADD for bystanders was 0.000454 mg/kg/day for infants and 0.000216 mg/kg/day for adults. Seasonal or annual exposure to application site airborne carbofuran levels is not expected because airborne concentrations are anticipated to reach ambient levels within a few days after the application, and seasonal and ambient air carbofuran exposure estimates are given in Table 9.

EXPOSURE APPRAISAL

Handler Exposure Estimates

PHED

Exposure estimates for handlers were based on surrogate data, due to lack of acceptable, chemical-specific data. Data from PHED were used to estimate handler exposures for the various application methods, with the exception of nursery stock dipping applicators. PHED, though useful, has limitations that prevent the use of distributional statistics on exposure estimates. For example, PHED incorporates exposure data from many studies, each with a different minimum detection level for the analytical method used to detect residues in the sampling media. Moreover, as the detection of dermal exposure to the body regions was not standardized, some studies observed exposure to only selected body parts. Consequently, the subsets derived from the database for dermal exposure may have different numbers of observations for each body part, a fact which complicates interpretation of values taken from PHED. However, use of PHED data provided the best exposure estimates possible.

The mean estimates provided by PHED for groundboom applicators were lower than results of exposure monitoring of applicators and M/L/A reported by Hussain *et al.* (1990). The arithmetic mean total exposure rate reported by Hussain *et al.* (1990) was 574.4 μg AI/lb handled. The six handlers (two applicators and four M/L/As) monitored by Hussain *et al.* (1990) had the following six total exposure estimates: 33.8, 42.6, 123.6, 223.6, 437.2, and 2,585.6 μg AI/lb handled. Note that five of the six handlers monitored by Hussain *et al*. (1990) had exposures below the arithmetic mean (574.4 μg AI/lb), a result that is fairly typical in exposure monitoring data sets. For comparison, the geometric of exposure results is also provided in Table 11. Three of the six handlers monitored by Hussain *et al*. (1990) had exposures below the geometric mean (188.6 μg AI/lb), while three handlers had exposures greater than the geometric mean; again, this result is fairly typical for exposure monitoring data sets.

To calculate PHED-based estimates of M/L/A exposure in Table 11, M/L and applicator exposure estimates were combined based on an assumption that during an 8-hour workday, 2 hours would be spent mixing/loading and 6 hours applying (actual mixing/loading and application times were not reported by Hussain *et al.* (1990), and may have differed from this assumption). PHED-based estimates are shown in Table 11 assuming conditions as in the study, and conditions that conform with California requirements. The exposure estimate that assumed

study conditions was nearly four times as great as the estimate assuming conditions that meet California requirements; however, it was only slightly greater than the geometric mean of exposures reported by Hussain *et al*. (1990).

In Table 5 in the Exposure Assessment section, the PHED mean estimates used in calculating Acute ADD for groundboom mixer/loaders and applicators are 77.8 and 107 µg/lb handled, respectively. If the two lowest results reported by Hussain *et al.* (1990) are for the two applicators, then PHED overestimated the applicator exposure by about three-fold (107 µg AI/lb handled vs. 33.8 and 42.6 µg AI/lb handled). However, insufficient information was provided by Hussain *et al.* (1990) to assign exposure results to handler activities in that study.

Table 11. Comparison of Groundboom Mixer/Loader/Applicator Exposure to Carbofuran Estimated from Surrogate Data by DPR with Chemical-Specific Exposure Monitoring

Exposure estimate	Exposure rate (µg AI/lb handled) [a]	STADD (mg/kg/day) [b]
From PHED, DPR policy, California and label requirements [c]	51.6	0.147
From PHED, according to DPR policy, study conditions [d]	201	0.573
From study, arithmetic mean of exposure data [e]	574.4	1.64
From study, geometric mean of exposure data [e]	188.6	0.539

[a] Total exposure rate, dermal plus inhalation. Estimates based on the Pesticide Handlers Exposure Database (PHED) were calculated by adding together exposure of mixer/loader (M/L) plus applicator, assuming 2 hours M/L and 6 hours application (i.e., ¼ and ¾ daily exposure estimates, respectively).

[b] Short-Term Absorbed Daily Dosage (STADD) estimates assumed a maximum application rate of 10 lbs AI/acre, maximum rate on field-grown ornamentals, and an 8-hour workday. Amount treated was assumed to be 40 acres treated/day (Haskell, 1998). Dermal absorption assumed to be 50% (Donahue, 1996), inhalation absorption assumed to be 100%, and body weight assumed to be 70 kg (Thongsinthusak *et al*., 1993a).

[c] Exposure rate estimates incorporated assumptions used in the Department of Pesticide Regulation (DPR) Exposure Assessment. For M/L, use of a closed system was assumed, and applicators were assumed to have open-cab tractors. Workers were assumed to wear long-sleeved shirt and long pants, gloves and respirator.

[d] PHED-based estimates prepared according to assumptions listed above, except for clothing and protective equipment open-pour mixing/loading. Applicators assumed to wear respirator and coveralls over long-sleeved shirt and long pants, but not wearing gloves; mixing/loading was open-pour and M/L assumed to wear coveralls over long-sleeved shirt and long pants, and chemical-resistant gloves and respirator.

[e] Hussain *et al*. (1990), based on passive dosimetry (patches beneath work clothing, hand rinses, personal air samplers). Total exposure estimates: 33.8, 42.6, 123.6, 223.6, 437.2, and 2,585.6 µg AI/lb handled. Four individuals were mixer/loader/applicators and two were applicators; however, the workers doing only application were not identified.

U.S. EPA also used PHED to estimate handler exposure (Weiss, 2005); however, U.S. EPA approaches PHED data somewhat differently than DPR. First, as explained in U.S. EPA's policy for use of PHED data (U.S. EPA, 1999): "Once the data for a given exposure scenario have been selected, the data are normalized (i.e., divided by) by the amount of pesticide handled resulting in standard unit exposures (milligrams of exposure per pound of active ingredient handled). Following normalization, the data are statistically summarized. The distribution of exposure values for each body part (i.e., chest upper arm) is categorized as normal, lognormal, or "other" (i.e., neither normal nor lognormal). A central tendency value is then selected from the

distribution of the exposure values for each body part. These values are the arithmetic mean for normal distributions, the geometric mean for lognormal distributions, and the median for all "other" distributions. Once selected, the central tendency values for each body part are composited into a "best fit" exposure value representing the entire body." In other words, U.S. EPA uses various central tendency estimates (often the geometric mean or median, as PHED data rarely follow a normal distribution), while DPR believes the arithmetic mean is the appropriate statistic regardless of the sample distribution (Powell, 2003). Second, for acute exposure estimates DPR uses a 95th percentile upper bound estimate, while U.S. EPA uses a central tendency estimate for all exposure durations (U.S. EPA, 1998b). Third, as explained in the Exposure Assessment section, DPR calculates upper 90% confidence limits for both upper bound and mean exposures, while U.S. EPA does not (note: DPR's policies for handling PHED data have been reviewed informally and are currently under formal review by a statistician at the University of California).

The acute exposure estimates from DPR (Table 5) and short-term exposure estimates for U.S. EPA (Weiss, 2005) are summarized in Table 12 for several scenarios. U.S. EPA did not provide separate long-term handler exposure estimates.

Table 12. Comparison of Estimated Short-Term Exposures to Carbofuran for Selected Handler Scenarios by DPR and U.S. EPA [a]

Scenario	DPR Exposure Rate (µg/lb AI handled)		DPR Exposure (mg/kg/day)	U.S. EPA Exposure Rate (µg/lb AI)		U.S. EPA Exposure (mg/kg/day)
	Dermal	Inhalation		Dermal	Inhalation	
Aerial M/L [b]	77.3	0.512	0.560	8.6	0.083	0.0102
Groundboom M/L [c]	77.3	0.512	0.224	8.6	0.083	0.00337
Aerial App [d]	891	2.86	6.40	5.0	0.068	0.0063
Groundboom App [e]	102	4.72	0.318	14	0.15	0.00566
LPHW M/L/A [f]	9,480	137	0.002	430	6	0.0000113

[a] Department of Pesticide Regulation (DPR) estimates reported in Table 5 of this document. U.S. Environmental Protection Agency (U.S. EPA) estimates reported in Appendix A of Weiss (2005) for conditions identical to those assumed in DPR estimates, unless otherwise stated. U.S. EPA did not provide separate long-term handler exposure estimates.

[b] Mixer/loader (M/L) using a closed system in support of aerial applications to alfalfa.

[c] M/L using a closed system in support of groundboom applications to ornamentals.

[d] Aerial applicator, alfalfa. DPR assumed open cockpit, while U.S. EPA provided estimates only for a closed cockpit.

[e] Groundboom applicator, ornamentals. Estimates assumed open cockpit.

[f] Mixerl/loader/applicator (M/L/A) applying carbofuran as a soil drench using a low pressure handwand (LPHW). Open-pour mixing/loading assumed.

Acute handler exposure estimates shown in Table 12 range from 0.002 – 6.40 mg/kg/day for DPR and from 0.0000113 - 0.0102 mg/kg/day for U.S. EPA. DPR exposure estimates shown in Table 12 are from 55 to 176 times larger than exposure estimates from U.S. EPA when conditions are assumed to be the same. There are several factors contributing to these differences, including dermal absorption (50% assumed by DPR versus 6% assumed by U.S. EPA, an eight-fold difference) and the use of an upper-bound estimates by DPR while U.S. EPA used central tendency estimates for exposure estimates reported by Weiss (2005).

The aerial applicator estimate for DPR is 888 times as great as the estimate for U.S. EPA. These values differ substantially, not only for the reasons explained above, but also because U.S. EPA assumes use of closed cockpits in all aerial exposure estimates; if planes with open cockpits can be used, U.S. EPA policy is to require an additional 10-fold safety factor in the risk calculation (U.S. EPA, 1998c). If DPR were to assume a closed cockpit, the total exposure rate would be 46.7 µg AI/lb handled, and the total exposure would be 0.667 mg/kg/day; this estimate is 106 times the estimate provided by U.S. EPA for this scenario. This comparison shows the extent to which assumption of an open cockpit affects DPR exposure estimates (nearly a ten-fold difference). The most recent information available about equipment used by aerial applicators shows that open cockpits are relatively rare, but may still be used (NAAA, 2004).

Dip/Slurry Applicators

Dermal exposure was estimated based on the RAGS-E model, which estimates skin permeability (K_p) to organic chemicals in aqueous solution (U.S. EPA, 2004a). There are many assumptions and uncertainties with this and other models that use K_p, many of which were discussed in U.S. EPA (2004a). Additional sources of uncertainty in models based on large and diverse data sets were discussed by Poda *et al.* (2001).

For carbofuran, an AI-specific K_p value was estimated based on an equation derived from a data set of about 200 diverse organic compounds in aqueous solutions. The calculated K_p for carbofuran may be either over- or underestimated; there are not enough data available to be sure. The diversity of chemicals in the data set on which the K_p equation is based decreases confidence in estimates based on the equation (Poda *et al*., 2001). As carbofuran is well within the range of MW and Log K_{ow} in which K_p estimates are considered valid, based on Equations 3.9 and 3.10 in U.S. EPA (2004a), use of this equation is expected to result in a skin permeability estimate that correlates reasonably well with available data.

