METHAMIDOPHOS

(MONITOR7)

VOLUME I
RISK CHARACTERIZATION DOCUMENT

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I. SUMMARY

Methamidophos is an organophosphate which was patented by Bayer in 1965 and Chevron in 1967, for the control of insects and mites in a range of vegetable crops. It is also used on non-food crops such as alfalfa, clover, Bermuda grass, cut/outdoor flowers and in greenhouses. Organophosphate insecticides, including methamidophos, act by the inhibition of the enzyme acetylcholinesterase. This target enzyme is present in both insects and mammals. In 1995, a total of 518,400 lb. of methamidophos was applied in California, to 13 food crops: cotton (45%), tomatoes (17%) and potatoes (5%) being the main ones. In 1996, following concerns expressed by US EPA about occupational safety, all registrations except these three crops were voluntarily canceled by Bayer. The use of methamidophos in California has declined in successive years such that by 2001, total usage had fallen to 47,000 lbs.

Field trials have indicated that residues of methamidophos in the above crops at harvest are generally below the tolerances of 0.1 ppm for cotton and potatoes and 1 ppm for tomatoes. Biotransformation products *i.e.* metabolites are not considered to be of toxicological concern.

Methamidophos is highly water-soluble (>200 g/l) and has been shown to be weakly adsorbed by soil giving it a high potential to leach. Environmental fate studies have indicated that methamidophos has low persistence in soil (t_2 values of □4 days). Its rapid breakdown in soil make it unlikely to leach under normal field conditions. In California, there have been no detections of parent methamidophos in groundwater monitoring studies. It has a high vapor pressure, giving methamidophos a tendency to volatilize, but because of its high solubility in water, it has a low Henry's Law constant and thus has a much lower tendency to volatilize under normal field conditions.

A human health risk assessment has been conducted for methamidophos because of its high acute toxicity in animal studies and because of documented illnesses following occupational exposure. The acute and chronic toxicological endpoints used in the risk characterization were from rat and dog studies, respectively: cholinesterase inhibition (plasma, RBC, brain) and FOB (functional observational battery) effects for acute dietary exposure based on a rat study; systemic toxicity (inhibition of brain ChE) for chronic dietary exposure, based on a dog study. In addition, a sub-chronic rat neurotoxicity study was used for assessing risks from seasonal occupational exposure.

Neurotoxicity was measured in studies conducted in the chicken, rat and human. In addition to the inhibition of ChE and clinical signs, the inhibition of NTE (neuropathy target esterase) was also measured, as a marker for OPIDN (organophosphate-induced delayed neuropathy). The lowest NOEL (no observed effect level) for an acute study was 0.3 mg/kg/day for FOB effects and ChE inhibition (brain) in the SD rat.

Developmental toxicity was measured in oral gavage studies in the rat (4) and the rabbit (3). Although none of these studies was acceptable to DPR, collectively, these were considered adequate to address data requirements for developmental toxicity. Maternal toxicity (clinical signs) showed similar NOEL values to those for developmental toxicity (reduced mean fetal body weight) in the rat. Inhibition of maternal RBC and brain AChE was reported at lower dosages. In a developmental neurotoxicity study, brain AChE

inhibition in the dam (LOEL = 1 ppm, $p<0.05$) was more marked than in pups (LOEL = 10 ppm, NOEL = 1 ppm). Reproductive toxicity was determined in a 2-generation rat study. Significant reductions in mean adult and pup body weight were noted with a LOEL of 10 ppm and a NOEL of 1 ppm. Similarly, the inhibition of plasma, RBC and brain AChE was observed consistently at 10 and 30 ppm, for adults and pups, of each litter. At 1 ppm, however, only low-level inhibition was reported, which was sporadically significant only for adults. The parental and reproductive LOEL and NOELs were both determined to be 10 ppm and 1 ppm, respectively.

Chronic toxicity from repeated exposure to methamidophos was identified as reduced brain AChE activity in three dietary studies employing rats, mice and dogs. The LOEL for this effect in each study was the lowest dose of 2 ppm, equivalent to 0.1, 0.3 and 0.06 mg/kg/day, respectively. All of these chronic studies were acceptable to DPR.

There was no evidence of oncogenicity in the rat or mouse. Genotoxicity was assessed in seven types of assay, in 10 studies. All of the studies gave negative results with the exception of a chromosomal aberration test *in vitro,* which was positive.

A NOEL of 3.0 mg/kg/day from an acute, rat dermal toxicity study was used as the critical NOEL to determine MOE values for potential acute occupational exposure. This dosage is equivalent to an absorbed dosage of 0.9 mg/kg/day, based on a (human) dermal absorption study indicating 29% dermal absorption. 0.3 mg/kg/day from a rat acute oral neurotoxicity study was used as the critical NOEL value to determine MOEs for potential acute dietary exposure. A sub-chronic NOEL of 0.75 mg/kg/day, equivalent to an absorbed dosage of 0.22 mg/kg/day, from a 21-day rat dermal toxicity study, was used to determine MOEs for seasonal and annual (chronic) occupational exposure. An estimated NOEL of 0.02 mg/kg/day, based on (18%, $p<0.001$) inhibition of brain ChE at the LOEL of 2 ppm (0.06 mg/kg/day) in a 1-yr. dog study in males was used as the critical NOEL value to determine MOE values for potential chronic dietary exposure.

Occupational exposure was estimated for three types of application and four work tasks, using PHED (Volume 2). For the M/L/A, ADDs ranged from 20 - 337 µg/kg/day; SADDs from 5.0 – 84.1 µg/kg/day; AADDs from 1.7 – 28.1 µg/kg/day. Flaggers had the highest estimated exposure, with ADDs of 190 – 653 µg/kg/day, SADDs from 47.6 – 163 µg/kg/day and AADDs from 15.9 – 54.4 µg/kg/day. In addition, five types of post-application exposure were assessed: scouting, irrigating, staking, pruning and harvesting. ADDs ranged from 0.8 - 4.4 µg/kg/day; SADDs from 0.3 – 0.9 µg/kg/day; AADDs from 0.07 - 0.2 µg/kg/day.

Dietary exposure was estimated using DEEM[7] software in combination with crop residue studies. Food consumption patterns were assessed primarily using the 1994-1998 CSFII survey. For comparison, a deterministic, point estimate approach was used as well as a probabilistic, Monte Carlo program. Two percentiles of exposure were used, 95th and 99.9,th the latter using Monte Carlo only. For all registered commodities combined (cotton, potato, tomato), at the 95$^{th.}$ percentile, acute dietary exposure ranged from 0.238 to 0.646 g/kg/day (point estimate) to 0.048 to 0.129 g/kg/day (Monte Carlo), for 20 population subgroups examined. At the 99.9$^{th.}$ percentile of exposure, the equivalent ranges of acute dietary exposure were 0.515 to 1.410 g/kg/day. Children, 1-6 yrs. had the greatest and seniors the lowest exposure. For mean (annualized) chronic

dietary exposure to methamidophos, for all crops, the calculated exposures ranged from 0.01 to 0.013 g/kg/day with the PCT adjustment and 0.003 to 0.027 g/kg/day, without this adjustment. The sub-groups with the highest and lowest exposures were children, 1-6 yrs. and nursing infants, respectively.

The MOEs for occupational exposure, for M/L/As, ranged from 3 - 45 (acute), 3 - 44 (seasonal); 8 - 130 (chronic, annual). Flaggers consistently had the lowest MOEs, from 1 to 14, for all durations of exposure. For post-application tasks, MOEs ranged from 200 - 1100 (acute); 240 - 730 (seasonal); 1100 - 3100 (chronic, annual).

The acute MOEs for all registered commodities, at the 95$^{th.}$ percentile, ranged from 460 for children (1-6 yrs), to 1260 for seniors, 55+ yrs., (point estimate). Using the Monte Carlo program, the range of MOE values was 2320 for children (1-6 yrs.) to 6230 for seniors, 55+. At the 99.9$^{th.}$ percentile of exposure, the equivalent MOEs were 210 for children (1-6 yrs) to 580 for females, 20+ (not pregnant or nursing) and seniors, 55+ yrs.

The chronic MOEs for each population subgroup following (annual, average) dietary exposure to methamidophos were calculated using the1994-1998 CSFII database. These values were derived from the exposure values using all registered commodities, with and without adjustment for percentage of crop-treated. The MOE values ranged from 1,550, for children (1-6 yrs.), to 16,700 for nursing infants (<1 yr.) using PCT and 730 to 7,950, without PCT, for the same population sub-groups.

The consumption of commodities with residues of methamidophos at tolerance (0.1 or 1.0 ppm) gave theoretical, acute, dietary exposures (at the 97.5$^{th.}$ percentile) ranging from 0.007 to 0.063 g/kg/day, for cottonseed; 0.424 - 1.870 g/kg/day, for potato and 3.93 - 11.30 g/kg/day, for tomato. The corresponding MOE values for these exposures were 4,780 to 43,380 for cottonseed; 160 to 710 for potato; 26 to 76 for tomato. The ranges reflect differing dietary exposure patterns for various population sub-groups. The groups with the lowest MOEs were: non-nursing infants, <1yr. for cottonseed and potato; children (1-6 yrs.) for tomato.

A MOE of at least 100 is generally considered adequate to protect people from the toxic effects of a chemical when the toxicology endpoints are derived from animal studies. For occupational exposure, MOEs were below 100 for all primary application tasks, and flagging, but not for reentry tasks, where the MOEs were above 100. MOEs for both acute and chronic estimated dietary exposure were above 100 for all population sub-groups examined, for cotton, potato and tomato, combined. MOEs for combined occupational and dietary exposure were below 100.

U.S. EPA tolerances for methamidophos for cotton and potato gave acute MOE values, for all population subgroups, above 100. However, tomato consumption with residues at tolerance gave acute MOE values ranging from 26 (children, 1-6 yrs.) to 76 (females, 13+ pregnant, not nursing) *i.e.* below 100. It is recommended that the tolerance for tomato be reviewed by USEPA.

II. INTRODUCTION

A risk assessment for methamidophos has been conducted based on the possible adverse effects identified in the following studies: low NOEL values in acute and chronic studies and evidence of neurotoxicity. Volume I comprises the toxicology profile, risk characterization, risk appraisal, tolerance assessment and conclusions. Appendix A gives the Toxicology Summaries (reviews) and Appendix B, the dietary analysis. Volume 2 comprises the estimates of occupational exposure. This RCD evaluates risk from potential occupational and dietary exposure.

A. CHEMICAL IDENTIFICATION

Methamidophos, (*O,S* - dimethyl phosphoramidothioate) is a broad spectrum insecticide/acaricide with both contact and systemic activity in a broad range of plants. It is an inhibitor of acetylcholinesterase (AChE, EC 3.1.1.7). It is active *per se* and also as the bioactive metabolite resulting from the use of the insecticide acephate.

B. REGULATORY HISTORY

Methamidophos was patented by Bayer in 1965 and by Chevron in 1967. It was registered by U.S. Environmental Protection Agency (U.S. EPA) to be sold by Bayer (formerly Mobay, Miles) and Chevron (subsequently by Valent U.S.A.), under the trade name, Monitor[7] or Tamaron.[7]

In an acute worker risk project, the Office of Pesticide Programs, USEPA (OPP) identified methamidophos as one of the five most acutely toxic chemicals in a review of (83) organophosphate (OP) and carbamate insecticides (U.S. EPA, 1993).

Following an occupational exposure report (U.S. EPA, 1996) with extremely low MOE values, Bayer AG, the principal registrant, prepared a risk mitigation document (Bayer, 1996). They volunteered to remove all food registrations except cotton, tomatoes and potatoes. US EPA agreed to this proposal, pending risk determinations with respect to the Food Quality Protection Act (FQPA, 1996). As can be calculated from the figures in Section II.D., applications to these (3) food crops made up 67% of the total of lbs. a.i. used in 1995 and 83% of the total amount applied to all food crops, combined. In this risk assessment, dietary exposure estimates have been limited to cotton, tomatoes and potatoes, since it is anticipated that the use on other crops will gradually decline to zero, as existing stocks are used up.

FQPA (US EPA, 1996) requires that certain groups of chemically-related pesticides, which often have relatively high mammalian acute toxicity and which act through a common mechanism, such as the organophosphates, be considered together for risk assessment purposes. Furthermore, home and garden uses should also be considered, along with pesticide residues in drinking water, as well as dietary intake, in the total pesticide exposure. Methamidophos is not currently registered for home and garden uses, although acephate is registered for residential uses.[2] Acephate is a pro-

[2]/ Residential indoor and turfgrass uses were canceled by USEPA in the IRED of 9/28/01

insecticide which is insecticidal only after conversion to methamidophos. Thus, aggregate exposure to methamidophos in agriculture and acephate in agriculture and home and garden together, could be considered appropriate for risk assessment purposes under FQPA. A RCD for acephate is nearing completion at DPR.

Rapid breakdown of methamidophos in soil (Section II.G) should ensure a low risk from drinking water exposure. Another aspect of FQPA (US EPA, 1996) concerns the possibility that fetuses/children may be more susceptible to an acutely toxic chemical than adults. In order to address this point, and notwithstanding the lack of specific developmental or reproductive effects in the studies previously submitted, a developmental neurotoxicity study was submitted to DPR by Bayer, in September, 2002. In this study, it was demonstrated that the rat fetus or neonate was not more susceptible to methamidophos than the adult. Prior to this study being completed and reviewed, US EPA had imposed a 3x additional uncertainty factor on methamidophos in calculating a RfD for chronic dietary exposure risk assessment. Since 1998, when the RfD was reviewed, the US EPA RfD has been 0.0001 mg/kg/day, based on a NOEL of 0.03 mg/kg/day (inhibition of plasma and RBC ChE and brain AChE in a 8-wk. rat dietary study) divided by an uncertainty factor of 300.

In 2002, USEPA announced an interim reregistration eligibility decision (IRED) for methamidophos. This decision concluded that dietary exposure to methamidophos through labeled uses (cotton, tomato, potato) did not require mitigation. However, the uses on cotton were to be discontinued by 2007 and three main issues would need to be addressed by the registrants for mitigation purposes: first, monitoring data were to be collected to address possible surface water contamination (as calculated using PRZM-EXAMS and GEENEC models); second, engineering controls were to be instituted to reduce worker exposure and finally, ecological risks to birds and mammals were considered excessive but would be mitigated adequately by the removal of labels for cotton (USEPA, 2002c). It was further pointed out by USEPA that this IRED remained "interim" pending the evaluation of acephate and other organophosphate insecticides, which were to be considered collectively under a "cumulative" risk assessment.

It was also determined by USEPA that tolerances for cottonseed were to be increased from 0.1 ppm to 0.2 ppm and for tomato, from 1 ppm to 2 ppm. The potato tolerance was to remain at 0.1` ppm. The CODEX MRLs, developed by the UN/FAO JMPR Committee, for these RACs, are 0.1 ppm, 1 ppm and 0.05 ppm for cottonseed, tomato and potato, respectively. For cottonseed and potato, these MRLs include methamidophos arising from the application of acephate, but for tomato, there is no MRL for tomato, so that residues are assumed to arise from the application of parent methamidophos (USEPA, 2002c).

C. TECHNICAL AND PRODUCT FORMULATIONS

The insecticidal properties of methamidophos were first described in 1970 (Hammann, 1970). It was introduced as water-soluble concentrates Tamaron7 (Bayer AG) and Monitor7 (Chevron, subsequently Valent) for the control of chewing and sucking insects. The products which are currently registered for use in California are Monitor7 4 insecticide and Monitor7 4 spray. These identical formulations are emulsifiable

concentrates, containing 4 lb. a.i.[3] /gallon (40% a.i.). Combination products of methamidophos, including Baythroid* TM (with cyfluthrin), Magnum* (with *beta* - cyfluthrin), Tamaron Combi* (with triflumuron) and Tamaron* EP (with parathion), are not available in California.

D. USAGE

Methamidophos products are registered in California as contact insecticides for the control of a broad range of insect and mite species. In 1995 (DPR, 1996), 518,400 lbs. a.i. were used, with approximately 80% of this on food crops and 20% on non-food crops (almost all on alfalfa). The main food crops on which it was used, along with the percentage of (total) lbs. of a.i., were as follows: cotton (45%), tomatoes (17%) sugar beets (5%) and potatoes (5%). The other food crops, in descending order, were broccoli, melons, lettuce, cauliflower, Brussels sprouts, cabbage, peppers (fruiting), celery and peppers (flavor). Each of these crops accounted for 2% or less of the total. Methamidophos was registered on cucumbers and eggplant but none was used in 1995. In successive years, the amount of methamidophos used in California has declined, such that by 2001, its use had fallen to 47,000 lbs. As previously mentioned, the only current registered uses in California are for cotton, potatoes and tomatoes.