However, use of K_p with solutions of formulated pesticide products may result in exposure being underestimated, as the formulations contain additives (e.g., solvents, emulsifiers, and surfactants) to increase water solubility of AIs. Numerous studies have shown enhanced dermal penetration of chemicals, including pesticides, when mixed with such additives, as they can alter the barrier properties of the skin (Baynes and Riviere, 1998; Nielsen *et al.*, 2000; Brand and Mueller, 2002; Williams and Barry, 2004). Alternately, flux could be decreased by additives in the formulation, as has been shown in some cases (Nielsen and Andersen, 2001; Riviere et al., 2001), perhaps by altering how the chemical partitions between solution and skin (van der Merwe and Riviere, 2005). Exposure estimates could be improved if skin permeability measures were made using solutions of formulated products in concentrations that are pertinent to typical product use. Because carbofuran is used in a clay slurry rather than an aqueous solution, some of the AI may be anticipated to partition to clay particles and not be available for exposure, resulting in lower exposures than estimated (U.S. EPA, 2004a).

Another uncertainty from the use of K_p in estimating dermal exposure is that skin permeabilities are almost always estimated from *in vitro* rather than *in vivo* data. In an *in vitro* skin permeability test, a section of skin is clamped between two cells, called the "donor cell" and the "receptor cell." The donor solution (in the donor cell) contains the compound of interest; as the

compound passes through the skin section it appears in the receptor solution, which is sampled periodically. A known concentration of compound is initially in the donor solution; the rate at which the compound concentration in the receptor solution increases is related to the permeability. The use of *in vitro* data introduces uncertainties because relationships between *in vivo* and *in vitro* test results have not been reliably established for many classes of compounds, and have been shown to vary for compounds that have been tested (Wester and Maibach, 2000; Zendzian and Dellarco, 2003). Nevertheless, these models rely on the assumption that *in vitro* dermal penetration is approximately the same as *in vivo*.

Other assumptions common to these models are that the chemical concentration of water in contact with skin (C_w) is constant; and that absorbed dose is a function of solution concentration, skin permeability, and amount of exposed skin surface. These are reasonable assumptions, but have not been tested for solutions of pesticide products.

Additional uncertainty exists in the RAGS-E model, in the parameters τ and B. Calculations for these parameters rely on many assumptions and limited, surrogate data. The RAGS-E model has undergone some validation, but not with carbofuran in formulated products (additives in the pesticide formulations may affect τ and B, as well as K_p).

Inhalation exposure for workers dipping pine seedling roots was estimated based on SWIMODEL equations. SWIMODEL estimates pesticides concentrations in air based on conditions that may not be met in the root dipping scenario. In fact, substantial deviations occur from the assumptions on which the model is based. SWIMODEL relies on water-air partitioning to determine concentration of a chemical in air, using the Henry's Law constant for the chemical. However, Henry's Law constant applies to dilute, single-chemical aqueous solutions only. Staudinger and Roberts (2001) give 10,000 mg/L as an upper boundary defining a "dilute" solution under Henry's Law. This concentration is exceeded in the carbofuran slurry (12,000 mg/L). Furthermore, other chemicals present in the pesticide formulation (as well as the clay mixed into the slurry) can interact with the pesticide molecules, potentially affecting the partitioning of the AI into air (Staudinger and Roberts, 2001). Because the calculated concentration of AI in air was higher than anticipated at saturation, the estimated saturation concentration was used instead in inhalation exposure calculations; in other words, it was assumed that the AI is present at air-saturating concentrations. Because of this assumption, inhalation exposure is anticipated to be overestimated. In spite of this, the inhalation exposure estimate was substantially below the dermal exposure estimate, and the inhalation contribution to total exposure is considered negligible in this scenario.

In the absence of exposure monitoring or surrogate data, the results obtained from these models are considered the best estimate of dermal and inhalation exposure based on available information.

Other Defaults

Most exposure estimates reported in this EAD assumed a median body weight of 70 kg (Thongsinthusak, 1998). Bystander estimates assumed a mean body weight of 71.8 kg, for consistency with the mean inhalation rates that are used in the calculation (Andrews and Patterson, 2001). Both of these might be underestimates, based on trends in body weights in

U.S. populations in general, in which mean weights of adults over age 21 increased between the two most recent intervals (Ogden *et al*., 2004). As exposure estimates are divided by assumed body weight, underestimates in body weight might result in overestimated exposure.

PUR data were used to estimate likely numbers of days workers were exposed, based on the distribution of applications in high-use California counties. These high-use periods describe a recent work history of the handler population, and they probably overestimate the workdays for any single individual. They provide the best available data for long-term exposure estimates, however.

PUR data could perhaps be used more extensively in estimating long-term exposure, by providing central tendency estimates of lbs AI/acre and acres treated; DPR is currently considering such a change. In this EAD, for both short-term and long-term exposure estimates, maximum allowed application rates were used, from product labels. The numbers of acres treated per day were based on defaults recommended by U.S. EPA (2001), with the exception of groundboom applications, which used an estimate provided by a county Deputy Agricultural Commissioner. These estimates are expected to be conservative but realistic; however, insufficient data exist to evaluate their accuracy.

Reentry Worker Exposure Estimates

Acceptable monitoring data were lacking for reentry worker exposures. Exposure estimates for reentry workers were based on chemical-specific, crop-specific DFR values. Two scenarios, scouting cotton and scouting alfalfa, are representative scenarios that cover activities in other crops. Residues may dissipate at different rates on different crops, due to factors such as leaf topography and physical and chemical properties of leaf surfaces, and exposures of workers in other crops might therefore vary from estimates.

Extent of foliage contact, unlike DFR, is not chemical specific, and TC values for various crop activities are readily available, based on studies using other chemicals. Where crop-specific TC were not available, general defaults were used. These defaults were likely to be health-protective (U.S. EPA, 2000).

Additionally, information is lacking about exposures resulting from some activities, such as weeding and roguing (removal of diseased crop plants) in cotton, and how these exposures might compare with those of scouts. And unlike most other reentry workers, cotton harvesters are working in plants which have been intentionally defoliated; DFR residues therefore cannot be used to estimate harvester exposures. The best available exposure estimate for weeders, roguers and harvesters in cotton is considered to be the estimate provided for cotton scouts. However, no data are available which would allow comparison of exposures between cotton scouts and those of other reentry workers in cotton.

Unlike handler exposure estimates, reentry exposures estimated by DPR and U.S. EPA did not differ substantially. For example, the exposure estimate for scouting potatoes in Table 7 of the Exposure Assessment section was slightly less than 9-fold greater than the estimate for that scenario in Appendix B of Weiss (2005). Most of that difference can be attributed to the eight-

fold difference in dermal absorption estimates (50% assumed by DPR versus 6% assumed by U.S. EPA). There were slight differences in DFR estimates.

In general, foliar residues are assumed to result from foliar applications, and this assumption was followed in worker exposures estimated in this document. That is, the only exposure scenarios considered to be potentially significant involved reentry following foliar, rather than soil applications. For example, reentry activities in grapes were considered to result in insignificant exposures, as only soil applications are allowed in grapes. However, carbofuran has been shown to be readily translocated to leaves in some plants following applications to soil (Arunachalam and Lakshmanan, 1982; Buyanovsky *et al*., 1995). Whether translocated carbofuran might be available as dislodgeable residues has apparently not been investigated. Even if residues were available for transfer to reentry workers, however, they are not likely to result in significant exposures.

Ambient Air and Bystander Exposure Estimates

Public exposures to airborne carbofuran were estimated based on concentrations of carbofuran in air and assumptions about uptake of carbofuran from the air. No biomonitoring or other exposure monitoring data were available. Exposure estimates were provided for adults for consistency with other scenarios, and for infants, as likely worst-case because infants have the greatest inhalation rate per body weight.

Ambient air exposure estimates were provided for five sites in Imperial County and for downtown Sacramento. Exposure estimates in Sacramento were approximately an order of magnitude lower than in Imperial County. Even in Imperial County, there were a number of samples in which carbofuran was not detected. Although ambient air monitoring sites were selected based on anticipated nearby carbofuran use, applications of carbofuran were not confirmed. It is possible that no applications occurred near the sites where carbofuran was not detected. The carbofuran concentrations used to estimate ambient air exposures are based on limited monitoring data and must be considered as having some degree of uncertainty. The representativeness of the sites monitored by ARB (1995) and Majewski and Baston (2002) is unknown. ARB (1995) monitored each site 4 days per week for a relatively short (4-week) period. Weekend days were not monitored. It is unknown whether weekdays and weekends differ systematically in numbers of carbofuran applications.

ARB (1995) reported results for samples above the LOD, rather than the LOQ (in fact, no LOQ was reported). If the LOQ were calculated as the usual 3 x LOD, then ½ LOQ would be substituted for all results below the LOQ. In this EAD, however, DPR followed the same approach as ARB (1995), substituting ½ LOD for results below the LOD; this was done to prevent exposures from being grossly overestimated. DPR believes this is the appropriate approach for these data, although it could result in some exposures being slightly underestimated. Nevertheless, this approach results in a higher exposure estimate for the site with the highest carbofuran concentrations, Site PM. As shown in Table 1-1 in Appendix 1, the 95th percentile concentration at Site PM would be decreased to 0.102 μg/m^3 if results were reported based on an LOQ calculated as 3 x LOD (in contrast, the 95th percentile concentration used to estimate acute exposure at this site is 0.118 μg/m^3; see Table 9). Acute ADD for infants

is 0.000070 mg/kg/day (Table 9); a concentration of 0.102 μg/m^3 would result in the Acute ADD for infants being 0.000060 mg/kg/day.

For bystander exposure estimates, data from the west monitoring station, 20 m from the application site, were used as a reasonable worst-case estimate for carbofuran concentration in air for Acute ADD estimates. For this reason, the mean carbofuran concentration at this site was used rather than the 95th-percentile upper bound estimate. However, this mean concentration was based on monitoring during an application to an alfalfa field where the application rate (0.3 lb AI/acre) was below the maximum allowed on alfalfa (1.0 lb AI/acre). Because of this, the mean concentration was adjusted, using an assumption that concentration would increase proportionately with application rate. This is a reasonable, though untested, assumption. In addition to application rate, bystander exposure may also be underestimated if other factors such as application method result in higher carbofuran concentrations near the application site than concentrations found by ARB (1994). For example, studies done with other pesticides comparing aerial and ground applications have found that drift is greater with aerial than ground application methods (Frost and Ware, 1970; MacCollom *et al.*, 1986). Finally, seasonal or annual exposure to application site airborne carbofuran levels is not expected because airborne concentrations are anticipated to reach ambient levels within a few days after the application.

REFERENCES

Air Resources Board (ARB). 1994. Ambient Air Monitoring for Carbofuran in Imperial County During Spring 1993, After an Application to an Alfalfa Field. Test Report No. C93-013A, Report Date March 24, 1994; Sacramento, CA: Toxic Air Contaminant Identification Branch, Air Resources Board, California Environmental Protection Agency. http://www.cdpr.ca.gov/docs/empm/pubs/tac/tacpdfs/carapp.pdf

Air Resources Board (ARB). 1995. Ambient Air Monitoring for Carbofuran in Imperial County During February and March 1995. Test Report No. C93-013, Report Date November 9, 1995; Sacramento, CA: Engineering and Laboratory Branch, Monitoring and Laboratory Division, Air Resources Board, California Environmental Protection Agency. http://www.cdpr.ca.gov/docs/empm/pubs/tac/tacpdfs/Carbofuranmonitrep.pdf

Alvarez, M. 1987. Carbofuran: Evaluation of Physical Properties – Part A. Unpublished study submitted by FMC Corporation, Philadelphia, PA. Laboratory Study No. 237AF8766. DPR Data Volume No. 254-122, Record No. 60023.

Alvarez, M. 1989. Analytical Support of Carbofuran Vapor Pressure Determination. Unpublished study submitted by FMC Corporation, Philadelphia, PA. Report No. P-2165, Laboratory Study No. 078AF88121. DPR Document No. 254-133, Record No. 72981.

Andrews, C.M. 2000. Worker Health and Safety Branch Policy on the Statistical Analysis for Dislodgeable Foliar Residue Data. Memo No. HSM-00011. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Andrews, C. and Patterson, G. 2000. Interim Guidance for Selecting Default Inhalation Rates for Children and Adults. HSM-00010. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Aprea, C., Sciarra, G., Sartorelli, P., Desideri, E., Amati, R. and Sartorelli, E. 1994. Biological monitoring of exposure to organophosphorus insecticides by assay of urinary alkylphosphates: influence of protective measures during manual operations with treated plants. International Archives of Occupational and Environmental Health 66:333-338.

Archer, T.E. 1976. Effects of light on the fate of carbofuran during the drying of alfalfa. Journal of Agricultural and Food Chemistry 24:1057-1062.

Archer, T.E., Stokes, J.D. and Bringhurst, R.S. 1977. Fate of carbofuran and its metabolites on strawberries in the environment. Journal of Agricultural and Food Chemistry 25:536-541.

Arunachalam, K. and Lakshmanan, M. 1982. Translocation, accumulation and persistence of carbofuran in paddy, ground nut, and cotton. Bulletin of Environmental Contamination and Toxicology 28:230-238.

Barros, A. and Dow, K. 1998. Determination of Foliar Dislodgeable Residues of Carbofuran and 3-Hydroxy Carbofuran from Potato Plants. Unpublished study submitted by FMC Corporation, Princeton, NJ. Report No. P-3327, Study No. 078WEX97R2. DPR Data Volume No. 254-187, Record No. 218300.

Baynes, R.E., Halling, K.B. and Riviere, J.E. 1997. The influence of diethyl-m-toluamide (DEET) on the percutaneous absorption of permethrin and carbaryl. Toxicology and Applied Pharmacology 144:332-339.

Baynes, R.E. and Riviere, J.E. 1998. Influence of inert ingredients in pesticide formulations on dermal absorption of carbaryl. American Journal of Veterinary Research 59:168-175.

Beauvais, S.L. 2004. Nursery Stock Root Dips: Applicator Exposure Estimates. Memo No. HSM-04029, dated December 29. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Bennett, K.P., Singhasemanon, N., Miller, N. and Gallavan, R. 1998. Rice Pesticides in the Sacramento Valley, 1995. Report No. EH 98-03. Sacramento, CA: California Department of Pesticide Regulation, Environmental Monitoring and Pest Management Branch. http://www.cdpr.ca.gov/docs/empm/pubs/ehapreps/eh983rep.pdf.

Brand, R.M. and Mueller, C. 2002. Transdermal penetration of atrazine, alachlor, and trifluralin: effect of formulation. Toxicological Sciences 68:18-23.

Brandau, E.G. 1975. Determination of Partition Coefficients for Carbofuran, FMC 33297, FMC 25213, Certain Potential Metabolites and Two Benchmark Chemicals. Unpublished study submitted by FMC Corporation, Philadelphia, PA. Report No. M-3779, Project No. P3. DPR Data Volume No. 254-120, Record No. 58689.

Bunge, A.L. and Cleek, R.L. 1995. A new method for estimating dermal absorption from chemical exposure: 2. Effect of molecular weight and octanol-water partitioning. Pharmaceutical Research 12:88-95.

Bunge, A.L., Cleek, R.L. and Vecchia, B.E. 1995. A new method for estimating dermal absorption from chemical exposure. 3. Compared with steady-state methods for prediction and data analysis. Pharmaceutical Research 12:972-982.

Buyanovsky, G.A., Kremer, R.J., Gajda, A.M. and Kazemi, H.V. 1995. Effect of corn plants and rhizosphere populations on pesticide degradation. Bulletin of Environmental Contamination and Toxicology 55:689-969.

CAST. 2002. Urban and Agricultural Communities: Opportunities for Common Ground. Task Force Report No. 138. Ames, IA: Council for Agricultural Science and Technology. http://www.cast-science.org/pubs/urbanagricultural.pdf

Curtis, C. 2002. Carbofuran Dislodgeable Foliar Residue Data from Cotton Fields Sampled in Fresno, Madera, Colusa and Yolo Counties in summer, 2001. Memo No. HSM-01019. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Das, R. Harrison, R, Sutton, P, Souter, A., Beckman, J., Santamaria, B., Steinmaus, C., Sablan, O., Edmiston, S., Mehler, L., Hernandez, B. and Schneider, F. 1999. Farm Worker Illness Following Exposure to Carbofuran and Other Pesticides -- Fresno County, California, 1998. Morbidity and Mortality Weekly Reports 48:113-116.

Donahue, J. 1996. Revised Policy on Dermal Absorption Default for Pesticides. Memo No. HSM-96005, dated July 5. Sacramento, CA: Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency.

Dong, M.H. 1990. Memorandum: Dermal Transfer Factor for Cotton Scouts. Memo No. HSM-90001, dated June 8. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Dorough, H.W. 1968. Metabolism of furadan (NIA-10242) in rats and houseflies. Journal of Agriculture and Food Chemistry 16:319-325.

DPR. 2000. Pesticide Use Report, Annual 1999 Indexed by Chemical. Sacramento, CA: Department of Pesticide Regulation, California Environmental Protection Agency. http://www.cdpr.ca.gov/docs/pur/pur99rep/chmrpt99.pdf

DPR. 2001. Pesticide Use Report, Annual 2000 Indexed by Chemical. Sacramento, CA: Department of Pesticide Regulation, California Environmental Protection Agency. http://www.cdpr.ca.gov/docs/pur/pur00rep/chmrpt00.pdf

DPR. 2002. Pesticide Use Report, Annual 2001 Indexed by Chemical. Sacramento, CA: Department of Pesticide Regulation, California Environmental Protection Agency. http://www.cdpr.ca.gov/docs/pur/pur01rep/chmrpt01.pdf

DPR. 2003. Pesticide Use Report, Annual 2002 Indexed by Chemical. Sacramento, CA: Department of Pesticide Regulation, California Environmental Protection Agency. http://www.cdpr.ca.gov/docs/pur/pur02rep/chmrpt02.pdf

DPR. 2004. Process for Human Health Risk Assessment Prioritization and Initiation. Sacramento, CA: Department of Pesticide Regulation, California Environmental Protection Agency. http://www.cdpr.ca.gov/docs/risk/raprocess.pdf

DPR. 2005a. Pesticide Use Report, Annual 2003 Indexed by Chemical. Sacramento, CA: Department of Pesticide Regulation, California Environmental Protection Agency. http://www.cdpr.ca.gov/docs/pur/pur03rep/chmrpt03.pdf

DPR. 2005b. California Pesticide Information Portal (CalPIP), Pesticide Use Report database. Website accessed for database queries on several dates. Sacramento, CA: Department of Pesticide Regulation, California Environmental Protection Agency. http://calpip.cdpr.ca.gov/cfdocs/calpip/prod/main.cfm

DPR. 2005c. Summary of Results from the California Pesticide Illness Surveillance Program, 2003. Report No. HS-1857. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch. http://www.cdpr.ca.gov/docs/whs/pdf/hs1857.pdf

Draper, W.M., Gobson, R.D. and Street, J.C. 1981. Drift from and transport subsequent to a commercial, aerial application of carbofuran: an estimation of potential human exposure. Bulletin of Environmental and Contamination Toxicology 26:537-543.

Drew, D., Liccione, J., Stanton, S. and Weiss, S. 2005. Carbofuran. HED Revised Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) Document (Phase 2). Chemical Number 090601. DP Barcode: D319934. Washington, DC: Health Effects Division, Office of Pesticide Programs, United States Environmental Protection Agency, Washington, DC.

Durham W.F. and Wolfe, H.R. 1962. Measurement of the exposure of workers to pesticides. Bulletin of the WHO 26:75-91.

Edmiston, S., Schneider, F., Hernandez, B., Fredrickson, A.S. and Quan, V. 1999. Exposure and Illness Following Early Reentry into a Carbofuran-Treated Field. Report No. HS-1779. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch. http://www.cdpr.ca.gov/docs/whs/pdf/hs1779.pdf.

Evert, S. 2002. Environmental Fate of Carbofuran. Sacramento, California: Environmental Monitoring Branch, Department of Pesticide Regulation. http://www.cdpr.ca.gov/docs/empm/pubs/fatememo/carbofuran.pdf

Fartasch, M. 1997. Ultrastructure of the epidermal barrier after irritation. Microscopy Research and Technique 37:193-199.

Ferguson, P.W., Jewell, S.A., Krieger, R.I. and Raabe, O.G. 1982. Carbofuran disposition in the rat after aerosol inhalation. Environmental Toxicology and Chemistry 1:245-258.

Ferguson, P.W., Day, M.S., Jewell, S.A. and Krieger, R.I. 1984. Carbofuran metabolism and toxicity in the rat. Fundamental and Applied Toxicology 4:14-21.

Ferraro, C.F. 1989. Henry's Law Constant – Revised Calculated Estimate of Water Volatility for Carbofuran. Unpublished study submitted by FMC Corporation, Philadelphia, PA. Report No. P-2164, Laboratory Study No. 078E6089E1. DPR Data Volume No. 254-133, Record No. 72980.

Franklin, C.A., Somers, D.A. and Chu, I. 1989. Use of percutaneous absorption data in risk assessment. Journal of the American College of Toxicology 8:815-827.

Frost, K.R. and Ware, G.W. 1970. Pesticide drift from aerial and ground applications. Agricultural Engineering 51:460-467.

Ganapathy, C., Nordmark, C., Bennett, K., Bradley, A., Feng, H., Hernandez, J. and White, J. 1997. Temporal Distribution of Insecticide Residues in Four California rivers. Report No. EH 97-06. Sacramento, CA: California Department of Pesticide Regulation, Environmental Monitoring and Pest Management Branch. http://www.cdpr.ca.gov/docs/empm/pubs/ehapreps/eh976rep.pdf.

Gupta, R.C. 1994. Carbofuran toxicity. Journal of Toxicology and Environmental Health 43:383-418.