E. ILLNESS REPORTS

During the period 1991-7, there were 93 individuals with definite (n=6), probable (n=59) or possible (n=27) illnesses related to methamidophos use, in California. The vast majority, 92/93 (99%), involved agricultural exposure. The term "definite" refers to cases where there were organophosphate-compatible symptoms and evidence of cholinesterase inhibition. The term Aprobable@ refers to cases where specific symptoms or signs (such as bradycardia, excessive salivation or bradycardia in the absence of organic heart disease) were suggestive of organophosphate poisoning. "Possible" indicates the presence of symptoms compatible with, but not specific for, OP poisoning following a recognized exposure. Most of the possible cases did not have any cholinesterase test data reported, but some had a single measurement in the normal range, without a baseline value for a comparison, or else follow-up which was inadequate for some other reason.

The six definite cases involved five incidents and all showed clinical signs and symptoms that were consistent with depression of AChE. Four of six had demonstrated inhibition of ChE (plasma and RBC); another had urinary metabolites of methamidophos. The sixth case involved a spillage of methamidophos onto coveralls while pouring a concentrated solution into a mixer/loader system. The types of task associated with definite or probable incidents were varied and included: M/L/A, re-entry during the reentry interval or REI (48h) without protective clothing, drift (from nearby

[3]/ a.i. = active ingredient

fields), harvesting and flagging.

The overall risk of illness induced by ChE inhibition resulting from methamidophos use is quite low compared with other OPs of less acute toxicity. This may result from the high proportion of drift cases in the 1982-1990 database, as these tend to result in low level exposure (O=Malley, 1995). When the database was restricted to cases of exposure related to M/L/A, the risk of ChE inhibition-related illness was increased significantly for methamidophos compared with other OPs (O=Malley, 1995). Part of the reason for a lack of a clear association for many of the cases relates to the use of mixtures of OPs, often in combination. One of the OPs often used in combination with methamidophos was mevinphos, an OP of similar toxicity to methamidophos but much greater volatility (higher vapor pressure), which resulted in higher inhalation exposure. Because of the excessively large number of cases of illness associated with mevinphos use, and the fact that available mitigation measures were exhausted, mevinphos use was cancelled by DPR (and US EPA) in 1994. It is also a potential problem that both methamidophos and mevinphos were/are liquid rather than solid formulations, giving rise to greater and more rapid absorption.

In an epidemiological analysis of multiple ChE inhibiting pesticides (O=Malley *et al.*, 1994), the odds ratios (ORs) were calculated. These measured the proportion of subjects with OP or carbamate-related systemic illness after exposure to ChE-inhibiting pesticides. The case group or AChE Illness Group@ comprised subjects who showed OP symptoms (definite or probable illness) along with depression of ChE (1982-1990, California pesticide illness registry). The comparison group, the Anon-ChE effect group@ included all subjects who were employed in agriculture and classified as unlikely illness, unrelated illness and asymptomatic (or symptomatic) but without inhibition of ChE. The tasks performed and the individual ChE inhibitors were separated for comparative purposes. It was shown that, in the case of application exposure (n=356 test subjects), three compounds showed significantly elevated comparative risk: mevinphos (OR=7.72, $p<0.001$), methomyl (OR=3.8, $p<0.001$) and methamidophos (OR=3.09, $p<0.05$). Thus, for these three pesticides, relative to other ChE-inhibiting pesticides, there was a high probability that application tasks would result in illness.

During the years 1996-2000, there were 14 cases of illness involving methamidophos reported to DPR. However, in each case, exposures were to pesticide mixtures which included methamidophos, rather than to the latter alone. This adds uncertainty to the precise role of methamidophos in causing worker illnesses.

F. PHYSICAL AND CHEMICAL PROPERTIES

1. Common Name:	Methamidophos
2. Chemical Name:	*O,S*-dimethyl phosphoramidothioate
3. Trade Names:	Monitor7 (Valent U.S.A.) Tamaron7 (Bayer) Swipe7 Nuratron7 (Atabay) Vetaron7 (VAPCO).
4. CAS Registry No.:	10265-92-6
5. Molecular Weight:	141 g/mole
6. Molecular Formula:	CH_3-O-P(=O)$SCH_3(NH_2)$
7. Empirical Formula:	$C_2H_8NO_2PS$
8. Physical State:	Colorless, crystalline solid
9. Odor:	smelly (sulfur)
10. Melting Point:	44.5 C -46.1 C
11. Solubility:	At 20 C, Water > 200 g/l; benzene, xylene <100 g/liter; chloroform dichloromethane, diethyl ether 20-25 g/liter; kerosene <10 g/liter (Pesticide Manual, 1983).
12. Vapor Pressure:	2.3 mPa (20 C) (Farm Chemicals Handbook, 1995) to 40 mPa (30 C) (Pesticide Manual, 1983)
13. Henry's Law Constant:	3.22^{-12} atmos.-m^3/mole at 20°C (Mobay, 1989)
14. Partition Coefficient (K_{ow}):	$\log K_{ow}$ = -0.66 (Magee, 1982)
15. Specific Gravity ($d^{44.5}$):	1.31
16. Refractive Index (n_D^{40}):	1.5092

G. ENVIRONMENTAL FATE

Summary

Methamidophos is hydrolyzed rapidly under alkaline conditions but is stable under sterile, acid conditions (pH5). Photolysis at pH5 reduced the hydrolytic half-life from 309 days to 37 days (continuous light) or 90 days (natural sunlight). Photolysis of an aqueous solution occurred readily, with a half-life of 1.8 days (continuous light) or 4.2 days (natural sunlight). Soil degradation occurred rapidly under aerobic conditions in the dark, with a half-life of 14h on sandy loam soil. Under dark anaerobic conditions, the half-life using the same soil type was 4 days. The main transformation products in these studies were identified. Methamidophos was weakly adsorbed to soil which, combined with its high aqueous solubility, suggests a high leaching potential. However its rapid breakdown in the environment suggests that it has little tendency to leach. Methamidophos has a relatively high vapor pressure (1.7 - 3.5 mm Hg, at 20 and 25 C, respectively), suggesting volatility but, because of its high water solubility (>1.2 x 10^6 ppm at 20 C) it has a low K_H (<3.22 x 10^{-12}) suggesting low field volatility. Except where stated, all of the studies were acceptable to DPR.

Hydrolysis

Methamidophos is stable to hydrolysis under sterile, acidic conditions, becoming more labile as pH is increased. In a study employing ^{14}C-SCH_3 labeled methamidophos, hydrolysis occurred in the dark at pH5, pH 7 and pH9 at 25°C with $t_{1/2}$ values of 309, 27 and 3.2 days, respectively (Chopade, 1985a). The hydrolysis products identified were *S*-methyl phosphoroamidothioate, *O,S*-dimethyl phosphorothioate and dimethyl disulfide.

Photolysis - Aqueous

The photolysis of ^{14}C-SCH_3 labeled methamidophos was measured at pH5, under natural and simulated sunlight (Chopade, 1985b). This pH was chosen because methamidophos is hydrolytically stable at pH5. The field site was Stilwell, KS (39°N) during August/September. Photolysis showed first order kinetics and under natural sunlight, the t_2 was *ca.* 90 days whereas under simulated sunlight (continuous light) the t_2 was 37 days. The principal degradates were *S*-methyl phosphoroamidothioate and *O,S*-dimethyl phosphorothioate.

Photolysis - Soil

The photodecomposition of ^{14}C-SCH_3 labeled methamidophos was measured by exposing a pH5 solution on thin layers of sandy loam soil to simulated sunlight (Chopade and Freeseman, 1985). Degradation followed first-order kinetics and the t_2 was 42h (1.8 days) under continuous light, equivalent to 101h (4.2 days) after adjusting for hours of sun/day. The principal degradates were *S*-methyl phosphoroamidothioate and *O,S*-dimethyl phosphorothioate.

Soil Metabolism - Aerobic

A preliminary, non-GLP study showed that methamidophos degraded rapidly in soil, in the dark, under aerobic conditions (Leary and Tutass, 1968). Using ^{14}C-SCH_3 labeled material, in silt, loam and sandy soils, the t_2 values were 1.9, 4.8 and 6.1 days at 21°C, respectively. The principal degradates were $^{14}CO_2$ (70%) and, of the ^{14}C which was extractable using acetone, *O,S*-dimethyl phosphorothioate. Minor amounts were also tentatively identified as parent, amino acids and carbohydrates. In a more recent study, [^{14}C-SCH_3]-methamidophos was incubated in the dark at 25°C with sandy loam soil at 75% of soil moisture content (Panthani, 1989a). The t_2 was 14h (0.583 days). After 5 days, the principal degradates were $^{14}CO_2$ (49%) and volatile organics (6%), which comprised methyl mercaptan, dimethyl sulfide and dimethyl disulfide. Extraction of ^{14}C from the soil using acetonitrile identified *S*-methyl phosphoroamidothioate, but *not O,S*-dimethyl phosphorothioate, which had been found in the earlier study.

Soil Metabolism - Anaerobic

As for aerobic soil metabolism, a preliminary, non-GLP study showed that methamidophos degraded rapidly in soil, in the dark, under anaerobic conditions (Pack, 1985). After 30 days of receiving a constant flow of oxygen-free nitrogen, a sandy loam soil sample was fortified with 10 ppm ^{14}C-SCH_3-labeled methamidophos. Samples were taken at 8 time intervals and the t_2 was determined to be 11 days. The principal degradates were $^{14}CH_4$ (50%) and $^{14}CO_2$ (8%) and, of the ^{14}C which was extractable from the soil using methanol, a single metabolite was found. This was neither O,S-dimethyl phosphorothioate nor *S*-methyl phosphoroamidothioate, the two main organic degradates under aerobic conditions. It was concluded that this metabolite was probably incorporated into the soil or was a precursor of methane. In a more recent study (Panthani, 1989b), a more current protocol was used: first, [^{14}C-SCH_3]-methamidophos was incubated aerobically in the dark at 25°C with sandy loam soil at 75% of soil moisture content for 14h (aerobic $t_{1/2}$); then, anaerobic conditions were created and maintained by flushing the system with nitrogen. Soil samples were analyzed at 0, 14h, 16, 31 and 61 days. Under these conditions, the anaerobic $t_{1/2}$ was 4 days. *S*-methyl phosphoroamidothioate, the major aerobic metabolite to be identified using [^{14}C-SCH_3]-methamidophos, did not degrade under anaerobic conditions. It comprised essentially

all of the ^{14}C that was extractable from soil over the 16 - 61 day period. During the study the principal volatile degradates were $^{14}CO_2$ (10%) and volatile organics (15%), which were identified by GC as methyl mercaptan, dimethyl sulfide and dimethyl disulfide. It was concluded that the major (85%) volatile organic was a derivative of methyl mercaptan. It was suggested that the formation of $^{14}CH_4$ could have occurred during the early anaerobic period, based on the previous report and low total recovery (78 - 87%).

Soil Adsorption

The leaching potential of methamidophos was evaluated by incubating [^{14}C-OCH_3]-methamidophos with 5 soil types (sand, sandy loam, sandy clay loam, silt loam and clay loam) and measuring binding by the batch adsorption/desorption method (Pack and Verrips, 1988). Freundlich soil adsorption coefficients (K_d) and K_{oc} (K_d adjusted for % organic carbon content) were determined for each soil. The K_d values were all below 0.029, except for the clay loam where the value was 0.029; similarly, the K_{oc} values were all below 0.88, except for the clay loam where the value was 0.88. The percentage of organic carbon in these soils ranged from 0.1 to 3.3% (for the clay loam). It was concluded that methamidophos is very weakly adsorbed by soil. This suggests that methamidophos may have a high leaching potential.

Volatility

During 2002, air monitoring was conducted by Air Resources Board of Cal/EPA at 5 sites in Fresno Co, CA. These were selected as high use locations. A total of 168 air samples were analyzed and of these, 10 were >3.5 ng/m^3 (EQL or estimated quantitation limit), 7 were <3.5 but >0.86 ng/m ^{3} (MDL or method detection limit) and 151 were <MDL. The peak concentration measured was 16 ng/m ^{3} (ARB, 2003).

Plant Metabolism/Residues

Methamidophos is readily absorbed by tomato plants following application to tomato leaves (Lubkowitz *et al.*, 1973a). Within 6h of application of [^{32}P]-labeled methamidophos, it was impossible to dislodge any radioactivity by washing with water. In tomatoes grown in the field, dosed with [^{32}P]- and/or [^{14}C]-labeled methamidophos, the initial loss of label from the leaf was rapid, followed by a slower phase, which was probably associated with metabolism (Hortler *et al.*, 1973).There was some movement of label from the leaf to the fruit on the same branch but little or no movement between branches was detected. Crisp *et al.* (1974) found that phloem transport was responsible for the bulk of the movement of methamidophos.

In a residue study on tomatoes ((Lubkowitz *et al.*, 1973b) the application of 0.5 kg/ha resulted in levels of 0.072 ppm at 2 weeks, 0.068 ppm at 4 weeks, 0.013 at 6 weeks and <0.01 at 8 weeks. Similarly, in 5 studies on potatoes, residues were <0.01 ppm at 15 or 30 days (Mobay, 1973a-c, 1976, 1977). Table 1 presents a summary of crop residue data. These data were used for the dietary exposure estimation in Section IX.B. on page 105.

Table 1. Summary of methamidophos residue data.[1/]

RAC	Tolerance, ppm	Residue acute, ppm[2/]	Residue chronic, ppm	%-Crop treated
Cottonseed, meal[3/]	0.1 (N)[6,7/]	0.044 (n=32)	0.042(N)	15%
Cottonseed, oil[3/]	0.1 (N)[7/]	0.01 (n=4)	0.005	15%
Potato[4/]	0.1 (N)	0.0091 (n=1401)	0.0019	30%
Tomato[5/]	1[8/]	0.082 (n=849)	0.013	20%; 85%

1/ data from Appendix B.
2/ PHI: 7 days, tomato, 14 days potato and 50 days, cottonseed; (n=no. of composite samples analyzed)
3/ data from Bayer, 1989 and 1998; LOQ = 0.01 ppm
4/ data from USDA - PDP program, 1994-5; Limit of detection (LOD) = 0.003 ppm
5/ data from USDA - PDP program, 1996-7; Limit of detection (LOD) = 0.001 ppm
6/ negligible residue
7/ tolerance increased to 0.2 ppm in IRED of April, 2002 (USEPA, 2002c).
8/ tolerance increased to 2 ppm in IRED of April, 2002 (USEPA, 2002c).

III. TOXICOLOGY PROFILE

Acceptability of the studies by DPR (except for genotoxicity studies) where noted, is determined according to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines. The acceptability of the genotoxicity studies by DPR is based on the guidelines of the Toxic Substances Control Act (TSCA), published in 1985 (Federal Register, 1985). Wherever appropriate, the term NOEL (no observed effects level) is used to refer to adverse effects and it is therefore synonymous with "NOAEL" (no observed adverse effects level). Developmental toxicity studies were also considered for estimating acute toxicity because it is assumed that certain effects on the fetus during pregnancy could result from a single day=s exposure. Cholinesterase (ChE) inhibition was the most sensitive endpoint; sources of enzyme generally included plasma, RBC and brain. A Summary of Toxicology Data is included as Appendix A.

A. PHARMACOKINETICS

Summary

Excretion of ^{14}C in the rat via the urine and expired air within 5 days following gastric intubation with ^{14}C methamidophos was 50%. Most of the excretion occurred in the first 24h. The feces contained *ca.* 1.5%, over 5 days. Assuming that the ^{14}C in the feces was not absorbed, >98% absorption took place from the gut, suggesting that oral absorption was essentially complete. Following intravenous injection in the rat, elimination of radiolabel was fairly rapid; >80% cleared the blood in 30 - 40 sec. and peak levels were present in most tissues within 60 sec. Urinary excretion mostly as parent was 47% and $^{14}CO_2$ loss was 34%, in the first 24h,. About 6% of the ^{14}C remained in the carcass at 7 days, but because this was evenly distributed throughout the body, it was attributed to the incorporation into body tissues. Metabolism in the rat occurred initially at the amine

group, which was replaced by a hydroxyl, followed successively by cleavage of the thio-methyl and methoxy groups, leaving phosphoric acid. None of these biotransformation products is likely to be an inhibitor of ChE with the possible exception of the (parent) hydroxylamine (N-hydroxymethamidophos).

Oral-Rat

Methamidophos, labeled as either the $^{14}CH_3S$ or with ^{32}P, was administered as a single dose to SD rats by gastric intubation at 0.16 to 0.21 mg/kg, as an aqueous solution (Crossley & Tutass, 1969). For the (preliminary) ^{14}C experiments, only females were used and for the ^{32}P studies, rats of both sexes were employed. Rats were pre-conditioned in the latter experiments by the administration of 0.5 mg/kg/day of unlabeled methamidophos for 2 weeks before and on the days following the ^{32}P treatment. Several rats were used for the ^{14}C experiments and two rats per sex for each time point (1, 3, 7, 14, 21 and 28 days) for the ^{32}P experiments. Approximately 75% of the ^{14}C was recovered over 5 days, in the urine (11%), breath (39%, as $^{14}CO_2$), carcass (23%) and feces (1.5%). The bulk of the label was lost within 24h. The urine, carcass and feces contained a mixture of parent and DMPT (*O,S*-dimethyl phosphorothioate). Using ^{32}P, over 70% was excreted in the urine. Two further metabolites were identified: methyl dihydrogen phosphate and phosphoric acid, thus defining the metabolism of methamidophos. It was concluded that hydrolysis occurred sequentially at the P-N bond, then the P-SMe bond and subsequently, the P-OMe bond, yielding hydroxides in each case, and culminating in phosphoric acid (H_3PO_4). There was no storage of radiolabel in any particular tissue and no apparent differences between the sexes. It was concluded that the radiolabel remaining in the body after about 3 days had been largely incorporated into the tissues after complete breakdown. The residual ^{14}C in the body after 7 days was below 0.004 ppm.

Intravenous-Rat

Methamidophos ($^{14}CH_3S$) at 8 mg/kg/0.5 ml saline was injected into the female rat tail vein (Gray *et al.*, 1982). This dose was sufficient to cause clinical signs but was below the LD_{50} (10.1 mg/kg, range 8.1 - 12.6). All rats survived until sacrifice. The tissue distribution, excretion and ChE inhibition were measured in rats killed at 1 min. to 24h after dosing. Mild tremors and salivation were observed within 5 min. of dosing and tremors became severe by 10 - 12 min. Prostration was noted at 20 - 60 min., recovery after 6 - 8 h. and rats appeared normal by 24 h. Tissue distribution of ^{14}C was rapid, peaking within 1 min. in most tissues but taking 10 min. for thymus and muscle. Tail vein cannulation experiments showed that *ca.* 80% of ^{14}C cleared the blood within 30 - 40 sec. and after 5 min. it was considered that the bulk of label in the blood represented excretion. Within 24 h, 47% had been excreted in urine and 34% as $^{14}CO_2$; at 7 days, 6.4% was found in carcass, <5% in feces and 0.7% in cage washings. The inhibition of ChE in spinal cord/brain stem, cerebellum and cerebrum was maximal at 30 - 60 min, being 80 - 85% inhibited. At 4 h, recovery was noted (47 - 57% ChE inhibition) and by 48 h, inhibition was 13 - 25% and animals appeared to be unaffected. Extraction of ^{14}C in brain, blood and liver of rats killed at 30 min. showed parent only, with a brain concentration of 50 nmol./g. When this concentration (equivalent to *ca.* 50 M) was incubated *in vitro* with rat brain, it produced >80% inhibition within 20 min. The distribution and AChE experiments, considered together, suggest that methamidophos

does not require bioactivation.

B. ACUTE TOXICITY

Summary:

Methamidophos and its Monitor7-4 formulation are very acutely toxic orally, with similar LD_{50} values in the rat and mouse, of 13 to 16 mg/kg, for both sexes (Danger, Category I). There was little or no dermal and eye irritation resulting from methamidophos dosing in the rabbit and no dermal sensitization in the guinea pig (Category IV). Dermal LD_{50} values were similar in the rabbit and rat, being122-162 (male) and 69-108 (female) mg/kg (Danger, Category I). By inhalation (4h) in the rat, methamidophos aerosol had a LC_{50}=63 (M) to 76 (F) mg/m^3 (LD_{50}=11 to 13 mg/kg) (Danger, Category I). The Monitor7-4 formulation had similar oral toxicity to the technical material, with LD_{50} values of 16.5 (M) and 21.3 (F) mg/kg/day in the rat. Dermal toxicity in the rabbit was lower than for technical, however, with LD_{50} values of 987 (M) and 516 (F) mg/kg/day (Category II). By inhalation, formulated methamidophos had (1h) LC_{50} values of 650 (F) to 779 (M) mg/m^3 (LD_{50}=27 to 33 mg/kg) (Warning, Category II). The clinical signs included the classic acute cholinergic ones associated with AChE inhibition. There appeared to be little difference in sensitivity between the sexes or between species, wherever comparisons can be made. The acute toxicity of methamidophos is summarized in Table 2.

Systemic Effects

Male Wistar rats (7-8 wks. old, 180 g, unfasted) were dosed with technical methamidophos by a single gavage at 10 to 31.5 mg/kg, dissolved in water (10 ml/kg), in an experiment conducted according to OECD guidelines. (Bayer,1990a). The racemic mixture () of 95.3% purity was administered to 5 groups of 5 rats, the D(+) to 7 groups of 5 rats and the L(-) to 6 groups of 5 rats. The clinical signs were identical for each isomer (or mixture) and initially consisted of trembling spasms, which commenced within 12 to 22 min.(), 29 to 52 min.(+) or 9 to 18 min.(-), followed by salivation and lacrimation, labored breathing, bristling fur and apathy. Mortality was rapid on Day 1, after 23 min. to 3 h., 35 min. to 4 h. and 21 min onwards, for the various isomers, respectively. Body weight loss was observed at 4 days, and this subsequently recovered. Gross pathological examination revealed patchy and distended lungs and dark liver in dying animals and no compound-related abnormalities in survivors, which were sacrificed at 14 days. Acute oral LD_{50} values were 14 or 16 mg/kg (Table 2).

Sprague Dawley rats (196-388 g, fasted) were dosed with Monitor7-4 (42.7% A.I., by wt.) by gavage at 10 to 27.4 (M) or 13 to 28.5 (F) mg/kg, dissolved in Carbowax (Hixson, 1980). Four dosage groups of each sex were used. The clinical signs were similar to those reported, above, for the technical material. Signs were apparent within 12 h of dosing and death occurred within one day. Acute oral LD_{50} values are given in Table 2.

Methamidophos technical was applied to the shaved skin of NZW rabbits (Mobay, 1980a). Groups of four rabbits were administered one of 6 doses from 30 to 342 mg/kg (males) and four doses, from 30 to 101.3 mg/kg (females). Clinical signs included

diarrhea, salivation, tremors, ataxia, constricted pupils and ataxia, generally commencing within 30 to 60 min. of dosing. Mortality occurred 12 h. to 2 days after dosing. Gross pathological examination revealed no abnormalities in several of the dosed animals which died, but in others there was a thin fundus of the stomach and fluid-filled abdominal cavity. Dermatitis was noted in both dosed and control rabbits and so was not treatment-related. Similar dermal toxicity was found for the rat (Heimann, 1981). Acute dermal LD_{50} values are given in Table 2.

Monitor7-4 (42.7% A.I., by wt.) was applied (undiluted) to the shaved backs of NZW rabbits (Mobay, 1979) that had their skin abraded. Groups of four rabbits were administered one of 4 doses from 304 to 2293 mg/kg (males) and seven doses, from 304 to 1170 mg/kg (females). Clinical signs were similar to those reported above and commenced within 1 h to 4 h of dosing. Mortality occurred between 19 and 28 h after dosing. Histopathological examination showed enteritis, which was probably secondary to severe diarrhea and pulmonary congestion. Acute dermal LD_{50} values are in Table 2.

Young SD rats (172 - 272 g) were exposed to an aerosol of technical methamidophos, (70.5% pure) nose-only for 4 h, at a range of concentrations of 19.0 to 172.5 mg/m^3 (anal.) (Sangha, 1984). Groups of 10 rats of either sex were exposed to 5 (M) or 7 (F) concentrations. The mass median diameter (MMD) was 0.32 - 0.88 m (average MMD, 0.53 m.) All rats showed typical cholinergic signs during the dosing period, indicating a LOEL of 19 mg/m^3 (and a NOEL of <19 mg/m^3). Signs commenced during the (4h) dosing period and mortality occurred within the first two (M) or five (F) days. The main gross pathological lesion observed was dark or red lungs. Acute inhalation LD_{50} values are given in Table 2.

Young SD rats (168 - 249 g) were exposed to an aerosol of Monitor7-4 (40% A.I., by wt.) head-only for one hour, at a range of concentrations of 344 to 1137 mg formulation/m^3 (anal.) (Sangha, 1983). Groups of 10 rats of either sex were exposed to 5 (M) or 4 (F) concentrations. The mass median diameter (MMD) was 1.2 - 1.7 m. All rats showed typical cholinergic signs, plus runny eyes and nose, during the dosing period, indicating a LOEL of 334 mg/m^3 (and a NOEL of <334 mg/m^3). Signs commenced during the (1h) dosing period and mortality occurred within the first four days. The main gross pathological lesions observed were pulmonary lesions. Acute inhalation LD_{50} values are given in Table 2.

The toxicity of (3) impurities of methamidophos was assessed in the rat and mouse by oral gavage (Mobay, 1968; 1972). Each of these is an organophosphate and therefore of potential toxicological concern. However, the toxicity was considerably less than methamidophos, with LD_{50} values of 112 to 708 mg/kg (Table 2).

C. SUBCHRONIC TOXICITY

Summary:

The subchronic studies using methamidophos are described in Section H, Neurotoxicity; the results are summarized in Table 24.

Table 2 Acute Toxicity of Methamidophos.

Route/Species	Sex	Dosage/Effect	Category	Reference[a/]
		TECHNICAL		
Oral LD_{50}				
Rat	M	()16 (13.3 - 19.2) mg/kg	I	1
	M	D(+) 14 (12.8 - 15.7) mg/kg	I	1
	M	L(-) 16 (13.1 - 20.0) mg/kg	I	1
Rat	M	(95%,()) 15.6 (9.8 - 25.0) mg/kg	I	15
	F	(95%,( )) 13.0 (9.0 - 18.9) mg/kg	I	15
Mouse	F	15.2 (11.8 - 19.7) mg/kg	I	14
Hen	F	25 (19.4 - 32.7) mg/kg	I	2
Dermal LD_{50}				
Rabbit	M	122 (53 - 296) mg/kg	I	3
	F	69 (45 - 127) mg/kg	I	3
Rat	M	162 mg/kg	I	6
	F	108 mg/kg	I	6
Inhalation LC_{50}				
Rat	M	63.2 (52-79) mg/m^3 (4h); 10.6 mg/kg[b]	I	7
Rat	F	76.5 (62-128) mg/m^3 (4h); 12.8 mg/kg[b]	I	7
Skin Irritation:rabbit	M	none	IV	8
Eye Irritation:rabbit	M	mild	IV	8
Skin Sensitization:guinea pig	M	none	IV	9
		Monitor7 4 (18.5% methamidophos)		
Oral LD_{50}				
Rat	M	16.5 (14.6 - 18.7) mg/kg	I	4
	F	21.3 (18.9 - 24.0) mg/kg	I	4
Inhalation LC_{50}				
Rat	M	779 mg/m^3 (1h); 32.7 mg/kg[b]	II	5
	F	650 mg/m^3 (1h); 27.3 mg/kg[b]	II	5
Dermal LD_{50}				
Rabbit	M	987 (590 - 1655) mg/kg	II	10
	F	516 (493 - 539) mg/kg	II	10
Skin Irritation:rabbit	M/F	mild	IV	11
Eye Irritation:rabbit	M/F	mild	IV	12
Skin Sensitization:guinea pig	M	none	IV	13
		Impurities		
		***O,O,S*-trimethyl phosphate**		
Oral LD_{50}				
Rat	M	229 (178-295) mg/kg	II	16
Mouse	M	112 (104-121) mg/kg	II	16
		***O,O*-dimethyl phosphoramidothioate**		
Oral LD_{50}				
Rat	M	633 (555-735) mg/kg	III	17
Rat	F	549 (525-573) mg/kg	III	17
		***O,O*-dimethyl phosphorodithioate**		
Oral LD_{50}				
Rat	M	694 (568-848) mg/kg	III	17
Rat	F	708 (539-931) mg/kg	III	17

a/ (1) **Bayer, 1990a**. (2) **Bayer, 1990b**. (3) **Mobay, 1980a**. (4) **Hixson, 1980** (5) **Sangha, 1983** (6) **Heimann, 1981.** (7) **Sangha, 1984**. (8) **Mobay, 1980b**. (9) **Chevron, 1984**. (10) **Mobay, 1979** (11) **Mobay, 1984a** (12) **Mobay, 1984b** (13) **Miles, 1987** (14) **Esber, 1983** (15) **Chevron, 1968.** (16) **Mobay, 1972.** (17) **Mobay, 1968.**
b/ based on a default inhalation rate of 0.175 L/min. for a 250 g rat (U.S. EPA, 1988).

D. CHRONIC TOXICITY AND ONCOGENICITY

Summary:

Reduction of group mean body weight compared with controls occurred in the rat and mouse, but not the dog. Similarly, there was a significant increase in relative brain weight at the HDT (highest dose tested) in these rodents, in both sexes, but not in the dog, which could have been related to the body weight reduction. Only in the rat was there an increase in absolute brain weight, in both sexes, at the HDT. In all three species, there was clear evidence of inhibition of ChE in plasma and erythrocytes, and of AChE in the brain. The LOEL for the inhibition of brain AChE was 2 ppm, equivalent to 0.1, 0.3 or 0.06 mg/kg/day in the rat, mouse and dog, respectively. There were few clinical signs at the doses employed in these studies. Benign and malignant tumor incidence did not increase with dose, in either sex; neither was an earlier tumor onset apparent. An estimated NOEL of 0.02 mg/kg/day, based on 11-18% inhibition of brain AChE activity at 0.06 mg/kg/d (LOEL) in the 1-yr. dog study, was used as the critical value for chronic risk characterization.

Dietary-Rat

Methamidophos (70% purity) was fed in the diet to F344 rats (60/sex/group) for 106 weeks, at 0, 2, 6, 18 or 54 ppm, equivalent to 0.095, 0.288, 0.848 or 2.847 mg/kg/day for males and 0, 0.115, 0.351, 1.056 or 3.49 mg/kg/day for females (measured) (Hayes, 1984a). An interim sacrifice was conducted at 52 weeks on 10 rats/sex/dose. In order to justify dose selection, a 5-week pilot study was also submitted in which 5 rats/sex/dose were subjected to 0, 1, 2, 4, 8, 16, 32 or 64 ppm methamidophos. Reduced group mean body weight compared with controls was reported at 54 ppm, in both sexes, although remaining >84% of control, without an effect on food intake. Relative brain weight was increased in both sexes,16% (M) and 20% (F), at 54 ppm ($p<0.05$, Duncan=s test), with no signs of abnormal histopathology. This may have been partly secondary to decreased body weight because absolute brain weight was elevated by only 2.1% (M) and 2.8% (F), both significant at $p<0.05$, at 54 ppm. There was no evidence of compound-related oncogenicity. Clinical signs, which were seen in most animals at the two highest doses in the main study but in none of the rats in the supplemental one, included loose stools, urine-stained fur, rough coat and skin lesions. The LOEL and NOEL for clinical signs were thus18 ppm and 6 ppm (~0.3 mg/kg/day), respectively.

ChE (including brain AChE) was inhibited in both sexes at all dose levels, in the main study (Table 3). At 6 ppm, group mean ChE inhibition (plasma, RBC and brain) was 26% to 51% ($p<0.001$) at 12 and 24 months. At 2 ppm, the inhibition of group mean plasma, RBC (ChE) and brain AChE was 28%, 13% and 12% (males) and 11%, 19% and 7% (females) for the three enzymes, respectively, after 24 months. This was also highly significant ($p<0.001$) for at least one sex at one or both time points. Inhibition of brain AChE of more than 10% is considered an adverse effect by DPR, Medical Toxicology Branch (Patterson, 2002). In the pilot study, reduced body weight was reported at 64 ppm, with no evidence of clinical signs. However, there were too few animals in this pilot study for definitive risk assessment. It was concluded that 2 ppm or *ca.* 0.1 mg/kg/day was the LOEL for chronic toxicity in the rat. After the pilot study review, Hayes (1984a) was accepted by DPR.