Hahn, G.J., and Meeker, W.Q. 1991. Statistical Intervals: A Guide for Practitioners. New York, John Wiley & Sons, Inc.

Haskell, D.E. 1998. Canada-United States Trade Agreement (CUSTA) Working Group, Final Draft of Position Paper for Issue Eight: Typical Workdays for Various Crops. Memo No. HSM-98001, dated June 19. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Hernandez, B.Z. 2001. Carbofuran Results for Alfalfa DFR Collected in Imperial County in March 2001. Memo No. HSM-01011, dated August 22. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Hernandez, B.Z., Spencer, J., Schneider, F., Welsh, A and Fredrickson, S. 2002. A Summary of Dislodgeable Foliar Pesticide Residues at Expiration of the Restricted Entry Interval. Report No. HS-1784. Sacramento, CA: Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency. http://www.cdpr.ca.gov/docs/whs/pdf/hs1784.pdf

Hussain, M., Yoshida, K., Atiemo, M. and Johnston, D. 1990. Occupational exposure of grain farmers to carbofuran. Archives of Environmental Contamination and Toxicology 19:197-204.

Iwata, Y., Knaak, J.B., Spear, R.C. and Foster, R.J. 1977. Worker reentry into pesticide-treated crops. I. Procedure for the determination of dislodgeable pesticide residues on foliage. Bulletin of Environmental Contamination and Toxicology 18:649-655.

Iwata, Y., Knaak, J.B., Dusch, M.E., O'Neal, J.R. and Pappas, J.L. 1983. Worker reentry research for carbosulfan applied to California citrus trees. Journal of Agricultural and Food Chemistry 31:1131-1136.

Jowa, L. 2000. Carbofuran in Drinking Water California Public Health Goal. Sacramento, CA: California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. http://www.oehha.org/water/phg/pdf/Carbofur.pdf.

Jones, D., Singhasemanon, N., Tran, D., Hsu, J., Hernandez, J. and Feng, H. 2000. Surface Water Monitoring for Pesticides in the Hupa and Karuk Territories. Report No. EH 00-12. Sacramento, CA: California Department of Pesticide Regulation, Environmental Monitoring and Pest Management Branch. http://www.cdpr.ca.gov/docs/empm/pubs/ehapreps/eh0012.pdf.

Kollman, W.S. 1995. Summary of Assembly Bill 1807/3219 Pesticide Air Monitoring Results. Report No. EH 95-10. Sacramento, CA: California Department of Pesticide Regulation, Environmental Monitoring and Pest Management Branch. http://www.cdpr.ca.gov/docs/empm/pubs/ehapreps/eh9510rep.pdf.

Kross, B.C., Vergara, A. and Raue, L.E. 1992. Toxicity assessment of atrazine, alachlor, and carbofuran and their respective environmental metabolites using Microtox. Journal of Toxicology and Environmental Health 37:149-159.

Lavy, T.L. and Mattice, J.L. 1985. Monitoring field applicator exposure to pesticides. In: Honeycutt, R.C., Zweig, G. and Ragsdale, N.N., editors. Dermal Exposure Related To Pesticide Use: Discussion of Risk Assessment. ACS Symposium Series No. 273, American Chemical Society, Washington, DC, pages 165-173.

Layton, D.W. 1993. Metabolically consistent breathing rates for use in dose assessments. Health Physics 64:23-36.

Leppert, B.C. 1986. Determination of Dislodgeable Carbofuran and 3-Hydroxy Carbofuran Residues in a Field Corn Study. Unpublished study submitted by FMC Corporation, Philadelphia, PA. DPR Data Volume No. 254-143, Record No. 97037.

Liu, D.D.W. 1987. Carbofuran Crop Reentry Trial (Residue Study No. 078WEXR07): Dislodgeable Residues Analysis of Carbofuran, 3-Hydroxy Carbofuran, and 3-Keto Carbofuran. Unpublished study submitted by FMC Corporation, Philadelphia, PA. DPR Data Volume No. 254-143, Record No. 97036.

Liu, K.-Y. and Kim, J.-H. 2003. In vitro dermal penetration study of carbofuran, carbosulfan, and furathiocarb. Archives of Toxicology 77:255-260.

MacCollom, G.B., Currier, W.W. and Baumann, G.L. 1986. Drift comparisons between aerial and ground orchard application. Journal of Economic Entomology 79:459-464.

Majewski, M.S. and Baston, D.S. 2002. Atmospheric Transport of Pesticides in the Sacramento, California, Metropolitan Area, 1996 – 1997. Water Resources Investigations Report 02-4100, National Water Quality Assessment Program.

Sacramento, CA: U.S. Geological Survey. http://www.cdpr.ca.gov/docs/sw/contracts/usgs024100.pdf

Markle, J.C. 1982. Determination of Dislodgeable Residues of Carbosulfan and Carbofuran on Orange Leaves. Unpublished study submitted by FMC Corporation, Philadelphia, PA. DPR Data Volume No. 254-143, record no. 97035.

Marshall, T.C. and Dorough, H.W. 1979. Biliary excretion of carbamate insecticides in the rat. Pesticide Biochemistry and Physiology 11:56-63.

Mayberry, K.S. 2000. Sample Cost to Establish and Produce Potatoes: Imperial County – 2000. University of California Division of Agriculture and Natural Resources, Cooperative Extension. http://coststudies.ucdavis.edu/uploads/cost_return_articles/potatoes.pdf

McCarthy, J.F. 1975. The chemistry, pharmacology, toxicology, metabolism and environmental impact of carbofuran. In: Furadan. FMC Corporation, Middleport, NY, pages 7-23.

Metcalf, R.L., Fukuto, T.R., Collins, C., Borck, K., Abd El-Aziz, S., Munoz, R. and Cassil, C.C. 1968. Metabolism of 2,2-dimethyl-2,3-dihydrobenzofuranyl-7 N-methylcarbamate (Furadan) in plants, insects, and mammals. Journal of Agricultural Food Chemistry 16:300-311.

Mohapatra, S. and Awasthi, M.D. 1997. Enhancement of carbofuran degradation by soil enrichment cultures, bacterial culture and by synergistic interaction among bacterial cultures. Pesticide Science 49:164-168.

Moody, R.P., Wester, R.C., Melendres, J.L. and Maibach, H.I. 1992. Dermal absorption of the phenoxy herbicide 2,4-D dimethylamine in humans: effect of DEET and anatomic site. Journal of Toxicology and Environmental Health 136:241-250.

NAAA. 2004. Pesticide Use Survey Report for Agricultural Aviation: A Study Conducted by the National Agricultural Aviation Association (NAAA). Unpublished report dated May 2004.

Newhart, K. and Bennett, K. 1999. Information on Rice Pesticides Submitted to the California Regional Water Quality Control Board Central Valley Region. Sacramento, CA: California Department of Pesticide Regulation, Environmental Monitoring and Pest Management Branch. http://www.cdpr.ca.gov/docs/sw/1999.pdf.

Nicosia, S., Carr, N., Gonzales, D.A. and Orr, M.K. 1990. Off-Field Movement and Dissipation of Soil-Incorporated Carbofuran from Three Commercial Rice Fields and Potential Discharge in Agricultural Runoff Water. Report No. EH 90-04. Sacramento, CA: California Department of Pesticide Regulation, Environmental Monitoring and Pest Management Branch. http://www.cdpr.ca.gov/docs/empm/pubs/ehapreps/eh9004.pdf

Nielsen, G.D., Nielsen, J.B., Andersen, K.E. and Grandjean, P. 2000. Effects of industrial detergents on the barrier function of human skin. International Journal of Occupational and Environmental Health 6:138–142.

Nielsen, J.B. and Andersen, H.R. 2001. Dermal *in vitro* penetration of methiocarb, paclobutrazol, and pirimicarb: effect of nonylphenolethoxylate and protective gloves. Environmental Health Perspectives 109:129-132.

Nigg, H.N., Stamper, J.H. and Knaak, J.B. 1984. Leaf, fruit, and soil surface residues of carbosulfan and its metabolites in Florida citrus groves. Journal of Agricultural and Food Chemistry 32:80-85.

NIOSH. 1987. Respirator Decision Logic. Washington, D.C.: National Institute for Occupational Safety and Health, U.S. Department of Health and Human Services.

Nordmark, C.E., Bennett, K.P., Feng, H., Hernandez, J. and Lee, P. 1998. Occurrence of Aquatic Toxicity and Dormant-Spray Pesticide Detections in the Sacramento River Watershed, Winter 1996-97. Report No. EH 98-01. Sacramento, CA: California Department of Pesticide Regulation, Environmental Monitoring and Pest Management Branch. http://www.cdpr.ca.gov/docs/empm/pubs/ehapreps/eh9801.pdf.

OEHHA. 2000. Air Toxics Hot Spots Program Part IV: Technical support document. Exposure assessment and stochastic analysis. Scientific Review Panel Draft. Sacramento, CA:. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. http://www.oehha.ca.gov/air/hot_spots/finalStoc.html#download

Ogden, C.L., Fryar, C.D., Carroll, M.D. and Flegal, K.M. 2004. Mean Body Weight, Height, and Body Mass Index, United States 1960–2002. Advance Data from Vital and Health Statistics, Report No. 347. Hyattsville, MD: National Center for Health Statistics, Centers for Disease Control and Prevention. http://www.cdc.gov/nchs/data/ad/ad347.pdf

PHED. 1995. The Pesticide Handlers Exposure Database, Version 1.1. Prepared for the PHED Task Force representing Health and Welfare Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association; prepared by Versar, Inc., 6850 Versar Center, Springfield, VA 22151.

Poda, G.I., Landsittel, D.P., Brumbaugh, K., Sharp, D.S., Frasch, H.F. and Demchuk, E. 2001. Random sampling or 'random' model in skin flux measurements? [Commentary on "Investigation of the mechanism of flux across human skin in vitro by quantitative structure-permeability relationships"]. European Journal of Pharmaceutical Sciences 14:197-200.

Powell, S. 2002. Approximating Confidence Limits for Upper Bound and Mean Exposure Estimates from the Pesticide Handlers Exposure Database (PHED V1.1). HSM-02037, dated September 27. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Powell, S. 2003. Why Worker Health And Safety Branch Uses Arithmetic Means in Exposure Assessment. HSM-03022, dated September 22. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Riviere, J.E., Qiao, G., Baynes, R.E., Brooks, J.D. and Mumtaz, M. 2001. Mixture component effects on the in vitro dermal absorption of pentachlorophenol. Archives of Toxicology 75:329-334.

Ross, J.H., Driver, J.H., Cochran, R.C., Thongsinthusak, T. and Krieger, R.I. 2001. Could pesticide toxicology studies be more relevant to occupational exposure risk assessment? Annals of Occupational Hygiene 45(Supplement 1):S5-S17.

Sanusi, A., Millet, M., Mirabel, P. and Wortham, H. 2000. Comparison of atmospheric pesticide concentrations measured at three sampling sites: local, regional and long-range transport. The Science of the Total Environment 263:263-277.