Table 3 Mean inhibition of cholinesterase, as % depression vs. control, by methamidophos in the F344 rat at (12 and) 24 mon., in a dietary study.[1,2/]

ChE assay	2	6	18	54 ppm
Blood plasma				
M	(18***) 28**	(38***) 47***	(62***) 70***	(84***) 91***
F	(27***) 11 n.s.	(51***) 26**	(78***) 71***	(93***) 91***
RBC				
M	(16) 13*	(42***) 32***	(66***) 65***	(79***) 75***
F	(12***) 19***	(39***) 36***	(66***) 68***	(70***) 81***
Brain				
M	(10***) 12***	(42***) 39***	(67***) 64***	(77***) 79***
F	(24***) 7 n.s.	(45***) 31***	(70***) 64***	(79***) 75***

1/ data from Hayes, 1984a.
2/ n = 10/sex/dose/time.
* different from control, p<0.05 (Student=s t test, using original data)
** different from control, p<0.01 (Student=s t test, using original data)
*** different from control, p<0.001 (Student=s t test, using original data)

Dietary-Mouse

Methamidophos technical (70% purity) was fed to CD mice (60/sex/level) at dietary levels of 0, 1, 5 or 25 ppm (0.14, 0.67 or 3.47 mg/kg/day, males, and 0.18, 0.78 or 3.98, females, measured) in a 106-week study (Hayes, 1984b). An interim sacrifice was conducted at 53 weeks on 10 mice/sex/dose. Also, a supplementary submission was made in which 20 mice/sex/dose were fed methamidophos at 2 to 100 ppm for 6 weeks (Hayes, 1994b). The main purpose of the supplementary study was to define effects of methamidophos on ChE and AChE (brain). In the main study, the reduction in group mean body weights at 25 ppm at 52 weeks was 4.9% (M) and 5.8% (F), not significantly different from controls. However, group mean body weights were depressed significantly, after 53 and 106 weeks, at 25 ppm (p<0.05, Duncan=s test). After 53 weeks, group mean body weights were always >86% of control weights. At 106 weeks, the reduction in body weight was 7.7% (p<0.05) and 11% (o<0.05), for males and females, respectively. Relative brain weight was increased in both sexes, by 11% (M) and 15% (F), at 25 ppm at 106 weeks (p<0.05), with no indications of abnormal histopathology. The effect on relative brain weight could have been secondary to the fall in body weight, as suggested by the authors of the report, because absolute brain weight was completely unaffected by methamidophos at 25 ppm (0%, M and 0.6%, F). Mean food consumption was significantly (p<0.05) reduced, by 12% (M) and 17% (F) at 25 ppm, consistently so from week 78, thus explaining the fall in body weight. There were no compound-related increases in tumor incidence or reduction in latency.

The inhibition of ChE was reported for plasma, erythrocyte (RBC) and brain (Table 4). In the 6-week supplemental study (Hayes, 1994), methamidophos was fed at 0, 2, 10, 50 or 100 ppm (equivalent to estimated dosages of 0.3, 1.5, 7.5 and 15 mg/kg/day, respectively). It inhibited all three enzymes, dose-dependently, at all dose levels, in both sexes. Blood samples were drawn at 1-week, 2-weeks, 5-weeks and 6-weeks and

plasma and RBC ChE was measured. Brain AChE was determined only at the 6-week sacrifice. At 2 ppm, the group mean inhibition was 3%, 0% (1-week) for males and 24%, 29% (1-week) for females for plasma and RBC ChE, respectively. At 6-weeks, the group mean inhibition was 33%, 21% and 20% (males) and 19%, 25% and 29% (females) for plasma, RBC and brain ChE, respectively. It is therefore concluded that 2 ppm was the LOEL for chronic toxicity in the mouse, equivalent to 0.3 mg/kg/day. The only clinical signs, in either the 106-week or 6-week study, were observed at 100 ppm: wet abdomens (two males) and a black tarry substance around the anus (one female). Thus, the LOEL and NOEL values for clinical signs were 100 ppm and 50 ppm (~7.5 mg/kg/day), respectively. Following the submission of this supplementary study, the Hayes (1984b) study was considered acceptable to DPR.

Table 4. Mean inhibition (% depression vs. control) of cholinesterase by methamidophos in the CD mouse at (1-wk and) 6-wk in a dietary study[1,2/]

ChE assay	2	10	50	100 ppm
Blood plasma				
M	(3%) 33%*	(58%***) 66%***	(90%***) 89%***	(90%***) 93%***
F	(24%**) 19%	(59%***) 63%***	(92%***) 86%***	(90%***) 94%***
RBC[3/]				
M	(-) 21%**	(30%**) 62%***	(83%***) 87%***	(74%***) 85%***
F	(29%***) 25%**	(43%***) 58%***	(78%***) 79%***	(69%***) 87%***
Brain				
M	20%***	58%***	87%***	90%***
F	29%***	63%***	87%***	89%***

1/ data from Hayes, 1994.
2/ n = 5/sex/dose/time.
* ** *** different from control, p<0.05, p<0.01, p<0.001 (Student=s t test, original data)

Dietary-Dog

In a one-year dietary study, methamidophos (70% purity) was administered to beagle dogs (6/sex/level) in the feed at 0, 2, 8, or 32 ppm, equivalent to measured dosages of 0, 0.06, 0.24 or 0.90 mg/kg/day, for males and 0, 0.06, 0.22 or 0.88 mg/kg/day for females (Hayes, 1984c). The results of a 90-day subchronic feeding study at doses of 0, 1.5, 5 or 15 ppm were also submitted in order to justify the selection of the dose range. Mean body weight was not significantly affected by treatment, in either sex. There was an increase in lacrimation for both sexes at 8 and 32 ppm, becoming significant (p<0.05) only when the sexes were combined (Table 5). Other clinical signs, such as salivation, diarrhea and vomiting also increased, though not significantly. There were no significant changes in absolute or relative organ weights, in either sex. Neither was there any abnormal histopathology that could be related to treatment. Plasma, erythrocyte and brain ChE were inhibited at all doses (Table 5). Because of the inhibition of brain ChE (18%, M, p<0.001; 11% F, p<0.05) at 2 ppm, (or 0.06 mg/kg/day) this dose was considered the LOEL for chronic toxicity. An estimated NOEL was obtained by dividing the LOEL by 3, to give 0.02 mg/kg/day. The justification for using 3 instead of 10 is discussed in the Hazard Identification and Risk Appraisal Sections. This NOEL was used as the critical one for chronic dietary risk assessment. This report, with dose

justification, was considered acceptable by DPR.

Table 5. Mean inhibition of cholinesterase (% depression vs. control) by methamidophos at (1-mon.) 1-yr. and clinical signs in the beagle dog, dietary study[1,2/]

ChE Assay	0	2	8	32 ppm
Blood plasma				
M	---	(5.6%) 20%	(26%**) 35%***	(44%***) 56%***
F	---	(2.8%) 12%	(13%) 7%	(31%**) 39%***
RBC				
M	---	(7.9%) 10%	(56%***) 62%***	(73%***) 81%***
F	---	(16%) 11%	(47%**) 56%***	(74%***) 83%***
Brain				
M	---	18%***	55%***	71%***
F	---	11%*	45%***	66%***
Clinical signs				
Lacrimation				
M	1/6	3/6	3/6	4/6
F	1/6 a/	1/6	4/6	3/6
Combined	2/12	4/12	7/12*	7/12*
Salivation				
M	0/6	0/6	1/6 b/	3/6 d/
F	0/6	0/6	0/6	0/6
Combined	0/12	0/12	1/12	3/12
Diarrhea				
M	1/6	1/6 c/	2/6	2/6
F	0/6	0/6	0/6	3/6
Combined	1/12	1/12	2/12	5/12
Vomiting				
M	1/6	2/6	2/6	4/6
F	1/6	0/6	1/6	1/6
Combined	2/12	2/12	3/12	5/12

1/ data from Hayes, 1984c. 2/ n = 6 dogs/sex/dose/time point

* different from control, p<0.05 (Student=s t test, ChE inhibition, original data)

* different from control, p<0.01 (Student=s t test, ChE inhibition, original data)

*** different from control, p<0.001 (Student=s t test, ChE inhibition, original data)

* different from control, p<0.05 (Fisher=s exact test, incidence of clinical signs)

a/ this female also exhibited vomiting

b/ this male also exhibited lacrimation and diarrhea

c/ this male also exhibited lacrimation; d/ also exhibited lacrimation and vomiting.

Table 6 Summary of chronic effects caused by methamidophos.

Species	Route	Effect	LOEL	NOEL	Ref.
Rat, 2-yr.	diet	ChE inhibition (plasma, RBC, brain) Clinical signs Absolute & relative brain wt. No compound-related in tumors	0.1[c/] 0.85 2.8	------ 0.29 0.85	1[b/]
Mouse, 2-yr.	diet	ChE inhibition (plasma, RBC, brain) Relative brain wt. Clinical signs No compound-related in tumors	0.3[d/] 3.5 15	------ 0.67 7.5	2,3[b/]
Dog, 1-yr.	diet	ChE inhibition (plasma, RBC, brain) clinical signs (lacrimation)	0.06[e/] 0.22	0.02[f/] 0.06	4[b/]

a/ References: 1 Hayes, 1984a; 2 Hayes, 1984b; 3 Hayes, 1994; 4 Hayes,1984c
b/ study acceptable to DPR, according to FIFRA guidelines.
c/ inhibition of ChE was 13%(M) - 19%(F) for RBC, 7%(F) - 12%(M) for brain
d/ inhibition of ChE was 21%(M) - 25%(F) for RBC, 20%(M) - 29%(F) for brain
e/ inhibition of ChE was 10%(M) - 11%(F) for RBC, 11%(F) - 18%(M) for brain
f/ estimated NOEL (LOEL/3)

E. GENOTOXICITY

Summary

Methamidophos has been examined for genotoxic effects in both mammalian and microbial cells. These assays included: the Salmonella and CHO/HGPRT gene mutation assays (S9), in vitro; in vivo and in vitro chromosome aberration assays, in mouse and CHO cells, and in mouse micronucleus and dominant lethal assays, in vivo; in DNA repair and unscheduled synthesis assays in E. coli and in rat primary hepatocytes. The vast majority of the tests were negative for genotoxicity, with only a few positive results. For example, gene mutation was reported in the CHO/HGPRT assay (+S9), in vitro, but only at the HDT, and there was only one trial. In an acceptable study with replicate assays, methamidophos did not cause mutations in this assay. There were no chromosome aberrations in a CHO cytogenetic assay (S9), in vitro. It appears, on balance, that methamidophos has a low potential to be genotoxic to humans. Genotoxicity tests are summarized in Table 7.

Gene Mutation

Methamidophos (73.4% purity) was tested at 16 to 5000 g/plate on *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 with and without S-9 rat liver homogenate activation (Herbold, 1994). The rate of reversion of these histidine auxotrophic strains was measured. No mutagenicity or cytotoxicity was observed. The report was considered unacceptable to DPR, according to TSCA guidelines, but upgradeable with the supply of appropriate analytical data.

In another study (Herbold, 1980), methamidophos (62.6% purity) was tested at 20 to 12,500 g/plate on *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 with and without S-9 rat liver homogenate activation and was not mutagenic. The report was considered unacceptable to DPR and not upgradeable, because of insufficient replicates.

Methamidophos (purity unstated) was tested at 0.1 to 10 g/plate on *Salmonella typhimurium* strains TA98, TA100 TA1535, TA1537 and TA1538 with and without S-9 liver homogenate activation and was not mutagenic (Machado *et al.*, 1982). The report was considered unacceptable to DPR and was not upgradeable, because of a lack of replicates.

The effect of methamidophos (Batch No. 0-06-7009) on forward mutation at the HGPRT (hypoxanthine-guanine phosphoribosyl transferase) locus in CHO cells was measured (Bigger & Sigler, 1993). The concentrations ranged from 1.0 to 5.0 mg/ml, with and without S-9 rat liver homogenate. A possible adverse effect was noted with an increased level of mutation at the HDT, in the presence of metabolic activation. The report was considered unacceptable to DPR and was not upgradeable, because there was only one trial and the concentrations were inadequate.

The effect of methamidophos (72.9% pure) on forward mutation in the HGPRT/ CHO system was measured in another report (Harbell & Jacobson-Kram, 1990). The concentrations ranged from 0.2 to 3.5 mg/ml, with and without S-9 rat liver homogenate. There was no evidence of mutagenicity or cytotoxicity. The report was considered acceptable to DPR.

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Structural Chromosomal Aberrations

Methamidophos (73.5% purity) did not induce chromosomal aberrations in bone marrow cells of CD1 mice following a single gavage dose of 0.8, 2.7, 8.1, 12.1 or 16.1 mg/kg (12/sex/dose) (Esber, 1983). Animals were killed at 6, 24 and 48 hrs. after dosing (4 mice/sex/dose) and cells were analyzed microscopically (50 metaphase cells/mouse). There were no effects on chromosome aberrations. A NOEL of <4.1 mg/kg/day for ChE inhibition and clinical signs was based on a preliminary study. However, Esber, 1983 was considered unacceptable by DPR due to lack of dose and sampling interval justification, no analysis of dosing solutions and inadequate numbers of mice.

Methamidophos (74.3% purity) did not cause dominant lethal mutations in male CD-1 mice following dietary administration for 5 days at doses of 0, 5, 50, or 150 ppm (Eisenlord *et al.*, 1984). On day 5, mice at 150 ppm had reduced food intake (47%) and

body weight (12%), giving a NOEL of 4.6 mg/kg/day. However the study was not acceptable to DPR due to lack of adequate rationale for dose selection and insufficient females, thus making it not upgradeable.

In a dominant lethal study using NMRI/ORIG Kissleg mice, methamidophos (62.6% purity) did not cause any effects on males or (mated) females following a single gavage of 0 or 5 mg/kg (Herbold, 1980). However the study was not acceptable to DPR due to lack of adequate rationale for dose and vehicle selection and no analysis of the dosing material. Because of a lack of a positive control, the study is not upgradeable.

In an *in vitro* chromosomal aberrations test using CHO cells, a treatment-related increase was seen, with or without a rat liver activation system (Hemalatha, 1990). The concentrations of methamidophos (74.5% purity) were 0, 1.87, 2.5, 2.57, 3.15, 3.85, 4.20, 5.14 or 5.25 g/ml. This study was acceptable to DPR. This was the only study of six cytogenicity tests to yield positive results for methamidophos; it is also the only one that was conducted *in vitro* since all the others were *in vivo* (Table 7).

In a micronucleus test, groups of five mice/sex/time point were given a single intraperitoneal injection of methamidophos (75% purity) at 8 mg/kg (Herbold, 1996). Bone marrow samples were collected at 16, 24 or 48 h. and polychromatic erythrocytes (1000/animal) examined microscopically. There was no treatment-related effect on micronuclei incidence. The study was accompanied by a pilot, range-finding study: five mice/sex/dose were given intraperitoneal injections of 8, 10 or 50 mg/kg and clinical signs were evident in all dosed animals, including mortality of 100% at 50 and 20% at 10 mg/kg. The study was acceptable by DPR.

In another micronucleus test, groups of five mice/sex/dose were given two gavage administrations of methamidophos (62.6% purity) at 0, 5 or 10 mg/kg (Herbold, 1981). Bone marrow samples were collected 6 h. after the second dose and polychromatic erythrocytes (1000/animal) examined microscopically. There was no treatment-related effect on micronuclei incidence. The only effect noted during the study was convulsions in one mouse/sex at 10 mg/kg. The study was considered unacceptable by DPR, but upgradeable with analytical data on the dosing solutions and a protocol rationale.

Other Genotoxic Effects

Methamidophos (71.2% purity) was tested at 0.001 to 10 l/ml for unscheduled DNA synthesis (UDS) *in vitro* in primary hepatocytes of the SD male rat (Curren, 1988). There was no evidence of UDS. The study was unacceptable to DPR, but possibly upgradeable, based on a lack of cytotoxicity data, assay protocol, rationale for the concentrations and solvents, and lack of raw data.

The potential for methamidophos to disrupt DNA repair was measured in a Pol test using two strains of *E. coli*, one of which was proficient and the other deficient in DNA repair (Herbold, 1983). The assay was conducted using concentrations of 625 to 10,000 g/plate, with and without a rat liver S-9 metabolic activation system. There was no treatment-related effect. The study was unacceptable to DPR based on the lack of an adequate assay protocol, rationale for the concentrations and solvents used and lack of individual data. The report is not upgradeable because there was no positive control for

metabolic activation and the two strains of *E. coli* were not equally sensitive to the negative control.