Scheuplein, R.J. and Ross, L.W. 1970. Effects of surfactants and solvents on the permeability of epidermis. Journal of Society of Cosmetic Chemists 21:853–873.

Serat, W.F. 1978. Estimating a worker reentry interval for the carbamate pesticide Furadan 4F Insecticide. Archives of Environmental Chemistry and Toxicology 7:1-11.

Shah, P.V., Monroe, R.J. and Guthrie, F.E. 1981. Comparative rates of dermal penetration of insecticides in mice. Toxicology and Applied Pharmacology 59:414-423.

Shah, P.V., Fisher, H.L., Sumler, M.R., Monroe, R.J., Chernoff, N. and Hall, L.L. 1987a. Comparison of the penetration of 14 pesticides through the skin of young and adult rats. Journal of Toxicology and Environmental Health 21:353-366.

Shah, P.V., Fisher, H.L., Month, N.J., Sumler, M.R. and Hall, L.L. 1987b. Dermal penetration of carbofuran in young and adult Fisher 344 rats. Journal of Toxicology and Environmental Health 22:207-223.

Shaw, F.R., Miller, D., Miller, M.C. and Yadava, C.P.S. 1969. Persistence of carbofuran and 3-hydroxycarbofuran on alfalfa. Journal of Economic Entomology 62:953-954.

Shehata-Karam, H., Monteiro-Riviere, N.A. and Guthrie, F.E. 1988. *In vitro* penetration of pesticides through human newborn foreskin. Toxicology Letters 40:233-239.

Shibamoto, T., Mourer, C. and Hall, G. 1993. Pilot Monitoring Study of Two Pesticides in Air. Final Report, Contract No. 92-314. Prepared for the California Air Resources Board by the Department of Environmental Toxicology, University of California, Davis. ftp://ftp.arb.ca.gov/carbis/research/apr/past/92-314.pdf

Staudinger, J. and Roberts, P.V. 2001. A critical compilation of Henry's law constant temperature dependence relations for organic compounds in dilute aqueous solutions. Chemosphere 44:561-576.

Thongsinthusak, T. 1994. Determination of Dermal Absorption of Pesticides in Animals. Memo No. HSM-94001, dated April 7. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Thongsinthusak, T. 1998. Position Paper: Standard Reference Values and Availability of Exposure Factors Handbook (1997). Memo No. HSM-98014, dated April 24.

Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Thongsinthusak, T., Ross, J.H. and Meinders, D. 1993a. Guidance for the Preparation of Human Pesticide Exposure Assessment Documents. Report No. HS-1612. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch. http://www.cdpr.ca.gov/docs/whs/pdf/hs1612.pdf.

Thongsinthusak, T., Ross, J., Sanborn, J. and Wang, R. 1993b. Dermal Absorption of Pesticides in Animals and Humans. Report No. HS-1676. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch. http://www.cdpr.ca.gov/docs/whs/pdf/hs1676.pdf

Thongsinthusak, T., Ross, J.H. and Dong, M.H. 1999. Significance of Dermal Dose Levels in Dermal Absorption Studies of Pesticides. Report No. HS-1801. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch. http://www.cdpr.ca.gov/docs/whs/pdf/hs1801.pdf.

Tsai, J.C., Sheu, H.M., Hung, P.L. and Cheng, C.L. 2001. Effect of barrier disruption by acetone treatment on the permeability of compounds with various lipophilicities: implications for the permeability of compromised skin. Journal of Pharmaceutical Sciences 90:1242-1254.

U.S. Bureau of the Census. 1995. Statistical abstract of the United States. Suitland, MD: Bureau of the Census, U.S. Dept. of Commerce.

U.S. EPA. 1984. Guidance for the Reregistration of Pesticide Products Containing Carbofuran. Washington, DC: Office of Pesticide Programs, United States Environmental Protection Agency.

U.S. EPA. 1992. Dermal Exposure Assessment: Principles and Applications. EPA/600/8-91/011B. Washington, DC: Office of Health and Environmental Assessment, United States Environmental Protection Agency.

U.S. EPA. 1996a. Occupational and Residential Exposure Test Guidelines. OPPTS 875.2100: Foliar Dislodgeable Residue. 712-C-96-267. Washington, DC: Office of Prevention, Pesticides and Toxic Substances, United States Environmental Protection Agency.

U.S. EPA. 1996b. Product Properties Test Guidelines. OPPTS 830.7950. Vapor Pressure. Document No. EPA 712–C–96–043. Washington, DC: Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency.

U.S. EPA. 1997. Exposure Factors Handbook. EPA/600/P-95/002Fa. Washington, D.C.: Office of Research and Development, U.S. Environmental Protection Agency.

U.S. EPA. 1998a. Health Effects Test Guidelines. OPPTS 870.7600: Dermal Penetration. EPA 712-C-98-350. Washington, DC: Office of Prevention, Pesticides and Toxic Substances, United States Environmental Protection Agency.

http://www.epa.gov/opptsfrs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/870-7600.pdf

U.S. EPA. 1998b. PHED Surrogate Exposure Guide. Estimates of Worker Exposure from the Pesticide Handler Exposure Database, Version 1.1. Washington, DC: Office of Prevention, Pesticides and Toxic Substances, United States Environmental Protection Agency.

U.S. EPA. 1998c. The Use of PHED Aerial Application Data. Policy Number 006, Science Advisory Council for Exposure. Dated August 12.

U.S. EPA. 1999. Use of Values from the PHED Surrogate Table and Chemical-Specific Data, Policy Number 007. Science Advisory Council for Exposure. Dated March 11.

U.S. EPA. 2000. Agricultural Transfer Coefficients, Policy Number 003.1. Science Advisory Council for Exposure. Revised August 7.

U.S. EPA. 2001. Standard Values for Daily Acres Treated in Agriculture. Policy Number 009.1, Science Advisory Council for Exposure. Revised September 25.

U.S. EPA. 2002. 2002 Edition of the Drinking Water Standards and Health Advisories. EPA 822-R-02-038. Washington, DC: Office of Water, United States Environmental Protection Agency.

U.S. EPA. 2003. User's Manual: Swimmer Exposure Assessment Model (SWIMODEL) Version 3.0. Washington, DC: Office of Pesticide Programs, Antimicrobials Division, United States Environmental Protection Agency. http://www.epa.gov/oppad001/swimodelusersguide.pdf

U.S. EPA. 2004a. Risk Assessment Guidance for Superfund (RAGS), Volume 1: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment). July 2004. http://www.epa.gov/superfund/programs/risk/ragse

U.S. EPA. 2004b. Exposure, Fate Assessment Screening Tool (E-FAST). May 2004, Beta 1.1Version. http://www.epa.gov/opptintr/exposure/docs/efast.htm

van der Merwe, D. and Riviere, J.E. 2005. Effect of vehicles and sodium lauryl sulphate on xenobiotic permeability and stratum corneum partitioning in porcine skin. Toxicology. 206:325-335.

Verder-Carlos, M. 2005. Case Reports Received by the California Pesticide Illness Surveillance Program, 2000 - 2003 in Which Health Effects Were Health Effects Definitely, Probably, or Possibly Related to Exposure to Carbofuran, Alone or in Combination. Internal report. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Versar. 1992. PHED: The Pesticide Handlers Exposure Database Reference Manual. Prepared for the PHED Task Force: Health and Welfare Canada, U. S. Environmental Protection Agency, National Agricultural Chemicals Association. Springfield, VA: Versar, Inc.

Wangsness, D.J. 1997. Carbofuran Occurrence and Distribution in Surface and Ground Waters 1991-1997, a Draft. U.S. Geological Survey in connection with the National Water Quality Assessment Program and National Stream Quality Accounting Network.

Ware G.W., Morgan, D.P., Estesen, B.J., Cahill, W.P. and Whitacre, D.M. 1973. Establishment of reentry intervals for organophosphate-treated cotton fields based on human data: I. Ethyl- and methyl parathion. Archives of Environmental Contamination and Toxicology 1:48-59.

Ware G.W., Morgan, D.P., Estesen, B.J. and Cahill, W.P. 1974. Establishment of reentry intervals for organophosphate-treated cotton fields based on human data: II. Azodrin, ethyl and methyl parathion. Archives of Environmental Contamination and Toxicology 2:117-129.

Ware G.W., Morgan D.P., Estesen B.J. and Cahill, W.P. 1975. Establishment of reentry intervals for organophosphate-treated cotton fields based on human data: III. 12 to 72 hours post-treatment exposure to monocrotophos, ethyl- and methyl parathion. Archives of Environmental Contamination and Toxicology 3:289-306.

Ware, G.W., Esteson, B. and Cahill, W.P. 1978. Dislodgeable insecticide residues on cotton (1975). Bulletin of Environmental Contamination and Toxicology 20:17-19.

Weiss, S. 2005. Carbofuran: HED's Occupational and Residential Exposure Chapter of the Reregistration Eligibility Decision Document (Phase 2). Washington, DC: Health Effects Division, Office of Pesticide Programs, United States Environmental Protection Agency, Washington, DC.

Wester, R.C. and Maibach, H.I. 2000. Understanding percutaneous absorption for occupational health and safety. International Journal of Occupational and Environmental Health 6:86-92.

Wiley, J.A., Robinson, J.P., Piazza, T., Garrett, K., Cirksena, K., Cheng, Y.T. and Martin, G. 1991. Activity Patterns of California Residents. Contract No. A6-177-33. Final Report. Sacramento, CA: Air Resources Board, Research Division, California Environmental Protection Agency. http://www.arb.ca.gov/research/abstracts/a6-177-33.htm

Williams, A.C. and Barry, B.W. 2004. Penetration enhancers. Advanced Drug Delivery Reviews 56:603-618.

Zendzian, R.P. and Dellarco, M. 2003. Validating *in vitro* dermal absorption studies: an introductory case study. Chapter 18 in: Salem, H. and Katz, S.A., editors. Alternative Toxicological Methods. CRC Press, Boca Raton.

Zweig, G., Adams, J.D. and Blondell, J. 1980. Minimizing occupational exposure to pesticides: federal reentry standards for farm workers (present and proposed). Residue Reviews 75:103-110.

Zweig, G., Leffingwell, J.T. and Popendorf, W. 1985. The relationship between dermal pesticide exposure by fruit harvesters and dislodgeable foliar residues. Journal of Environmental Science and Health B20:27-59.