Table 7. Summary of genotoxicity tests with methamidophos.

Test		Route	Results	Reference
		Gene Mutation		
Salmonella/ microsome	.S9	*in vitro*	-	Herbold, 1994[c]
Salmonella/ microsome	.S9	*in vitro*	-	Herbold, 1980[b]
Salmonella/ microsome	.S9	*in vitro*	-	Machado *et al.*, 1982[b]
CHO/HGPRT cells	.S9	*in vitro*	+ (+S9)	Bigger & Sigler, 1993[b]
CHO/HGPRT cells	.S9	*in vitro*	-	Harbell & Jacobson-Kram, 1990[a]
		Cytogenetics Assays		
mouse bone marrow		*in vivo*	-	Esber, 1983[b] Eisenlord
mouse dominant lethal		*in vivo*	-	*et al.*, 1984[b]
mouse dominant lethal		*in vivo*	-	Herbold, 1980[b]
CHO cells/chrom. aber.	.S9	*in vitro*	+ (.S9)	Hemalatha, 1990[a]
mouse micronucleus		*in vivo*	-	Herbold, 1996[a]
mouse micronucleus		*in vivo*	-	Herbold, 1981[c]
		DNA Damage/Repair		
rat hepatocytes, UDS	-S9	*in vitro*	-	Curren, 1988[c]
E. coli, DNA repair	.S9	*in vitro*	-	Herbold, 1983[b]

a/ study acceptable to DPR, according to TSCA guidelines.
b/ study unacceptable and not upgradeable.
c/ study unacceptable but upgradeable.

F. REPRODUCTIVE TOXICITY

Summary

The toxicity of methamidophos in a 2-generation rat reproduction study included reduced body weight in adults and pups. However, this was not a result of reduced food intake because this was paradoxically often increased *e.g.* F1 adult males showed an increased food intake ($p<0.05$) of 9-19% from week 1 onwards. The NOEL for adult and pup body weight loss was 1 ppm. There were dose-dependent reductions in ChE activity in both adults and pups, and at 10 ppm and 30 ppm, there were significant reductions in plasma, RBC and brain ChE for both adults and pups of both sexes in both generations. At 1 ppm, there was no significant inhibition of plasma ChE, giving a NOEL of 1 ppm or 0.1 mg/kg/day, for both adults and pups. For RBC ChE at 1 ppm, significant inhibition ($p<0.05$) was only evident in adult males, with 21% (F0) and 18% (F1); an estimated NOEL was therefore considered to be 0.03 mg/kg/day for adult RBC ChE inhibition, with a pup NOEL of 0.1 mg/kg/day. Brain AChE was significantly inhibited ($p<0.05$) only in female adults, but only by 7% (F0) and 5% (F1); for pups, mean brain AChE activity ranged from 3% inhibition to 2% stimulation, relative to control. It was concluded that these low levels of inhibition/stimulation of brain AChE were probably not toxicologically relevant and that 1 ppm (0.1 mg/kg/day) was the NOEL for adults and pups for brain ChE inhibition. There was no evidence of reproductive toxicity.

Dietary-Rat

Methamidophos (69.0 - 76.7% purity) was tested in Sprague-Dawley rats at 0, 1, 10

and 30 ppm (30 rats/sex/dose level) over two generations, with two litters per generation, commencing 10 weeks before the first mating (Eigenberg *et al.*, 1998). The equivalent dosages were: 0.1, 0.9 and 2.4 mg/kg/day (premating); 0.1, 0.7 and 1.9 mg/kg/day (gestation); 0.2, 1.5 and 3.9 mg/kg/day (lactation) and 0.1, 0.9 and 2.5 mg/kg/day (males), based on food consumption data. Reductions in group mean body weights for both adults and pups were reported at 10 and 30 ppm (Table 8). Significantly lower body weight was found at 30 ppm in adults in both matings of each generation in males, reaching a peak of 17% in the F2a at 0 days. Pups also generally showed a significant lower body weight at 30 ppm, peaking at 25% for F1a pups at 21 days. At 10 ppm, body weight was significantly reduced for F1 adults (at each time point) and for F1 and F2b pups, at 21 days but not at 4 days. Because rat pups at 21 days were probably eating (some) solid food, in addition to milk from dams, they could have been receiving an "overdose" of methamidophos relative to the 4 day pups (receiving 100% of their dose from the dam's milk). In addition, the significantly lower body weight for F1a pups at 4 days in the 1 ppm group was not clearly dose-related and is therefore probably not toxicologically relevant. Therefore, the LOEL and NOEL for lower body weight in adults and pups were considered to be 10 ppm and 1 ppm, respectively.

A dose-related inhibition of ChE was reported for plasma, RBC and brain enzymes. At 10 and 30 ppm, the inhibition was statistically significant ($p<0.05$) for both sexes, for each group of adults and pups, for each generation (Table 9). The degree of mean inhibition was 39 - 85% (plasma), 71 - 90% (RBC) and 43 - 81% (brain) for adults and 22 - 65% (plasma), 22 - 69% (RBC) and 18 - 53% (brain) for pups. Because of the statistical significance as well as the magnitude of the inhibition, it is assumed that the inhibition was toxicologically significant. Clearly, based on these ranges, the adults were more severely affected than were pups; this applies to pups of each sex and for each generation. Both the lower and upper ends of the ranges for mean percentage of inhibition were higher for adults than for pups. The statistical and toxicological significance of the inhibition at 1 ppm, however, requires further scrutiny.

At 1 ppm, plasma ChE was not significantly inhibited in adults or pups. The degree of mean enzyme inhibition ranged from 4% inhibition in F0 and F1 females to 13% stimulation in F1 adult males. For pups, the range was from 8% inhibition in F1b pups (F) to 6% stimulation in F2a (F). It is concluded that any apparent inhibition (or stimulation) of plasma ChE at 1 ppm is part of the background "noise" rather than being a "true" methamidophos-induced effect. Thus,10 ppm is considered to be the LOEL and 1 ppm the NOEL, for both adults and pups, for plasma ChE inhibition.

Mean RBC ChE was reduced significantly ($p<0.05$) at 1 ppm for adult males, by 21% in F0 and 18% ($p<0.05$) in F1. In females, mean inhibition was by 11% (n.s.) and 13% (n.s.) in F0 and F1, respectively. Thus, it is concluded that 1 ppm is the LOEL for RBC ChE inhibition, equivalent to 0.1 mg/kg/day. A NOEL value for adult rats has not been estimated for this study. For pups, the inhibition at 1 ppm was not statistically significant. It ranged from 19% inhibition (F1a, F) to 6% stimulation (F2a, F). It is, therefore, considered that 10 ppm is the LOEL and 1 ppm represents the NOEL for pup RBC ChE inhibition.

Brain AChE was inhibited significantly ($p<0.05$) at 1 ppm in adult females, but only by

7% (F0) and 5% (F1). For males, however, the enzyme was apparently stimulated (n.s.) relative to controls, by 6% (F0) and 1% (F1). It is therefore concluded that the statistically significant inhibition of brain AChE in females was not toxicologically significant and is a result of background "noise" in the assay rather than being a result of "true" inhibition. Furthermore, in pups, there was no significant inhibition, with a range of activity ~~of~~ from 2% stimulation (F1a, F) to 3% inhibition (F2a, F and F2b, M), relative to concurrent controls. It is therefore considered that 10 ppm is the LOEL and 1 ppm represents the NOEL for adult and pup brain AChE inhibition.

In conclusion, based on the inhibition of plasma and brain ChE, 10 ppm was established as the LOEL for adults and pups and 1 ppm the NOEL. For RBC ChE, the LOEL for adults was 1 ppm (0.1 mg/kg/day) and the estimated adult NOEL was 0.03 mg/kg/day. The LOEL and NOEL values for RBC ChE inhibition in pups were 10 ppm and 1 ppm, respectively. These LOEL/NOEL values were the same as those for lower body weight in adults and pups, respectively. There were no other significant toxic effects, including clinical signs, reported in the study with the possible exception of an increase in cannibalism, which was significant only for the F1a generation at 30 ppm, and may have resulted from increased numbers of still-born pups at this dose. The study was acceptable to DPR.

The dose selection and rationale for this study were based, in part, on an earlier study (Hixson, 1984). In this study, methamidophos (70.5% purity) was fed to adult (F0) CD rats (26 rats/sex/dose level) at 0, 3, 10 or 33 ppm for two generations, with two litters per generation, dosing commencing 100 days prior to the first pairing. There were no significant effects on adults, giving a parental NOEL of ∟33 ppm. There was decreased mean live litter size and pup growth at 33 ppm and decreased live litters at 3, 10 and 33 ppm, giving a reproductive NOEL of <3 ppm. The study was unacceptable to DPR based on inadequate numbers of litters and rationale for the doses, inadequate necropsy and histopathology and because male reproductive performance could not be assessed.

Table 8. Mean adult and pup body weight (g) following feeding of methamidophos in a 2-generation rat reproductive toxicity study[1/]

Generation/Time (d)	0	1 ppm	10 ppm	30 ppm
F0 adults / F1a (M)[2/]				
0	216	213	217	218
28	331	330	323	310** (6.3%)[4/]
56	382	369	374	358
84	409	405	406	389
112	433	429	427	407
140	451	444	447	419** (7.1%)
F0 adults / F1b (M)[2/]				
0	454	445	450	422** (7.0%)
28	463	455	465	422** (8.9%)
F1 adults/ F2a (M)[2/]				
0	167	160	150* (10%)	138** (17%)
28	318	326	293** (7.9%)	280** (12%)
56	381	394	347** (8.9%)	338** (11%)
84	412	430	383* (7.0%)	370** (10%)
112	439	458	406** (7.5%)	383** (13%)
140	455	483* (+6%)	423* (7.0%)	397** (13%)
F1 adults/ F2b (M)[2/]				
7	459	479	427* (7.0%)	405** (12%)
28	471	494	461	407** (14%)
F1a pups[3/]				
4	10.5	9.7* (7.6%)	10.2 (2.9%)	8.3* (21%)
21	52.8	48.9*(7.6%)	47.4**(10%)	39.5** (25%)
F1b pups[3/]				
4	10.7	10.9	10.4	8.7* (19%)
21	52.9	52.4	49.4* (6.6%)	40.4* (24%)
F2a pups[3/]				
4	10.6	10.2	10.8	10.0
21	51.1	49.6	47.6	44.2* (13%)
F2b pups[3/]				
4	10.4	10.7	9.7	9.1
21	53.8	53.2	47.4* (12%)	42.0** (22%)

1/ Eigenberg *et al.,* 1998
2/ 30 rats/sex/dose
3/ all pups weighed immediately after birth and 4/sex/litter at 4, 7, 14 and 21d.
4/ % decline compared with control
* significantly different from control, $p<0.05$, using Bartlett=s test.
** significantly different from control, $p<0.01$, using Bartlett=s test.

Table 9. Mean changes (% change vs. control) in cholinesterase activity after methamidophos dosing in a 2-generation rat reproductive toxicity study[1/]

ChE assay	1 ppm		10 ppm		30 ppm	
	M	F	M	F	M	F
F0 adults[2/]						
Plasma	(+8%)	4%	39%*	55%*	71%*	85%*
RBC	21%*	11%	73%*	71%*	84%*	88%*
Brain	(+6%)	7%*	45%*	58%*	75%*	76%*
F1 adults[2/]						
Plasma	(+13%)	4%	43%*	62%*	72%*	82%*
RBC	18%*	13%	72%*	71%*	88%*	90%*
Brain	(+1%)	5%*	43%*	60%*	68%*	81%*
F1a pup,21 d[3/]						
Plasma	(+3%)	(+3%)	34%*	30%*	44%*	35%*
RBC	(+2%)	19%	23%	31%*	35%*	31%*
Brain	(+1%)	(+2%)	23%*	20%*	40%*	34%*
F1b pup, 21 d[3/]						
Plasma	(0%)	8%	35%*	38%*	39%*	44%*
RBC	8%	18%	34%*	34%*	37%*	40%*
Brain	(+1%)	(+1%)	18%*	20%*	31%*	35%*
F2a pup, 21 d[3/]						
Plasma	6%	(+6%)	22%*	29%*	63%*	65%*
RBC	6%	9%	19%*	22%*	64%*	69%*
Brain	2%	3%	21%*	18%*	50%*	53%*
F2b pup, 21 d[3/]						
Plasma	4%	2%	37%*	31%*	48%*	48%*
RBC	(+5%)	5%	28%*	31%*	45%*	44%*
Brain	3%	2%	24%*	24%*	41%*	39%*

1/ Eigenberg *et al.,* 1998

2/ 10 rats/sex/dose

3/ one pup of each sex from each of 10 litters/dose, at 4 and 21 days.

* significantly different from control, $p<0.05$, using Bartlett=s test on raw data.

G. DEVELOPMENTAL TOXICITY

Summary

Developmental toxicity of methamidophos has been described in oral gavage studies in the rat (4) and the rabbit (3). Most of these studies were either range-finding or else were considered by DPR not to meet FIFRA guideline testing requirements. However, collectively, they were considered to fulfill these data requirements. In the SD rat, no fetal malformations were noted and reduced mean fetal body weight was the only developmental effect observed, with a LOEL of 5.49 and a NOEL of 1.41 mg/kg/day. Maternal toxicity included reduced body weight gain, food intake, and increased clinical signs, also with a LOEL of 5.49 and a NOEL of 1.41 mg/kg/day. Significant inhibition of maternal plasma, RBC and brain ChE was reported, with NOEL values of <0.05, 0.05 and 0.15 mg/kg/day, respectively. Thus, based on significant lower body weight or body weight gain, the LOEL and NOEL values for maternal and developmental toxicity were both 5.49 and 1.41 mg/kg/day, respectively. Based on the inhibition of AChE, maternal toxicity had LOEL and NOEL values of 0.15 and 0.05 mg/kg/day, respectively. In rabbits, a similar range of effects was noted, with a developmental LOEL of 7.73 mg/kg/day and a NOEL of 4.90 mg/kg/day for reduced mean live fetal body weight. For maternal toxicity, a LOEL of 2.47 mg/kg/day with a NOEL of 0.65 mg/kg/day was obtained for both increased clinical signs (hyperactivity) and significantly reduced body weight increase during dosing. Significant inhibition of plasma and RBC ChE was reported in dams, with a NOEL of 0.46 and a NOEL of 0.2 mg/kg/day. In a developmental neurotoxicity study, the NOEL for pup ChE inhibition was 1 ppm, equivalent to 0.1 mg/kg/day, based on 5% to 53% ($p<0.05$) inhibition of brain AChE at the LOEL of 10 ppm; for dams, 1 ppm was the LOEL, since inhibition of brain AChE of 8% ($p<0.05$) was recorded at this dose. There is thus no evidence that indicates that developmental effects occur at lower doses than those causing maternal toxicity. A summary of the developmental toxicity studies is presented in Table 15.

Gavage-Rat

Methamidophos (76% purity) was given by oral gavage to groups of 36 mated, female Sprague-Dawley rats at 0, 0.05, 0.14 and 5.49 mg/kg/day (measured) on gestation days 6-15 (Astroff, 1996a). Interim sacrifice animals (6/group) were killed 1.5 h after the last dose for ChE determination. The other rats were sacrificed on Day 20 and necropsy performed on the dams and litters. The low dose caused no effects on either ChE activity or clinical signs and the mid-dose caused only a 13% reduction (n.s.) in plasma ChE activity (Table 10). At 5.49 mg/kg/day, however, there were two developmental effects: a significant ($p<0.01$) reduction in mean fetal weight (7.5%) and an increased incidence of seven types of skeletal anomalies (significant only at the fetal level and not the preferred, litter level), resulting in incomplete ossification. Maternal toxicity at this dose consisted of a significant fall in mean weight gain (40% of control) during the treatment period ($p<0.01$), a large (*c.* 80 - 90%) inhibition of plasma, RBC and brain ChE activity and the appearance of clinical signs in all dams at the HDT. The LOEL for developmental and maternal toxicity was therefore 5.49 mg/kg/day and the NOEL was 0.14 mg/kg/day. This study was originally unacceptable to DPR because of inadequate dose justification, but it was subsequently upgraded to acceptable.