APPENDICES

Appendix 1: Carbofuran Concentrations in Ambient Air Monitoring

Table 1-1: Carbofuran Concentrations in Ambient Air Monitoring in Imperial County [a]

Date	Site C [b]			Site M	Site EC	Site H	Site PM
	C1 [c]	C2 [c]	Mean				
February 14, 1995	0.031	*0.006*	0.019	0.023	*0.006*	*0.006*	*0.004*
February 15, 1995	*0.006*	*0.006*	*0.006*	*0.006*	*0.006*	*0.006*	NS [d]
February 16, 1995	*0.006*	*0.006*	*0.006*	*0.006*	*0.006*	*0.006*	NS
February 21, 1995	*0.007*	*0.007*	*0.007*	0.027	*0.006*	*0.006*	**0.084** [e]
February 22, 1995	*0.006*	*0.006*	*0.007*	0.014	*0.007*	*0.007*	**0.081**
February 23, 1995	*0.006*	*0.006*	*0.006*	0.017	0.014	*0.006*	**0.110**
February 27, 1995	*0.007*	*0.007*	*0.007*	0.017	*0.006*	*0.006*	0.028
February 28, 1995	*0.006*	*0.006*	*0.006*	0.017	*0.006*	*0.006*	0.018
March 1, 1995	*0.006*	*0.006*	*0.006*	*0.006*	*0.006*	*0.006*	*0.006*
March 2, 1995	*0.006*	*0.006*	*0.006*	*0.006*	*0.006*	*0.006*	0.017
March 6, 1995	*0.007*	*0.007*	*0.007*	*0.007*	*0.007*	*0.006*	*0.006*
March 7, 1995	*0.007*	*0.007*	*0.007*	*0.007*	*0.007*	*0.007*	*0.007*
March 8, 1995	*0.007*	*0.007*	*0.007*	0.027	*0.006*	*0.008*	0.017
March 9, 1995	*0.007*	*0.007*	*0.007*	0.018	*0.006*	*0.006*	0.019
Mean [f]	0.008	0.006	0.007	0.014	0.007	0.006	0.033
SD [f]	0.007	0.0003	0.003	0.008	0.002	0.0006	0.037

[a] Monitoring at sites in Imperial County (ARB, 1995). Concentrations are reported in μg/m^3. For results below the limit of detection (LOD), ½ of the LOD was reported; these values are italicized. The LOD for each sample was dependent on the volume of air sampled. The analytical LOD was 0.25 μg/ml sample (about 0.012 μg/m^3 for a 24-hour sample).

[b] Site C: Calipatria Fire Department, duplicate samplers. Site M: Meadows Union School, Holtville. Site EC: El Centro Air Pollution Control District (APCD) Office (urban background site). Site H: Felipe and Ramon School, Heber. Site PM: APCD PM-10 Monitoring Station, Brawley.

[c] Results from duplicate samplers labeled C1 and C2. Means of each pair of samples used to calculate overall mean, which was used in estimating exposure.

[d] NS: No sample on this date, due to instrument malfunction.

[e] Concentrations in bold are above the limit of quantification (LOQ), calculated for this exposure assessment as the usual 3 x LOD (ARB (1995) did not report an LOQ). The calculated LOQ was 0.75 μg/ml sample (about 0.036 μg/m^3 for a 24-hour sample). If concentrations at Site PM were reported above the LOQ rather than the LOD, with ½ LOQ used for values below the LOQ, the mean $\pm$ standard deviation concentration at this site would be 0.036 μg/m^3 $\pm$ 0.034 μg/m^3, and the 95th percentile concentration for Site PM would be 0.102 μg/m^3. That is, the mean concentration would be slightly greater than and the 95th percentile concentration would be slightly less than the concentrations used to estimate exposure to carbofuran at this site (the 95th percentile concentration used to estimate acute exposure at this site is 0.118 μg/m^3; see Table 9).

[f] Arithmetic mean and standard deviation (SD).

Appendix 1, Continued...

Table 1-2: Carbofuran Concentrations in Ambient Air Monitoring in Sacramento County [a]

Date	Carbofuran		Date	Carbofuran		Date	Carbofuran	
	South [b]	North [b]		South	North		South	North
Jan 2, 1996	*0.000069*	NS [c]	Jul 15, 1996	*0.000078*	*0.00026*	Apr 7, 1997	0.00242	0.00255
Jan 9, 1996	*0.000070*	NS	Aug 12, 1996	*0.000056*	NS	Apr 14, 1997	0.00367	NS
Jan 16, 1996	*0.000074*	NS	Sep 3, 1996	*0.00015*	NS	Apr 21, 1997	0.00194	0.00044
Jan 22, 1996	*0.000072*	NS	Sep 23, 1996	*0.000082*	NS	Apr 28, 1997	*0.000087*	*0.000351*
Jan 29, 1996	*0.000071*	NS	Oct 15, 1996	*0.000275*	*0.00011*	May 5, 1997	0.00183	*0.000631*
Feb 5, 1996	*0.00017*	NS	Nov 4, 1996	*0.000084*	*0.000119*	May 12, 1997	0.00206	*0.000214*
Feb 13, 1996	*0.000082*	NS	Nov 19, 1996	*0.000115*	*0.000148*	May 20, 1997	0.00134	*0.000548*
Feb 20, 1996	*0.000077*	NS	Dec 2, 1996	*0.000062*	*0.000568*	May 27, 1997	0.00309	0.00032
Feb 27, 1996	*0.000072*	NS	Dec 16, 1996	*0.000074*	*0.0010*	Jun 2, 1997	0.00050	0.00351
Mar 4, 1996	*0.00011*	*0.00020*	Dec 30, 1996	*0.000434*	*0.000164*	Jun 10, 1997	0.00099	0.013
Mar 11, 1996	NS	*0.000011*	Jan 7, 1997	*0.000334*	*0.000131*	Jun 16, 1997	0.00099	*0.000179*
Mar 18, 1996	*0.000086*	NS	Jan 13, 1997	*0.000129*	*0.000116*	Jun 23, 1997	0.00008	*0.000301*
Mar 25, 1996	*0.000080*	NS	Jan 21, 1997	*0.000082*	*0.000226*	Jul 7, 1997	0.00046	*0.000531*
Apr 1, 1996	*0.000221*	*0.00021*	Jan 28, 1997	*0.000245*	*0.000228*	Aug 4, 1997	0.00067	*0.000393*
Apr 8, 1996	*0.000095*	NS	Feb 3, 1997	*0.000337*	0.00017	Aug 18, 1997	0.00071	0.00017
Apr 15, 1996	*0.000080*	*0.00041*	Feb 10, 1997	0.000169	0.00093	Sep 2, 1997	0.00016	*0.000598*
Apr 22, 1996	*0.00016*	*0.000071*	Feb 18, 1997	*0.000217*	0.00118	Sep 15, 1997	*0.000187*	0.00094
Apr 29, 1996	NS	*0.00016*	Feb 24, 1997	0.00149	*0.000101*	Sep 29, 1997	0.00031	*0.000211*
May 6, 1996	*0.000068*	*0.00048*	Mar 3, 1997	*0.000622*	*0.000111*	Oct 13, 1997	0.00065	*0.000527*
May 13, 1996	*0.000058*	*0.00062*	Mar 10, 1997	0.00574	*0.000184*	Nov 10, 1997	*0.000105*	NS
May 20, 1996	*0.000058*	*0.000074*	Mar 17, 1997	0.00447	0.00472	Nov 24, 1997	0.000179	0.00091
Jun 10, 1996	*0.000043*	NS	Mar 24, 1997	0.00199	0.00245	Dec 22, 1997	*0.000856*	0.000078
June 24, 1996	*0.000091*	*0.00058*	Mar 31, 1997	*0.000252*	0.00231			
						Mean [d]	0.00069	0.00092
						SD [d]	0.00112	0.00198

[a] Monitoring at the "downtown metro" site in Sacramento County (Majewski and Baston, 2002); the other two sites had just a single detect each. Each sample was collected over a one-week interval. Concentrations are reported in µg/m^3. For results below the detection limit, ½ of the detection limit was reported; these values are italicized. The detection limit was 0.00015 µg/m^3 for a 100-m^3 sample.

[b] Results from samplers with directional wind sensors. Sampling was triggered when 15-min mean wind speeds were >1 m/sec in a southerly or northerly direction, and continued until the directional wind speed decreased below the trigger velocity; maximum sampling was 20 min/hr.

[c] NS: No sample, due to low sample volume (e.g., due to low wind conditions during the sample period) or instrument malfunction. Samples were collected over one-week intervals; dates in which no sufficient samples were collected from either north- or south-wind samplers have been omitted.

[d] Arithmetic mean and standard deviation (SD). Statistics are for all valid samples collected during the two-year period shown in this table. The number of observations for south was 66, and the number of observations for north was 50.

Appendix 2: Subset from PHED for Exposures of Mixer/Loaders to Liquid Formulation Using a Closed System

Table 2-1. Description of PHED subsets [a]

Parameter	Specifications used to generate subsets [a]	Actual characteristics of resulting subsets
Data Quality Grades [b]	A,B	A
Liquid Type	Emulsifiable concentrate, aqueous suspension, microencapsulated, solution, or undiluted liquid	All emulsifiable concentrate
Mixing Procedure	Closed, mechanical pump or gravity feed	Closed

[a] Subsets of Mixer/Loader data in the Pesticide Handlers Exposure Database (PHED). Parameter descriptions are from screens displayed in the PHED program.

[b] Data quality for Airborne, Dermal Uncovered, Dermal Covered and Hand are all Grade A. Data quality grades are defined in the text and in Versar (1992).

Figure 2-1. Summary of results from the Pesticide Handlers Exposure Database (PHED) dermal subset [a]

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	MICROGRAMS PER LB AI MIXED Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	1.6959	121.3279	.9508	22
NECK.FRONT	1.5225	278.5222	.2418	22
NECK.BACK	.456	280.8991	.0729	22
UPPER ARMS	1.3441	96.6967	.7988	21
CHEST	1.8416	93.4405	1.0577	16
BACK	1.8416	93.4405	1.0577	16
FOREARMS	.5474	98.5203	.3206	21
THIGHS	2.3398	81.9301	1.5773	16
LOWER LEGS	1.292	85.7276	.8778	21

Subset Name:
S6DERMAL.MLOD

[a] Subset criteria included actual and estimated head patches. Of the 22 head observations, all were actual.

Table 2-2. PHED data from dermal, hand, and inhalation subsets [a]

Exposure Category	Exposure (µg/lb AI handled)	Replicates in subset	Acute Multiplier [b]	Long-Term Multiplier [b]
Dermal (non-hand) [c]	13.6	21 [d]	4	1
Hand (with gloves)	5.72	31	4	1
Inhalation	0.128	27	4	1

[a] Results from subsets of Mixer/Loader data in the Pesticide Handlers Exposure Database (PHED). Results rounded to three significant figures.

[b] Multipliers are explained in the text and in Powell (2002).

[c] Dermal total includes addition of default feet value of 0.52 x (value for lower legs); ratio of feet/lower leg surface area (U.S. EPA, 1997).

[d] Median number of replicates was used in determining subset multipliers.

Table 2-3. Values Used in Exposure Calculations [a]

	Acute Exposure	Long-Term Exposure
Total Dermal (with gloves)	4(13.6) + 4(5.72) = 77.3 µg/lb AI handled	1(13.6) + 1(5.72) = 19.3 µg/lb AI handled
Total Dermal (no gloves) [b]	4(13.6) + 40(5.72) = 283 µg/lb AI handled	1(13.6) + 10(5.72) = 70.8 µg/lb AI handled
Inhalation	4(0.128) = 0.512 µg/lb AI handled	1(0.128) = 0.128 µg/lb AI handled

[a] Values from Table 2-2. Results rounded to three significant figures.

[b] Gloves assumed to provide 90% protection (Aprea *et al*, 1994); exposure of bare hands is calculated as ten times exposure of gloved hands.

Appendix 3: Groundboom Applicator; Open Cab

Table 3-1. Description of Pesticide Handlers Exposure Database (PHED) subsets [a]

Parameter	Specifications used to generate subsets [a]	Actual characteristics of resulting subsets
Data Quality Grades [b]	A,B	A,B,C
Liquid or Solid Type	Not specified	Emulsifiable concentrate or wettable powder
Application Method	Groundboom, Truck or Tractor	Groundboom, Tractor
Cab Type	Open Cab or Closed Cab with Open Window	Open Cab or Closed Cab with Open Window

[a] Subsets of Applicator data in the Pesticide Handlers Exposure Database (PHED). Parameter descriptions are from screens displayed in the PHED program.

[b] Data quality grades for Airborne, Dermal Uncovered, Dermal Covered and Hand are all Grade A or B, with the exception of one dermal replicate that has Dermal Uncovered Grade C (Dermal Covered for that replicate is Grade B). Data quality grades are defined in the text and in Versar (1992).

Figure 3-1. Summary of results from the PHED dermal subset [a]

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, no gloves

PATCH LOCATION	MICROGRAMS PER LB AI SPRAYED Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	2.7891	136.1192	1.0464	33
NECK.FRONT	1.5763	167.9503	.3296	23
NECK.BACK	1.0063	173.5765	.2335	29
UPPER ARMS	1.6914	88.749	1.1637	32
CHEST	1.7581	98.5154	1.1329	42
BACK	3.0175	233.2361	1.3959	42
FOREARMS	2.7301	419.1055	.564	32
THIGHS	3.1255	185.5703	1.1806	33
LOWER LEGS	2.1148	172.3425	.7466	35

Subset Name: S11DERMAL.APPL

[a] Subset criteria included actual and estimated head patches. Of the 33 head observations, all were actual.

Table 3-2. PHED data from dermal, hand, and inhalation subsets [a]

Exposure Category	Exposure (µg/lb AI handled)	Replicates in subset	Acute Multiplier [b]	Long-Term Multiplier [b]
Dermal (non-hand) [c]	20.9	33 [d]	4	1
Hand (no gloves)	45.6	29	4	1
Inhalation	1.18	22	4	1

[a] Results from subsets of Applicator data in the Pesticide Handlers Exposure Database (PHED). Results rounded to three significant figures.

[b] Multipliers are explained in the text and in Powell (2002).

[c] Dermal total includes addition of default feet value of 0.52 x (value for lower legs); ratio of feet/lower leg surface area (U.S. EPA, 1997).

[d] Median number of replicates was used in determining subset multipliers.

Table 3-3. Values Used in Exposure Calculations [a]

	Acute Exposure		Long-Term Exposure	
Total Dermal (with gloves) [b]	4(20.9) + 0.4(45.6) =	102 µg/lb AI handled	1(20.9) + 0.1(45.6) =	25.5 µg/lb AI handled
Total Dermal (no gloves)	4(20.9) + 4(45.6) =	266 µg/lb AI handled	1(20.9) + 1(45.6) =	66.5 µg/lb AI handled
Inhalation	4(1.18) =	4.72 µg/lb AI handled	1(1.18) =	1.18 µg/lb AI handled

[a] Values from Table 3-2. Results rounded to three significant figures.

[b] Gloves assumed to provide 90% protection (Aprea *et al*, 1994); exposure of gloved hands is calculated as one tenth exposure of bare hands.

Appendix 4: Aerial Applicator (Pilot) Applying Liquids

Table 4-1. Description of Pesticide Handlers Exposure Database (PHED) subsets [a]

Parameter	Specifications used to generate subsets [a]	Actual characteristics of resulting subsets
Data Quality Grades [b]	A,B,C	A,B,C
Liquid Type	Not specified	All emulsifiable concentrate
Solid Type	Exclude granular	none
Application Method	Fixed- or rotary-wing	All fixed-wing
Cab Type	Open Cab or Closed Cab with Open Window	Open Cab or Closed Cab with Open Window

[a] Subsets of Applicator data in the Pesticide Handlers Exposure Database (PHED). Parameter descriptions are from screens displayed in the PHED program.

[b] Data quality for Dermal Uncovered, Dermal Covered, and Hand were Grade A or C; Airborne data were Grade B or C. Data quality grades are defined in the text and in Versar (1992).

Figure 4-1. Summary of results from the Pesticide Handlers Exposure Database (PHED) subset [a]

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	MICROGRAMS PER LB AI SPRAYED Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	4.212	118.2574	1.2438	10
NECK.FRONT	.414	143.6715	.1169	10
NECK.BACK	.3124	139.1485	.0741	10
UPPER ARMS	8.5554	109.6232	5.7532	10
CHEST	6.3065	158.1987	2.1395	17
BACK	8.7497	141.5614	3.131	17
FOREARMS	2.7901	131.7516	1.1744	17
THIGHS	9.55	157.4126	3.4718	13
LOWER LEGS	7.4494	138.0769	3.3312	10

Subset Name:
S17DERMAL.APPL

[a] Subset criteria included actual and estimated head patches. Of the 10 head observations, 7 were actual and 3 were estimated from nearby patches (Versar, 1992).

Table 4-2. PHED data from dermal, hand, and inhalation subsets [a]

Exposure Category	Exposure (µg/lb AI handled)	Replicates in subset	Acute Multiplier [b]	Long-Term Multiplier [b]
Dermal (non-hand) [c]	52.2	10 [d]	6	2
Hand (with gloves)	9.63	9	6	2
Inhalation	0.573	14	5	2

[a] Results from subsets of Applicator data in the Pesticide Handlers Exposure Database (PHED). Results rounded to three significant figures.

[b] Multipliers are explained in the text and in Powell (2002).

[c] Dermal total includes addition of default feet value of 0.52 x (value for lower legs); ratio of feet/lower leg surface area (U.S. EPA, 1997).

[d] Median number of replicates was used in determining subset multipliers.

Table 4-3. Values Used in Exposure Calculations [a]

	Acute Exposure	Long-Term Exposure
Total Dermal (with gloves)	6(52.2) + 6(9.63) = 371 µg/lb AI handled	2(52.2) + 2(9.63) = 124 µg/lb AI handled
Total Dermal (no gloves) [b]	6(52.2) + 60(9.63) = 891 µg/lb AI handled	2(52.2) + 20(9.63) = 297 µg/lb AI handled
Inhalation	5(0.573) = 2.86 µg/lb AI handled	2(0.573) = 1.15 µg/lb AI handled

[a] Values from Table 4-2. Results rounded to three significant figures.

[b] Gloves assumed to provide 90% protection (Aprea *et al*, 1994); exposure of bare hands is calculated as ten times exposure of gloved hands.

Appendix 5: Flagger, Liquids

Table 5-1. Description of Pesticide Handlers Exposure Database (PHED) subsets [a]

Parameter	Specifications used to generate subsets [a]	Actual characteristics of resulting subsets
Data Quality Grades [b]	A,B	A,B
Liquid Type or Solid Type	Not specified	Emulsifiable concentrate or dry flowable
Application Method	Fixed- or rotary-wing	All rotary-wing

[a] Subsets of Flagger data in the Pesticide Handlers Exposure Database (PHED). Parameter descriptions are from screens displayed in the PHED program.

[b] Data quality for Dermal Uncovered and Dermal Covered are all Grade A; Airborne and Hand data are all Grade A or B. Data quality grades are defined in the text and in Versar (1992).

Figure 5-1. Summary of results from the Pesticide Handlers Exposure Database (PHED) subset [a]

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	MICROGRAMS PER LB AI SPRAYED Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	11.3028	127.5702	5.6188	18
NECK.FRONT	.9533	134.3334	.5146	18
NECK.BACK	1.4111	215.8529	.4931	18
UPPER ARMS	3.9285	195.1025	.8284	28
CHEST	5.1065	188.8378	1.0384	26
BACK	5.1065	188.8378	1.0384	26
FOREARMS	1.802	179.5283	.3837	28
THIGHS	4.0404	308.6996	.9165	26
LOWER LEGS	2.448	305.6618	.612	28

Subset Name:
S7DERMAL.FLAG

[a] Subset criteria included actual and estimated head patches. Of the 18 head observations, all were actual.

Table 5-2. PHED data from dermal, hand, and inhalation subsets [a]

Exposure Category	Exposure (µg/lb AI handled)	Replicates in subset	Acute Multiplier [b]	Long-Term Multiplier [b]
Dermal (non-hand)	37.4	26 [d]	4	1
Hand (no gloves)	5.97	30	4	1
Inhalation	0.200	28	4	1

[a] Results from subsets of Flagger data in the Pesticide Handlers Exposure Database (PHED). Results rounded to three significant figures.

[b] Multipliers are explained in the text and in Powell (2002).

[c] Dermal total includes addition of default feet value of 0.52 x (value for lower legs); ratio of feet/lower leg surface area (U.S. EPA, 1997).

[d] Median number of replicates was used in determining subset multipliers.

Table 5-3. Values Used in Scenario 7 Exposure Calculations [a]

	Acute Exposure	Long-Term Exposure
Total Dermal (with gloves)	4(37.4) + 0.4(5.97) = 152 µg/lb AI handled	1(37.4) + 0.1(5.97) = 38.0 µg/lb AI handled
Total Dermal (no gloves) [b]	4(37.4) + 4(5.97) = 173 µg/lb AI handled	1(37.4) + 1(5.97) = 43.4 µg/lb AI handled
Inhalation	4(0.200) = 0.800 µg/lb AI handled	1(0.200) = 0.200 µg/lb AI handled

[a] Values from Table 4-2. Results rounded to three significant figures.

[b] Gloves assumed to provide 90% protection (Aprea *et al*, 1994); exposure of gloved hands is calculated as one tenth exposure of bare hands.

Appendix 6: Mixer/Loader/Applicator; Low Pressure Hand Wand

Table 6-1. Description of Pesticide Handlers Exposure Database (PHED) subsets [a]

Parameter	Specifications used to generate subsets [a]	Actual characteristics of resulting subsets
Data Quality Grades [b]		
Airborne	A,B	A, B
Dermal and Hand	A, B, C	A, B, C
Liquid Type	Emulsifiable concentrate, aqueous suspension, microencapsulated, solution, or undiluted liquid	Solution or Microencapsulated
Application Method	Low Pressure Handwand	Low Pressure Handwand
Mixing Procedure	Not specified	All open

[a] Subsets of Mixer/Loader/Applicator data in the Pesticide Handlers Exposure Database (PHED). Parameter descriptions are from screens displayed in the PHED program.
[b] Data quality grades are defined in the text and in Versar (1992).

Figure 6-1. Summary of results from the Pesticide Handlers Exposure Database (PHED) subset [a]

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES
SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	MICROGRAMS PER AVERAGE LB AI Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	658.5361	136.7049	290.5017	80
NECK.FRONT	137.9226	369.6483	18.9272	80
NECK.BACK	86.3274	429.9868	14.8349	79
UPPER ARMS	111.8313	232.934	32.6211	10
CHEST	235.1875	185.929	48.9756	10
BACK	163.797	202.4421	41.5723	10
FOREARMS	40.9585	267.6492	9.412	10
THIGHS	37.9878	115.1859	27.6737	9
LOWER LEGS	66.9309	164.3135	30.0241	9

Subset Name:
S22DERMAL.MLAP

[a] Subset criteria included actual and estimated head patches. Of the 80 head observations, 10 were actual and 70 were estimated from nearby patches (Versar, 1992).