In a subsequent range-finding study conducted to address this deficiency, groups of 6 mated female SD rats were given methamidophos at 0, 0.05, 0.15, 1.41 and 6.04 mg/kg/day (measured) by gavage on gestation days 6-20 (Astroff, 1996b). Animals were killed 1.5 h after the last dose for ChE determination and a necropsy was performed on the dams and litters. The lowest dose caused a reduction (24%) in only plasma ChE, $p<0.05$ (Dunnett=s test), giving a LOEL for this effect of 0.05 mg/kg/day (Table 11). At 0.15 mg/kg/day, there were significant ($p<0.05$) reductions in plasma ChE (26%) and brain AChE (11%), which were considered to be of possible toxicological significance. Pronounced inhibition of plasma, RBC and brain ChE (69%, 73% and 47%, respectively) occurred at 1.41 mg/kg/day and at 6.04 mg/kg/day (93%, 92% and 75%, respectively). Thus, the LOEL for maternal ChE inhibition of possible toxicological significance was 0.15 mg/kg/day and the NOEL, 0.05 mg/kg/day. At the HDT, significant reductions were also observed in maternal body weight gain and mean fetal body weight per litter, as well as an increase in clinical signs in dams, giving maternal and developmental LOEL values of 6.04 mg/kg/day and NOELs of 1.41 mg/kg/day for these effects. The data reported in Astroff, 1996b were insufficient to upgrade the definitive study (Astroff, 1996a) to acceptable by DPR.

In an earlier study, methamidophos (70.5% purity) was given by oral gavage to groups of 24 - 27 mated, female CD rats at nominal dosages of 0, 0.3, 1.0 0 and 3.0 mg/kg/day (recovery, 97.3□9.5%) on gestation days 6-15 (Hixson, 1984a). A positive control group received hydroxyurea at 350 mg/kg/day. The rats were sacrificed on Day 21 and necropsy performed on the dams and litters. Measurements of ChE were not made. Maternal effects were limited to the HDT: reductions in body weight (10% at day 13, 11% at day 21) and body weight gain (26% and 43%, corrected for uterine weight) over the dosing period were significant at $p<0.01$ (Duncan=s test). There were corresponding reductions in food consumption of 29%, day 13 and 17%, day 21 ($p<0.01$); clinical signs of fasciculations, salivation and lacrimation were noted in all (27) dams. It was stated that developmental effects were also limited to the HDT: reduced total litter weight and mean fetal body weight ($p<0.05$, Duncan=s test). These effects could have been secondary to reduced maternal body weight, but because individual data were not supplied, it was not possible to confirm. The report was considered unacceptable by DPR, based on the lack of rationale for dose selection and lack of individual data.

In a pilot study, groups of 4 mated female SD rats were given methamidophos (70% purity) at 0, 0.1, 0.3, 1.0, 3.3 and 10.0 mg/kg/day (nominal) by gavage on gestation days 6-20 (Mobay, 1980c). There was a dose-dependent reduction in maternal body weight gain during the dosing period, accompanied by lower mean fetal weight (14% at 3.3 mg/kg/day and 22% at 10.0 mg/kg/day). Mild to severe clinical (cholinergic) signs were observed in dams at the top two doses. The study was considered by DPR to be inadequate to justify the dose selection for the definitive study (Astroff, 1996a).

Table 10. Developmental and maternal toxicity of methamidophos to the SD rat.[1]

Observation	Dosage (mg/kg/day)			
	0	**0.05**	**0.14**	**5.49**
# Animals tested[2/]	35	35	32	34
Mean live litter size	13	12.2	12	12.7
Mean live fetal weight (g)	4.0	4.0	4.0	3.7**
Incidence of fetal skeletal variations (litters)				
frontal bones	28/194 13/29 (45%)	28/186 15/29 (52%)	17/162 11/26 (42%)	49/184* 20/28 (71%)
sacral arches	128/194 28/29 (97%)	107/186 25/29 (86%)	88/162 24/26 (92%)	145/184* 28/28(100%)
sternebrae (segment 3)	29/194 17/29 (59%)	22/186 15/29 (52%)	21/162 15/26 (58%)	52/184** 21/28 (75%)
sternebrae (segment 4)	64/194 25/29 (86%)	73/186 25/29 (86%)	43/162 19/26 (73%)	106/184** 27/28 (96%)
sternebrae (segment 5)	27/194 19/29 (66%)	28/186 16/29 (55%)	26/162 16/26 (62%)	49/184** 20/28 (71%)
xiphoid	122/194 28/29 (97%)	115/186 27/29 (93%)	94/162 24/26 (92%)	144/184** 28/28 (100)
metacarpals	3/194 2/29 (7%)	1/186 1/29 (3%)	3/162 3/26 (12%)	12/184* 7/28 (25%)
Mean maternal body wt. (g)				
Day 0	214	212	214	212
Day 6	243	239	240	239
Day 15	282	276	278	255
Day 20	359	351	351	335
Change, mean maternal b.wt.(g)				
Days 0 - 6	28.6	26.8	25.7	27.3
Days 6 - 15	38.9□1.2	37.5□1.3	38.2□1.5	15.7□1.4*
Days 15 - 20	75.5	72.6	71.7	78.7
Days 0 - 20	143.1□4.1	135.6□4.5	134.3□3.7	120.5□3.8**
ChE, day 15 (% *vs.* control)				
Plasma	-	+1.9%	13%	91%*
RBC	-	+5.4%	1.8%	82%*
Brain	-	0.7%	4.1%	79%*
Clinical signs [3/]	0	0	0	34*** (100%)

1/ data taken from Astroff, 1996a
2/ six rats/group were sacrificed on Day 15 of gestation for ChE measurements.
3/ tremors, muscle fasciculations, salivation after dosing.
* significantly different from vehicle control, $p<0.05$.
** significantly different from vehicle control, $p<0.01$.
*** significantly different from vehicle control, $p<0.001$.
Dunnett=s test for body wt. data; Fisher=s exact test for incidence data.

Table 11. Developmental and maternal toxicity of methamidophos to the SD rat: a pilot range-finding study[1]

Observation	Dosage (mg/kg/day)				
	0	**0.05**	**0.15**	**1.41**	**6.04**
Change in mean maternal body wt. (g)[2]	(n=5)	(n=5)	(n=6)	(n=6)	(n=6)
Day 6 - Day 7	5.4□2.0	2.4□3.5	0.7□1.1	0.7□2.4	-12.0□3.8**
Day 6 - Day 20	100□11.0	91□5.7	97□11.1	107□7.3	55.1□5.3*
Day 0 - Day 20	116□10.9	113□7.7	124□11.7	131□7.8	76□6.8*
ChE, day 20 (% *vs.*control)[2]					
Plasma	0	24%*	26%*	69%*	93%*
Erythrocyte (RBC)	0	9%	10%	73%*	92%*
Brain		5%	11%*	47%*	75%*
Clinical signs[3]					
Muscle fasciculations	0/6	0/6	0/6	0/6	5/6**
Tremors	0/6	0/6	0/6	0/6	5/6**
Mean fetal b.wt. (g/litter)[4,5]					
Male	4.1□0.09	4.1□0.1	4.1□0.13	4.2□0.15	3.2□0.19*
Combined	3.9□0.07	4.1□0.1	4.0□0.11	4.1□0.09	3.1□0.19*

1/ data taken from Astroff, 1996b
2/ Dunnett=s test
3/ Fisher=s exact test
4/ Healy=s test
5/ includes both viable and nonviable fetuses

* significantly different from vehicle control, p<0.05.
** significantly different from vehicle control, p<0.01.

Gavage-Rabbit

Methamidophos (76% purity) was given by oral gavage to mated New Zealand rabbits (23/group) at 0, 0.2, 0.65 and 2.47 mg/kg/day (measured) on days 6-18 of gestation (Hoberman, 1996a). Dams were sacrificed on Day 29 and necropsies conducted on the litters and dams. The 0.2 and 0.65 mg/kg/day levels produced no adverse effects on the dams or fetuses, with the possible exception of minor reductions in food intake and maternal body weight gain (Table 12). These effects were more pronounced at 2.47 mg/kg/day. Hyperactivity was also observed in dams at this dose (Table 12). The NOEL for maternal toxicity was therefore considered to be 0.65 mg/kg/day, based on significantly reduced body weight gain and hyperactivity at 2.47 mg/kg/day. No fetal toxicity was observed in the study, making the developmental NOEL □2.47 mg/kg/day. The study was unacceptable to DPR because the rationale for the doses used, including the data supplied in Hoberman, 1996b (below), was considered inadequate.

A pilot, range-finding study was also submitted (Hoberman, 1996b) with the earlier study. In the latter study, methamidophos (76% purity) was given by oral gavage to mated New Zealand rabbits (5/group) at 0, 0.2, 0.46, 2.46, 4.90 and 7.73 mg/kg/day (measured) on days 6-18 of gestation. Blood samples were taken on Day 18 of gestation for ChE determinations (plasma and RBC) and dams were sacrificed on Day

29 for necropsy (Table 13). There was lower maternal body weight gain during the dosing period (n.s.) at the two highest doses; a significant ($p<0.05$) inhibition of ChE (plasma and RBC) with a LOEL of 0.46 mg/kg/day and a NOEL of 0.20 mg/kg/day; an increase in clinical signs with a LOEL of 4.90 mg/kg/day and a NOEL of 2.46 mg/kg/day and mortality with a LOEL of 7.73 mg/kg/day and a NOEL of 4.90 mg/kg/day. There was a possible reduction in mean fetal body weight at the HDT (n.s.), giving a developmental LOEL of 7.73 and a NOEL of 4.90 mg/kg/day.

A third rabbit developmental toxicity study for methamidophos was conducted using the Himalayan variety (Machemer, 1979). Methamidophos (62% purity) was given by oral gavage to mated Himalayan rabbits (15/group) at 0, 0.1, 0.5 and 2.5 mg/kg/day (nominal) on days 6-18 of gestation. Dams were sacrificed on Day 29 and the litters and dams were subjected to necropsy. There were no treatment-related or significant effects on any parameters measured. The report was considered inadequate by DPR owing to lack of dose justification and individual data.

Developmental and reproductive effects of methamidophos in the rat and rabbit are summarized in Table 15.

Table 12. Developmental and Maternal Toxicity of Methamidophos to the NZ Rabbit[1/]

Observation	Dosage (mg/kg/day)			
	0	0.2	0.65	2.47
# Animals tested	23	23	23	23
Mean live litter size	7	7.4	7.2	8
Mean live litter weight (g)	45.08	45.93	42.89	45.25
Mean maternal body wt. (kg)				
Day 0	3.28	3.27	3.33	3.42
Day 6	3.34	3.35	3.38	3.48
Day 9	3.42	3.41	3.44	3.46
Day 19	3.66	3.66	3.67	3.68
Day 29	3.91	3.91	3.86	3.91
Increased mean maternal b. wt.(kg)				
Days 6 - 9	0.07□0.04	0.06□0.05	0.05□0.06	-0.01□0.07**
Days 6 - 19	0.32□0.06	0.31□0.08	0.28□0.13	0.20□0.12**
Days 0-29	0.61□0.21	0.64□0.18	0.63□0.28	0.49□0.26
Days 6-29 [2/]	0.10□0.17	0.08□0.15	0.03□0.22	-0.07□0.20**
Hyperactivity [3/]	0	0	0	14/23** (61%)

1/ data taken from Hoberman, 1996a
2/ day 29 of gestation body wt. minus gravid uterine wt.
3/ thumping of cage w/ hindlimbs **significantly different from control, $p<0.01$ (Dunnett=s test)

Table 13. Developmental and Maternal Toxicity of Methamidophos to the NZ Rabbit: a pilot, range-finding study[1]

Observation	Dosage (mg/kg/day)					
	0	0.2	0.46	2.46	4.90	7.73
Mean maternal b.wt. (kg)						
Day 0	3.37	3.47	3.45	3.44	3.48	3.46
Day 6	3.35	3.47	3.42	3.37	3.42	3.44
Day 19	3.63	3.76	3.94[a]	[a]	3.42[a]	3.32
Day 29	3.87	3.98	4.08	3.86	3.85	3.66
Change in mean maternal b.wt.						
Day 0 - Day 6 **(kg)**	-0.02	0	-0.03	-0.07	-0.06	-0.02
Day 6 - Day 19	+0.27	+0.29	+0.30	-0.10	-0.09	-0.14
Day 6 - Day 29	+0.52	+0.51	+0.65	+0.49	+0.43	+0.20
ChE, day 18 (% *vs.* control)						
Plasma	0	16%	44%*	82%*	84%*	84%*
Erythrocyte	0	6%	52%*	86%*	76%*	92%*
Clinical signs						
Soft/liquid feces	0/5	0/5	0/5	0/5	5/5**	5/5**
Rapid breathing	0/5	0/5	0/5	0/5	2/5	5/5**
Excess salivation	0/5	0/5	0/5	0/5	1/5	5/5**
Mortality	0/5	0/5	0/5	0/5	0/5	2/5
Mean live fetal b.wt. (g/litter)	46.9	37	45.9	43.6	41.3	38.3

1/ data taken from Hoberman, 1996b

a/ and Excludes the body weights of 1, 5, and 2 rabbits of the respective 0.46, 2.46, 4.90 mg/kg/day groups due to water deprivation.

** significantly different from vehicle control, $p<0.01$ (Fisher=s exact test).

* significantly different from vehicle control, $p<0.05$ (Dunnett's test using raw data).

H. DEVELOPMENTAL NEUROTOXICITY

Dietary-Rat

Methamidophos (72.3-74.2% purity) was fed to mated female Wistar rats, in dose groups of 30, from Day 0 of gestation to Day 21 of lactation at 0, 1, 10 or 30 ppm (Sheets, 2002). These were equivalent to mean measured dosages of 0, 0.1, 0.9 or 2.5 mg/kg/day (gestation) and 0, 0.2, 2.4 or 7.9 mg/kg/day (lactation). Pups were fed on these treated diets until Day 21 of lactation and selected pups were maintained on untreated diet until necropsy at 75 days, to estimate recovery.

In general, there were no effects on any parameters associated with developmental or reproductive toxicity or on FOB tests in dams. Neither was there a reduction in body weight relative to controls in dams (Table 14). However, there was a dose-related delay in preputial separation, reaching 4.6% ($p<0.01$) at 30 ppm, along with a reduction in body weight in pups on days 11, 17 and 21 ($p<0.01$) at 30 ppm, of 8.5 to 12% (Table

14). For later timepoints (PND 28, 42, 56 and 70), a significant ($p<0.05$) reduction in body weight was also found for both sexes at each timepoint, of 4% to 10%. At 10 ppm, a significant reduction in pup body weight ($p<0.05$) during the PND 28-70 day period was found only for females, and was only 4 - 5%. Because dosing ceased at 21 days, it is possible to interpret this observation as a slower recovery in female than in male pups. The only FOB effect reported (using 10-16 pups/sex/dose level) was a reduction in motor activity, in both sexes, at 10 and 30 ppm, on PND 13. However, because this effect was not statistically significant, and was not observed on PND 17, 21 or 60, it is difficult to consider that it is clearly a compound-related effect. Organ weights were unaffected and there were no histopathological abnormalities found. However, ChE was inhibited in both dams and pups.

The degree of inhibition of ChE was similar for plasma, RBC and brain (Table 14). At 30 ppm, inhibition ($p<0.05$) was 77 - 83% of control activity for dams and 12 - 40% for pups (PND 4) to 34 - 53% (PND 21). At 10 ppm, the dams again clearly showed substantial ChE inhibition, of 50 - 63% ($p<0.05$), at PND 21. However, for the pups, variable inhibition was reported at 10 ppm, on PND 4, from 5% (n.s.) for plasma and brain to 20% ($p<0.05$) inhibition for RBC ChE. By PND 21, inhibition ranged from 8% (plasma ChE, F) to 53% (brain ChE, F), only the latter being significant ($p<0.05$). At 1 ppm, dams on PND 21 had ChE inhibited by 5% (n.s.), 12% (n.s.) and 8% ($p<0.05$), for plasma, RBC and brain ChE, respectively. Because of the statistical significance of this effect in brain, it was considered to be of toxicological significance by the report=s author and by the DPR reviewer, thus making 1 ppm the LOEL for AChE inhibition in dams. In pups, however, there was no significant inhibition of ChE at PND 4 or 21. Enzyme activity ranged from 4% inhibition for RBC ChE in females to 10% stimulation for plasma ChE in females, both at PND 21. It is therefore appropriate to consider 10 ppm as the LOEL and 1 ppm, the NOEL, for pups, for methamidophos. This NOEL is equivalent to 0.1 to 0.2 mg/kg/day. Moreover, the results are very similar to those obtained in the 2-generation reproductive toxicity study, using the same doses (Eisenberg, 1998). As in that study, it appears that the rat fetus/pup is not more susceptible to methamidophos toxicity than the dam.