Table 6-2. PHED data from dermal, hand, and inhalation subsets for Scenario 22 [a]

Exposure Category	Exposure (µg/lb AI handled)	Replicates in subset	Acute Multiplier [b]	Long-Term Multiplier [b]
Dermal (non-hand) [c]	1,570	10 [d]	6	2
Hand (with gloves)	10.4	10	6	2
Inhalation	22.8	10	6	2

[a] Results from subsets of Mixer/Loader/Applicator data in the Pesticide Handlers Exposure Database (PHED). Results rounded to three significant figures.
[b] Multipliers are explained in the text and in Powell (2002).
[c] Dermal total includes addition of default feet value of 0.52 x (value for lower legs); ratio of feet/lower leg surface area (U.S. EPA, 1997).
[d] Median number of replicates was used in determining subset multipliers.

Table 6-3. Values Used in Exposure Calculations [a]

	Acute Exposure		Long-Term Exposure	
Total Dermal (with gloves)	6(1,570 + 10.4) =	9,480 µg/lb AI handled	2(1,570 + 10.4) =	3,160 µg/lb AI handled
Total Dermal (no gloves) [b]	6(1,570) + 60(10.4) =	10,000 µg/lb AI handled	2(1,570) + 20(10.4) =	3,350 µg/lb AI handled
Inhalation	6(22.8) =	137 µg/lb AI handled	2(22.8) =	45.6 µg/lb AI handled

[a] Values from Table 6-2. Results rounded to three significant figures.
[b] Gloves assumed to provide 90% protection (Aprea *et al*, 1994); exposure of bare hands is calculated as ten times exposure of gloved hands.

Appendix 7: Calculation of Parameters Used in Estimating Dermal Exposure to Workers Dipping Nursery Stock

1. K_p is the skin permeability coefficient, calculated as follows (U.S. EPA, 2004):

$$\log Kp = -2.80 + 0.66 \log Kow - 0.0056 MW$$

With MW of 221.3 and Log Kow of 1.42, the Kp is 0.000791 cm/hr for carbofuran.

2. B is the dimensionless ratio of two permeability coefficients, one for the stratum corneum (SC) and one for the epidermis (EPI). However, as explained by Bunge and Cleek (1995), the permeability coefficient for the epidermis is exceedingly difficult to determine: "Although experimental protocols exist for removing the EPI leaving an intact SC, techniques for removing the SC without damaging the EPI do not exist." Because the permeability of the epidermis is almost never known, Bunge and Cleek (1995) proposed four methods of estimating B without knowing the epidermal permeability, based on empirical data and theory. B is estimated from Method 4, which was the method recommended by Bunge and Cleek (1995):

$$B = P_{cw}[(MW)^{0.5}/(2.6 \text{ cm/hour})]$$

where P_{cw} is the estimated steady-state permeability of the stratum corneum from water, calculated as follows (Bunge and Cleek, 1995):

$\log P_{cw} = -2.8 - 0.006(MW) + 0.74 \log K_{ow} = -3.077$, and $P_{cw} = 0.00084$ cm/hour. Thus,

$B = (0.00084)[(221.3)^{0.5}/(2.6)] = 0.00479$.

3. τ is the lag time per event (hours). The lag time is how long it takes for a chemical to cross the skin, including both the SC and EPI (Bunge *et al*., 1995). τ is calculated as follows (U.S. EPA, 2004a):

$$\tau = 0.105 \times 10^{(0.0056 MW)}$$

For carbofuran, MW = 221.3. Thus,

$$\tau = 0.105 \times 10^{(0.0056 * 221.3)} = 0.105 \times 10^{(1.239)} = 0.105 (17.35) = 1.82 \text{ hours}$$

4. The equation for dermal exposure per event DA_{event} in RAGS-E is as follows (modified from Equation 3.3 in U.S. EPA (2004a), surface area term added to get result in mg/event rather than mg/cm2):

$$DA_{event} = FA * K_p * SA * C_w * (0.001 L/cm^3) * [t/(1+B) + 2\tau((1+3B+3B^2)/(1+B)^2)]$$

where

DA_{event} is the absorbed dose per event (mg per event);
FA is the fraction absorbed water (dimensionless, default = 1);
SA (cm^2) is surface area of exposed skin;
C_w is the concentration of the pesticide in water (multiply by the appropriate protection factor);
t is the event duration (hours); and
other parameters are as defined above.

Appendix 7, Continued...

5. Absorbed daily dose is calculated by dividing the DA_{event} by body weight (BW).

Results of above calculations are summarized in Table 7-1.

Table 7-1. Dermal Carbofuran Exposure Estimates Calculated with Equations from RAGS-E [a]

Parameter	Value
K_p (cm/hr) [b]	0.000791
τ (hours) [c]	1.82
B [d]	0.00479
Hands	
DA_{event} (mg per day) [e]	9.97
ADD (mg/kg/day) [f]	0.142
Non-Hand Dermal	
DA_{event} (mg per day) [g]	80.6
Dermal ADD (mg/kg/day) [h]	1.15
Total Dermal	
Total Dermal ADD (mg/kg/day) [i]	1.29

[a] C_w = 12,000 mg/L for carbofuran (concentration in slurry prepared according to directions on Furadan® 4F product label). Concentration reaching skin is assumed to be reduced due to gloves and clothing; default protection factors are 90% for both (Thongsinthusak *et al.*, 1993a; Aprea *et al.*, 1994).

[b] Skin permeability coefficient (K_p) calculated from Equation 3.8 in U.S. EPA (2004a).

[c] Lag time for carbofuran to cross skin (τ) calculated from Equation A.4 in U.S. EPA (2004a).

[d] Ratio of permeability coefficients for the stratum corneum and the epidermis estimated from Equation A.1 in U.S. EPA (2004), which is also Method 4 in Bunge and Cleek (1995).

[e] Estimated hand exposure per day. Calculated from Equation 3.3 in U.S. EPA (2004a), SA = 904 cm^2 (surface area both hands; combined male and female medians from EPA, 1997). ET = 8 hours.

[f] ADD is absorbed daily dose. DA_{event} divided by 70 kg default body weight to obtain dermal dose (Thongsinthusak *et al*., 1993).

[g] Estimated dermal exposure per day. Calculated from Equation 3.3 in U.S. EPA (2004a), SA = 7,306 cm^2 (surface area of chest/stomach, forearms, front of thighs and lower legs; combined male and female medians from EPA, 1997). ET = 8 hours.

[h] Dermal ADD is absorbed daily dose. AD_{Derm} divided by 70 kg default body weight to obtain dermal dose (Thongsinthusak *et al*., 1993a).

[i] Total Dermal ADD is the sum of ADD for hands and Dermal ADD.

Appendix 8: Calculation of Parameters Used in Estimating Inhalation Exposure to Workers Dipping Nursery Stock

SWIMODEL estimates ambient vapor concentration of a chemical from its air-water partitioning using its unitless Henry's Law constant, which is calculated as follows (U.S. EPA, 2003):

$$C_{vp} = H' * C_w * (1{,}000\ L/m^3)$$

where

C_{vp} ($\mu g/m^3$) is the concentration of the pesticide in air;
H' is the unitless Henry's Law constant; and
C_w is the concentration of chemical in water ($\mu g/L$).

The unitless Henry's Law constant is calculated based on the Henry's Law constant in units of atm-m^3/mole using the following equation:

$$H' = H/(R * T)$$

where

H' is the unitless Henry's Law constant;
H is the aqueous Henry's Law constant (atm-m^3/mole);
R is the gas constant (8.19×10^{-5} atm-m^3/mole-K); and
T is the ambient air temperature (degrees Kelvin, or 273 added to degrees Celsius).

SWIMODEL calculates the potential dose rate in mg per event ($AD_{Inhalation}$) as:

$$AD_{Inhalation} = Cvp * ET * IR * (1\ mg/1{,}000\ \mu g)$$

where

C_{vp} ($\mu g/m^3$) is the concentration of the pesticide in air;
ET (hrs/event) is exposure time; and
IR (m^3/hr) is inhalation rate.

However, carbofuran products contain additives to increase water solubility. Because of this, the vapor concentration calculated from the SWIMODEL equation is quite high, perhaps above concentrations that could actually occur. To check this, the equation used to estimate vapor pressure by the gas saturation method (U.S. EPA, 1996b) can be re-arranged to provide an estimate of saturated vapor concentration based on reported vapor pressure. The equation is given below.

$$C_{sat} = [(VP/760) * MW * (1{,}000\ mg/g)(1{,}000\ L/m^3)]/R*T$$

where

C_{sat} ($\mu g/m^3$) is the saturated concentration of the pesticide in air;
MW is the molecular weight;
R is the gas constant (8.19×10^{-5} atm-m^3/mole-K); and
T is the ambient air temperature (degrees Kelvin, or 273 added to degrees Celsius).

The estimated C_{sat} is given in Table 8-1. This value is considerably lower than the estimated C_{vp}, suggesting that C_{vp} is unrealistically high. Therefore, C_{sat} was used in calculating inhalation exposure. This approach is used by another model to estimate inhalation exposure (U.S. EPA, 2004b).

Appendix 8, Continued...

Table 8-1. Inhalation Carbofuran Exposure Estimate Based on SWIMODEL Equations [a]

Parameter	Value
H' [b]	2.08×10^{-8}
C_{vp} [c]	250
C_{sat} [d]	36.6
$AD_{Inhalation}$ (mg per day) [e]	0.0732
Inhalation ADD (mg/kg/day) [f]	0.00105

[a] C_w = 12,000 mg AI/L for carbofuran (concentration in slurry prepared according to directions on Furadan® 4F product label).

[b] Unitless Henry's Law constant. See text for equation.

[c] Calculated concentration of pesticide in air. See text for equation.

[d] Saturated vapor concentration, based on a vapor pressure of 6×10^{-8} mm Hg @ 25°C (Alvarez, 1989). See text for equation.

[e] Estimated inhalation exposure per day. See text for equation. C_{sat} used for C_{vp}, IR = 20 m^3/day, ET = 1 day. A default protection factor of 90% is factored in for use of a respirator (NIOSH, 1987).

[f] ADD is absorbed daily dose. To calculate, $AD_{inhalation}$ was divided by 70 kg default body weight to obtain dose (Thongsinthusak *et al*., 1993a).

A default value of 20 m^3/day was used for IR (Andrews and Patterson, 2000); this value assumes moderate to heavy activity during an 8 hour workday. Because IR is given for the workday rather than on an hourly basis, ET is set to 1 day in the exposure calculation. This result is multiplied by 0.1 for use of a respirator (NIOSH, 1987). The inhalation contribution to the ADD is calculated by dividing by the default body weight of 70 kg (Thongsinthusak *et al*., 1993a). Exposure estimates are given in Table 8-1.