Table 14. Developmental and Maternal Toxicity of Methamidophos to the Wistar rat: a developmental neurotoxicity study [1/]

	0	1	10	30 ppm
Mean body wt, g (M+F) [2/]				
Dams, Day 20	308□6.2	323□3.5	308□4.8	300□6.0
Pups, Day 0	5.7	5.7	5.7	5.6
Pups, PND 4	8.9	8.9	8.7	8.2
Pups, PND 11`	21.5	21.7	20.8	18.9** (12%)
Pups, PND 17	32.8	33.6	32.3	30.0** (8.5%)
Pups, PND 21	42.8	43.2	42.1	38.6** (9.8%)
Pups, PND 28, M	75.3	76.9	73.0	67.8* (10%)
Pups, PND 28, F	74.9	73.3	71.4* (5%)	67.9* (9%)
Pups, PND 42, M	169	170	167	157* (7%)
Pups, PND 42, F	140	137	134* (4%)	130* (7%)
Pups, PND 56, M	256	253	250	236* (8%)
Pups, PND 56, F	176	172	168* (5%)	164* (7%)
Pups, PND 70, M	312	306	306	288* (7%)
Pups, PND 70, F	197	194	189* (4%)	188* (4%)
Preputial separation, d	45.9	46.1 (0.0%)	46.7 (1.7%)	48.0**(4.6%)
FOB, motor activity, % [3/]				
PND 13 (M,F)	N/A	+29,-8	-25,-33	-45,-27
PND 17 (M,F)	N/A	-23,+12	-15,+29	-22,+8
PND 21 (M,F)	N/A	+10,-12	+3,-10	+7,-10
PND 60 (M,F)	N/A	+11,+4	-4,+9	+6,+9
ChE % I (% *vs.* control)	(n=10)	(n=10)	(n=10)	(n=10)
Dams, Day 21: Plasma	N/A	5	50*	77*
RBC	N/A	12	64*	84*
Brain	N/A	8*	63*	83*
Pups, PND 4 (M+F)	(n=21)	(n=18)	(n=19)	(n=18)
Plasma	N/A	+3	5	12*
RBC	N/A	3	20*	40*
Brain	N/A	0	5	14*
Pups, PND 21 (M/F)	(n=10/10)	(n=10/10)	(n=10/10)	(n=10/8)
Plasma	N/A	+2 / +10	22* / 8	34* / 40*
RBC	N/A	+6 / 4	12 / 16	37* / 53*
Brain	N/A	3 / 2	37* / 53*	34* / 43*

1/ Sheets, 2002

2/ Rats were dosed until 21 days and then given an untreated diet.

3/ Percent motor activity relative to controls; bolded numbers may be significant.

*** ** p<0.05, p<0.01 (Dunnett's test)**

N/A: not applicable.

Table 15. Summary of developmental and reproductive toxicity for methamidophos.

Study	Toxicity endpoint		LOEL	NOEL	Ref.
		DEVELOPMENTAL TOXICITY	**(mg/kg/day)**		
Rat	Maternal	ChE (R BC, plas., br.)	5.49	0.14	1[b/]
	Dev=tal	fetal mean B.Wt. incomplete ossific.	5.49	0.14	
Rat	Maternal	ChE (p lasma)			2[c/]
		ChE (b rain)	0.05	-----	
		ChE (R BC)	0.15	0.05	
		B.Wt. gain	1.41	0.15	
		clinical signs	6.04	1.41	
Rat	Dev=tal	fetal mean B.Wt.			3[b/]
	Maternal	B.Wt. gain	6.04	1.41	
		clinical signs	3.0	1.0	
	Dev=tal	fetal mean B.Wt. mean litter wt.	3.0	1.0	
Rat	Maternal	B.Wt. gain			4[c/]
		clinical signs	3.3	1.0	
Rabbit (NZW)	Dev=tal	fetal mean B.Wt.			5[b/]
	Maternal	B.Wt. gain	3.3	1.0	
		food consumed	2.47	0.65	
		hyperactivity			
Rabbit (NZW)	Dev=tal	no fetal effects	2.47	0.65	6[c/]
	Maternal	ChE (R BC, plas.)	------	□2.47	
		B.Wt. gain	0.46	0.2	
		clinical signs	4.90	2.46	
		death	4.90	2.46	
Rabbit (Himal.)	Dev=tal	fetal mean B.Wt.	7.73	4.90	7[b/]
	Maternal	no effects	7.73	4.90	
	Dev=tal	no effects	------	□2.5	
		DEVELOPMENTAL NEUROTOXICITY	------	□2.5	
Rat	Dev'tal	B.Wt.			8
		ChE (R BC, plas., brain)	2.5	0.9	
	Maternal	B.Wt.	0.9	0.1	
		ChE (b rain.)	----	□2.5	
		REPRODUCTIVE TOXICITY	0.1	<0.1	
Rat 2-gen.	Parental	ChE (p las., brain)	**(ppm)**		9
		ChE (R BC)	10	1	
		B.Wt. gain	1	n.d.	
	Reprod=ive	ChE (p las., brain)	10	1	
		ChE (R BC)	10	1	
		pup B.Wt. gain	10	1	
Rat 2-gen.	Parental	no effects	10	1	10[b/]
	Reprod=ive	number live litters	30	10	
		live litter size	-------	□33	
		pup growth	3	<3	
			33	10	
			33	10	

a/ References: 1. Astroff, 1996a; 2. Astroff, 1996b; 3. Hixson, 1984a; 4. Mobay, 1980c; 5. Hoberman, 1996a; 6. Hoberman, 1996b; 7. Machemer, 1979; 8. Sheets, 2002; 9. Eigenberg *et al*., 1998; 10. Hixson, 1984b. b/ these studies were unacceptable to DPR. c/ range-finding or pilot studies.

I. NEUROTOXICITY

Summary

The acute neurotoxicity of methamidophos has been described in oral gavage studies in the rat (2) and the hen (4) and in a dermal study in the rat. In addition, sub-chronic neurotoxicity studies, with durations ranging from 3 to 13 weeks, have been conducted in the rat (4) and the hen (2). The studies in the rat were dietary (2), dermal or inhalation and in the hen they were dermal and oral (gavage). Five of the studies were acceptable and the others were either range-finding, supplementary or else failed to meet FIFRA guideline testing requirements. Inhibition of ChE (plasma, RBC, brain) was measured in these studies, along with NTE (neuropathy target esterase) inhibition in some of them. A critical NOEL of 3.0 mg/kg/day (equivalent to an absorbed dosage of 0.9 mg/kg/day) for inhibition of rat (plasma, RBC and brain) ChE (cholinesterase), from an acute, rat dermal study, was used to estimate risks for acute, occupational exposure. A critical NOEL of 0.75 mg/kg/day (equivalent to an absorbed dosage of 0.22 mg/kg/day) for inhibition of rat (plasma, RBC and brain) ChE (cholinesterase), from a 21-day rat dermal study, was used to estimate risks for seasonal and chronic occupational exposure. A critical, acute NOEL of 0.3 mg/kg/day, for inhibition of rat (plasma, RBC and brain) ChE (cholinesterase) and FOB (functional observational battery) effects, after a single dosing with 0.6 mg/kg/day, was used for estimating acute dietary risks from exposure to methamidophos. A developmental neurotoxicity study is described in Section II.G. The other neurotoxicity studies for methamidophos are summarized in Table 24.

Acute Toxicity

Gavage-Rat

Methamidophos (75.6% purity) was given by oral gavage to groups of 18 SD rats/sex at 0, 0.3 and 0.6 mg/kg, measured (Sheets, 1994a). There were no treatment-related effects on body weight or clinical signs. FOB effects were reported as increased landing foot splay in males ($p<0.05$), at 0.6 mg/kg, 2 h after dosing. This was correlated with inhibition of ChE (plasma, RBC and brain) at the HDT (Table 16). RBC and brain ChE inhibition were significant ($p<0.05$) for males and females. However, the inhibition of plasma ChE, compared with control, was significantly different only for males at 0.6 mg/kg/day, by 27% ($p<0.05$) but not for females, even though inhibition was similar (25% at 0.6 and 24% at 0.3 mg/kg/day). It was concluded that the LOEL for FOB effects and ChE inhibition was 0.6 mg/kg and the NOEL, 0.3 mg/kg; the study was acceptable to DPR.[4] The study above was a follow-up to one in which groups of 24 SD rats/sex were dosed by oral gavage at 0, 0.9, 3.3 and 9.0 mg/kg, measured (Hamilton, 1993). ChE (plasma, RBC and brain) was inhibited ($p<0.05$) dose-dependently, at all (3) dose levels, by 24% to 91%, in both sexes (Table 16). FOB tests showed increased landing foot splay, in both sexes, at □0.9 mg/kg , when measured on Day 0, two hours after dosing. In addition, cholinergic clinical signs were significantly increased at the top two doses in this study (with no mortality). Only 1/24

[4]/ U.S. EPA used a NOEL of 0.3 mg/kg/day from this study for acute dietary risk estimation (based on ChE inhibition vs. ChE inhibition and FOB effects, by DPR) in the draft RED of 1/99, as well as in the IRED (USEPA, 2002c).

(4.2%) of the (male) rats showed clinical signs at 0.9 mg/kg. An increase in serum aspartate aminotransferase, AST (~6-fold) was observed at the HDT, in both sexes ($p<0.05$); at the mid-dose the increase was 43% ($p<0.05$) for males and 39% (n.s.) for females. An increase in serum alanine aminotransferase, ALT, was also observed, at the HDT, of 70% for males ($p<0.05$) and 81% for females ($p<0.05$). An elevation (in males, only) of serum cholesterol of 30% was reported at the HDT ($p<0.05$). It is probable that these effects, taken together, are a reflection of damage to the liver. It was concluded that the overall LOEL from this acceptable, supplementary study was 0.9 mg/kg, which was the NOEL for clinical signs.

Dermal-Rat

Technical or analytical grade methamidophos (75.6% purity) was applied in a single application to the shaved skin of the dorsal surface (6.6 - 8.7% of body surface area) of Sprague-Dawley rats, in groups of 5/sex/dose, at 0, 1.00, 2.50, 6.25 and 15.6 mg/rat (Easter & Rosenberg, 1986). These were equivalent to the following (measured) dosages of a.i.: 3.0, 8.9, 22 and 59 mg/kg (males) and 3.9, 9.7, 24 and 66 mg/kg (females) for technical and 4.1, 9.8, 26 and 66 mg/kg (males) and 4.4, 11, 30 and 73 mg/kg (females) for analytical grade. Rats were sacrificed at 24 or 72 h and ChE activity was measured (plasma, RBC and brain). Inhibition was particularly marked at 24 h (Table 17). Plasma and RBC ChE from females were inhibited ($p<0.01$) by 42% to 96%, at all (4) dose levels, whereas for males, inhibition was significant ($p<0.01$) by 46% to 92%, only at the three highest doses. Clinical signs of red ocular and nasal discharges were reported in males, within the first 24 h, at the top two doses. At the HDT, tremors, fasciculations and yellow anogenital stains were also noted at 72 h. For females, severe clinical signs, including the latter, were reported within the first 24 h, at the top two doses, and mortality of 60% of females occurred within the first few hours of dosing. Thus, females appeared to be more susceptible, both to ChE inhibition, and also to clinical signs. However, it should be noted that the dosages given to females were slightly greater than the corresponding ones received by males. It is also possible that the small number of animals at each dose level (5) may have limited the precision with which measurements were made or that females absorbed greater amounts than males. The inhibition of brain ChE, unlike RBC and plasma ChE, was more pronounced at 72h than at 24h (Table 17). The LOEL at 24h was 6.25 mg/rat (M and F) and at 72h, 2.5 mg/rat (M and F), giving 24h and 72h NOEL values of 2.5 mg/rat (M and F) 1.0 mg/rat (M and F), respectively. These NOEL values are equivalent to 8.9 (M) and 9.7 (F) mg/kg of technical at 24h and 3.0 (M) and 3.9 (F) mg/kg at 72h. The NOEL of 3.0 mg/kg/day, for the inhibition of plasma, RBC and brain AChE in males, is equivalent to an absorbed dosage of 0.9 mg/kg/day (based on 29% dermal absorption). This value was used for characterizing the risk for acute occupational exposure (Section IV.C). The 72h data (vs. 24h) for brain AChE inhibition were used for the choice of critical NOEL in order to be health protective and because inhibition of brain AChE at 24h (11%M, 16%F) was similar to that at 72h (15%M, 15%F), but lacked statistical significance. It is probable that inhibition of brain AChE had reached equilibrium after 24h.

Table 16. Acute, oral neurotoxicity of methamidophos in the rat

Observation	Dosage (mg/kg/d)[1/] 0	0.3	0.6[1/]	Dosage (mg/kg/d)[2/] 0	0.9	3.3	9.0[2/]
ChE (%I)[3/] (M)							
Plasma	0	6%	27%*	0	39%*	81%*	91%*
RBC	0	5%	21%*	0	32%*	73%*	92%*
Brain	0	0%	15%*	0	33%*	70%*	82%*
ChE (%I)[3/] (F)							
Plasma	0	24%	25%	0	24%*	67%*	89%*
RBC	0	8%	26%*	0	33%*	68%*	86%*
Brain	0	6%	26%*	0	29%*	72%*	84%*
FOB effects (M) landing footsplay)[4/]							
Day -1 **(mm)**	81	69	84	--	--	--	--
Day 0	75	63	92* (23%)	83	89	92	--[5/]
Day 7	77	68	84	85	80	92	92
Day 14	78	72	86	84	83	88	90
FOB effects (F) landing footsplay[4/]							
Day -1 **(mm)**							
Day 0	59	61	67	--	--	--	--
Day 7	60	64	61	82	92	87	--[5/]
Day 14	62	63	65	84	88	86	90
	63	62	63	78	77	79	85
Clin. signs (M)							
muscle fascicul.							12/24***
urine stained fur	--[6/]	--[6/]	--[6/]	0/24	0/24	7/24**	12/24***
oral stain				0/24	1/24 [7/]	9/24***	8/24**
nasal stain				0/24	1/24 [7/]	3/24	6/24*
				0/24	1/24 [7/]	10/24***	
Clin. signs (F)							
muscle fascicul.							7/24**
urine stained fur	--[6/]	--[6/]	--[6/]	0/24	0/24	0/24	12/24***
oral stain				0/24	0/24	5/24*	7/24**
nasal stain				0/24	0/24	0/24	6/24*
				0/24	0/24	2/24	

1/ from Sheets, 1994a
2/ from Hamilton, 1993
3/ mean % inhibition *vs.* control, measured 2 h after dosing (n=6/sex/dose).
4/ measured 2 h after dosing (n=12/sex/dose).
5/ rats were showing cholinergic signs and were unable to complete the (FOB) test
6/ none of the rats in Sheets, 1994a, exhibited any clinical signs (n=18/sex/dose).
7/ the same rat showed all of these clinical signs.
* significantly different from control at p<0.05 (Dunnett=s test, raw data).
for clinical signs: * p<0.05; ** p<0.01; *** p<0.001 (Fisher=s exact test)

Table 17. Mean inhibition of ChE after acute dermal dosing of the rat with methamidophos[1/]

ChE Assay [2/]	0 mg/kg/d	3.0 (M) 3.9 (F)	8.9 (M) 9.7 (F)	22 (M) 24 (F)	59 (M) 66 (F)
Plasma ChE					
male (24h)	1.02	1.05 (2 %)	0.48** (5 3%)	0.29** (7 2%)	0.12** (8 8%)
male (72h)	1.19	0.90 (2 4%)	0.84 (2 9%)	0.54** (5 4%)	0.34** (7 1%)
female (24h)	3.35	1.56** (5 3%)	0.98** (7 1%)	0.25** (9 3%)	0.18 (n=1) (9 5%)
female (72h)	4.52	3.81 (1 6%)	2.89** (3 6%)	1.10** (7 6%)	0.21** (9 5%)
RBC ChE					
male (24h)	2.78	2.21 (2 0%)	1.49** (4 6%)	0.72** (7 4%)	0.22** (9 2%)
male (72h)	2.94	2.91 (1 %)	2.19 (2 5%)	1.63** (4 5%)	0.14** (9 5%)
female (24h)	3.39	1. 95** (4 2%)	1.20** (6 5%)	0.12** (9 6%)	----- (n=2) ----- (n=2)
female (72h)	2.73	2.43 (1 1%)	2.66 (3 %)	0.81** (7 0%)	0.37** (8 6%)
Brain ChE					
male (24h)	0.096	0.10 (4 %)	0.085 (1 1%)	0.052** (4 6%)	0.038** (6 0%)
male (72h)	0.11	0.10 (6 .4%)	0.093* (1 5%)	0.069** (3 7%)	0.044** (6 0%)
female (24h)	0.073	0.73 (0%)	0.061 (n=4) (1 6%)	0.027** (6 3%)	0.009(n=2) (8 8%)
female (72h)	0.10	0.10 (2 .9%)	0.087** (1 5%)	0.062** (4 0%)	0.036** (6 5%)

1/ data from Easter & Rosenberg, 1986; measured dosages of: 3.0, 8.9, 22 and 59 mg/kg/day (males) and 3.9, 9.7, 24 and 66 mg/kg/day (females)

2/ enzyme activity: substrate hydrolyzed, µmoles/min./mg. protein, $x10^{-3}$; n=5/sex/dose/time (% inhibition vs. control)

* ** significantly different from control, $p<0.05$, $p<0.01$

Gavage-Hen (Acute)

Methamidophos was given to hens by oral gavage at doses of 100, 200 and 400 mg/kg and clinical signs were noted (Bayer, 1990c). Three isomer mixtures were employed: (−), (+) or (±). For the (−) mixture, mortality of 2/10 (20%) at 200 and 7/10 (70%) at 400 was observed; for the (+) isomer, mortality of 0/5, 0/5 and 3/13 (23%) at 100, 200 and 400 mg/kg, respectively, was noted; for the (−) isomer, mortality of 9/10 (90%) and 6/13 (46%) was observed at 400 mg/kg in two experiments. It is difficult to conclude from these experiments the degree of stereospecificity of the toxic responses. Clinical signs of apathy, ruffled feathers, staggering gait, diarrhea, rapid shallow breathing, spasm and cases of flat, lateral prostration were common to all groups treated. In addition, for the (−) isomer (at 400 mg/kg), signs of salivation, labored breathing and dry/limp comb were recorded. For the (+) isomer, at 100 mg/kg, there were no signs but at 200 mg/kg, an abnormal gait developed, reversibly, suggesting possible OPIDP. Because of a lack

of histopathology of target tissues, the report was unacceptable to DPR and not upgradeable.

White Leghorn hens were administered methamidophos at 0, 30 and 50.6 mg/kg on days 0 and 21 and observed for 42 days (Kruckenberg *et al.*, 1979). Hens were simultaneously given atropine sulfate at 50 mg/kg i.m. to ameliorate the cholinergic signs of intoxication. Mortality was 2/10 (20%) at 30 mg/kg and 4/12 (33%) at 50.6 mg/kg but there were no signs of delayed neuropathy. There was no histological evidence of neuropathy in the spinal cord or sciatic nerve. The report was unacceptable to DPR, based on the lack of analytical data on the dosing solutions.

In another study using adult, white Leghorn hens (5-30/group) methamidophos was administered at 0, 25, 30 and 35 mg/kg/day on 5 consecutive days and observed for 42 days (Thyssen & Eben, 1982). Hens were simultaneously given atropine sulfate at 50 mg/kg i.m. to ameliorate the cholinergic signs of intoxication. Different protocols were used to describe the possible neuropathies. All of the dosed hens displayed cholinergic signs and there was mortality in some dose groups. However, although NTE (from spinal cord and sciatic nerve) was severely depressed on day 1, it gradually recovered on days 2, 3 and 5, reaching normal activity by day 38. No delayed neurotoxicity was observed within 42 days post-treatment. The study was considered supplemental by DPR.

Isomer differences were reported in another study of NTE in the adult white Leghorn hen. Groups of (6 or 9) hens were dosed with methamidophos at one of the following: (□) 50 mg/kg (2xLD_{50}); D(+) 50, 100 or 400 mg/kg; L(□) 50, 200 or 400 mg/kg (Bayer, 1990b). Atropine sulfate was administered at 20 or 50 mg/kg, immediately prior to the insecticide. For low dose hens, 2-PAM was also given as an antidote. The activity of NTE was measured in lymphocyte, brain, spinal cord and sciatic nerve at 1 day, 2 days and 7 days after dosing (Bayer, 1990d). The degree of aging of the enzyme was studied by attempting to re-activate it using KF. A dose-dependent inhibition of NTE was noted with all isomers, but the nervous system enzyme was inhibited by (□) and D(+) to a much greater degree than by the (□) isomer. However, the brain enzyme inhibited by the L(□) isomer could not be re-activated by KF *i.e.* it had aged, whereas the NTE inhibition by the D(+) isomer could be re-activated by 88% *i.e.* only 12% had aged. The □ racemic mixture behaved more like the D(+) isomer *i.e.* it could be re-activated, indicating a lack of aging. Compared with nerve NTE, the lymphocyte enzyme recovered from inhibition by either isomer much more readily. The study was considered supplemental by DPR.

Subchronic Toxicity

Diet-Rat

Methamidophos was fed to F-344 rats (25/sex/dose) for 8 weeks at (nominal) doses of 0, 0.5, 1, 2 and 4 ppm, corresponding to mean dosages of 0, 0.028, 0.055, 0.122 and 0.244 mg/kg/day (M) and 0, 0.033, 0.065, 0.143 and 0.284 mg/kg/day (F) (Mobay, 1991). There were no clinical signs that could be considered treatment-related but there was a dose-dependent inhibition of ChE (plasma, RBC, brain) during the study (Table 18). The inhibition was statistically significant ($p<0.05$) at all dose levels for at least one enzyme or sex. Based on statistical significance, 1 ppm was the LOEL for plasma and RBC ChE and 0.5 ppm was the NOEL. The brain AChE was inhibited

significantly at all dose levels in males, but by only 3% at 0.5 ppm; females also showed 3.5% inhibition at 0.5 ppm (n.s.). Because of the low level of inhibition (3.5%) and the fact that it was only significantly different from control in one sex, it is considered probable that it is not toxicologically significant. The data showing changes in inhibition of brain AChE with time are given in Table 18A. At 14d, 35d and 56d, inhibition ranged from +0.7% to 4.7% at 0.5 ppm. Significant inhibition ($p<0.05$) was reported for only 1 of 3 timepoints for each sex (35d M, 56d F). On balance therefore, it is likely that 0.5 ppm (0.03 mg/kg/day) represents the NOEL. The great similarity of the inhibition of brain AChE at each timepoint (Table 18A) indicates that an equilibrium was reached within 2 wks in sub-chronic studies in the rat. This study was unacceptable to DPR due to inadequate analytical data for the dosing solutions.[5]

Table 18. Mean ChE inhibition in the F-344 rat after dietary methamidophos for 8 weeks[1/]

ChE Assay [2/]	0 .5 ppm	1.0 ppm	2.0 ppm	4.0 ppm
Plasma ChE [3/]				
Male (n=15)	0%	0	6%	25%*
Female (n=15)	3%	16%*	20%*	27%*
RBC ChE [3/]				
Male (n=15)	1%	4%*	8%*	16%*
Female (n=15)	1%	3%*	9%*	19%*
Brain ChE [4/]				
Male (n=15)	3.5%*	6.9%*	14%*	26%*
Female (n=15)	3.5%	6.3%*	13%*	32%*

1/ data from Mobay, 1991
2/ mean enzyme activity, % inhibition *vs.* control
3/ measured at 51 days
4/ measured at 56 days
* significantly different from control, $p<0.05$ (ANOVA + Dunnett=s test)

Table 18A. Brain AChE inhibition in the rat after dietary methamidophos for ≤ 56 days.[1/]

ChE Assay [2/]	0 ppm	0 .5 ppm	1.0 ppm	2.0 ppm	4.0 ppm
Brain ChE [3/] 14d					
Male (n=5)	14.8± 0.5	14.1± 0.3 (4.7%)	13.8±0.5* (6.8%)	12.9±0.6* (13%)	11.6±0.6* (22%)
Female (n=5)	14.5±1.3	14.6±1.5 (+0.7%)	12.7±0.9* (12%)	13.1±0.4 (9.7%)	11.3±0.4* (22%)
Brain ChE [3/] 35d					
Male (n=5)	15.0± 0.4	14.5±0.4 (3.3%)	13.9±0.5* (7.3%)	13.4±0.4* (11%)	11.1±0.3* (26%)
Female (n=5)	15.0±0.1	14.3±0.2* (4.7%)	13.7±0.3* (8.7%)	12.6±0.3* (16%)	10.7±0.3* (29%)
Brain ChE [4/] 56d					
Male (n=15)	14.4± 0.3	13.9±0.3* (3.5%)	13.4±0.3* (6.9%)	12.4±0.4* (14%)	10.7±0.6* (26%)
Female (n=15)	14.2±0.2	13.7±0.3 (3.5%)	13.3±1.1* (6.3%)	12.3±0.8* (13%)	9.7±0.5* (32%)

1/ data from Mobay, 1991
2/ mean enzyme activity ± SD, (% inhibition *vs.* control)
* significantly different from control, $p<0.05$ (ANOVA + Dunnett=s test)

[5] used by U.S. EPA as the critical one for chronic risk assessment in the RED of 1/99 and the IRED of 2002 (USEPA, 2002c); LOEL = 1 ppm, NOEL = 0.5 ppm for females or 0.03 mg/kg/day.

A 13-week dietary study of the toxicity of methamidophos (purity, 75.6%) in the F-344 rat was conducted by Sheets, 1994b. Rats (18/sex/dose) were dosed at 0, 1, 12 and 60 ppm (nominal) corresponding to mean measured dosages of 0, 0.067, 0.787 and 4.26 mg/kg/day (M) and 0, 0.074, 0.899 and 4.89 mg/kg/day (F). Clinical signs were assessed weekly and the incidence of muscle fasciculation, urine-stained fur, lacrimation and reactivity were all increased significantly ($p<0.001$) at 60 ppm, but not at lower doses, except for urine-stained fur in females at 12 ppm ($p<0.05$). The incidence of rats showing clear and red lacrimation was increased significantly at 60 ppm and showed some cases at 1 and 12 ppm. However, there was no clear dose-response in either sex and DPR considers that toxicologically relevant, compound-related lacrimation occurred only at 60 ppm. FOB effects were measured monthly; the only compound-related effect was a moderate to severe reduction in mean forelimb grip strength, in both sexes, at 60 ppm. This was significant at each time point ($p<0.05$) for males and at 8 and 13 weeks for females. ChE (plasma, RBC, brain) was inhibited significantly ($p<0.05$ or $p<0.01$) at 12 and 60 ppm, by □41%. At 1 ppm, significant inhibition ($p<0.05$) was recorded only for male brain AChE (Table 19), but the level of inhibition was only 5.8%; for females the inhibition was 5.5% (n.s.). It is thus considered, because significant inhibition of AChE was only noted in one sex and because it was at such a low level (5.8%), that it is not toxicologically significant. Thus 1 ppm represents the NOEL for ChE inhibition. Thus, the LOEL for FOB effects was 60 ppm and the NOEL,12 ppm; for plasma, RBC and brain ChE and clinical signs, the LOEL was 12 ppm, the NOEL, 1 ppm. The study was acceptable to DPR.

Dermal-Rat

Methamidophos (purity, 76.9%-80.5%) was applied as an aqueous solution (1 ml/kg) to the shaved back of groups of 9 or 10 SD rats/sex/dose for 6 h/day for a total of 18/22 days (M) or 17/21 days (F) at (nominal) doses of 0, 1, 15 or 50 mg/kg/day, equivalent to 0, 0.745, 11.2 or 36.5 mg/kg/day measured (Sheets & Gastner, 1997). No effects were observed on a variety of parameters, including clinical observations, changes in body weight or food intake, and the only effects found were inhibition of ChE. The activity of plasma, RBC and brain ChE was suppressed dose-dependently at 11.2 and 36.5 mg/kg/day, but not at 0.745 mg/kg/day (Table 20). Thus the LOEL and NOEL values for the subchronic, dermal toxicity of methamidophos were 11.2 and 0.745 mg/kg/day, respectively. There were no apparent differences between males and females. The study was unacceptable to DPR due to a lack of clinical chemistry data. However, because the NOEL is based on AChE inhibition, it is unlikely that clinical chemistry data would change the NOEL assignation. Therefore, the NOEL of 0.75 mg/kg/day (rounded) was used for risk assessment for seasonal, occupational exposure. Because of the numerical similarity of subchronic and chronic rat NOEL values for AChE inhibiting pesticides, this value was also chosen for conducting risk assessment for chronic (annual) occupational exposure. This value (0.75) is equivalent to an absorbed dosage of 0.22 mg/kg/day, assuming 29% dermal absorption (as estimated in a human *in vivo* study, Volume 2).

Inhalation-Rat

Methamidophos (purity, 73.4%) was diluted in PEG E 400/Ethanol and administered as an aerosol to groups of 10 Wistar rats/sex/dose (nose-only) at measured concentrations of 0, 1.1, 5.4 and 23.1 mg/m^3 for 6 h/day, 5 days/week, for 3 months (Pauluhn, 1988). This is equivalent to 0.26, 1.28 and 5.46 mg/kg/day, based on a rat inhalation rate of 960

l/kg/day, adjusted for rats weighing 170 g (Zielhuis & van der Kreek, 1979). The particles had a MMAD (mass median aerodynamic diameter) □5 µm. A dose and time-dependent reduction in body weight relative to controls was observed in both sexes, of 8% (3 weeks), 11% (6 weeks) and 12% (13 weeks) for males (p<0.01); 1.7%, 2.3% and 3.3% for females. A 12% lower spleen weight relative to body weight, though not absolute weight, was also observed at the HDT (p<0.01 in females). During the course of the study, measurements were made of ChE inhibition and lung function, using the ACh provocation test after each exposure period.

Table 19. Neurotoxicity of methamidophos to the rat: subchronic dietary study.[1/]

Observation	0 ppm	1	12	60
ChE (%I)[2/] (M) (n=6)				
Plasma	0.58	0.57 (1.8%)	0.34*(4 1%)	0.15* (74%)
RBC	1.50	1.39 (7.3%)	0.36* (76%)	0.05* (97%)
Brain	15.6	14.7* (5.8%)	6.5* (5 8%)	2.4* (8 5%)
ChE (%I)[2/] (F) (n=6)				
Plasma	2.35	2.2 (6 .4%)	0.94* (60%)	0.25* (91%)
RBC	1.34	1.22 (9.0%)	0.41* (69%)	0.06* (96%)
Brain	16.4	15.5 (5.5%)	6.5**(6 0%)	2.4** (85%)
FOB effects (M) (n=12)				
grip strength (kg)				
4 weeks, fore	0.89	0.80	0.88	0.75*[3/]
hind	0.39	0.36	0.37	0.37
8 weeks, fore	1.01	1.05	1.03	0.79*[4/]
hind	0.42	0.45	0.43	0.37
13 weeks, fore	1.13	1.09	1.06	0.78*[4/]
hind	0.42	0.47	0.47	0.35
FOB effects (F) (n=12)				
grip strength (kg)				
4 weeks, fore	0.72	0.71	0.74	0.62
hind	0.26	0.28	0.26	0.34
8 weeks, fore	0.87	0.82	0.85	0.65*[4/]
hind	0.27	0.28	0.29	0.33
13 weeks, fore	0.88	0.91	0.90	0.63*[4/]
hind	0.29	0.31	0.34	0.35
Clinical signs (M)				
muscle fasciculation	0/12	0/12	0/12	12/12***
urine stain	0/12	0/12	0/12	8/12***
lacrimation	0/12	0/12	0/12	6/12**
reactivity	0/12	0/12	0/12	11/12***
Clinical signs (F)				
muscle fasciculation	0/12	0/12	0/12	12/12***
urine stain	4/12	4/12	10/12*	12/12***
lacrimation	0/12	3/12	1/12	9/12***
reactivity	0/12	0/12	0/12	11/12***
Clinical signs (M+F)				
muscle fasciculation	0/24	0/24	0/24	24/24***
urine stain	4/24	4/24	10/24	20/24***
lacrimation	0/24	3/24	1/24	15/24***
reactivity	0/24	0/24	0/24	22/24***

1/ from Sheets, 1994b

2/ mean ChE activity, at 86 days; IU/ml or IU/g (brain), and (% inhibition *vs.* control); 6/sex/dose

3/ slight effect on grip strength (12/sex/dose for FOB) 4/ moderate/severe effect on grip strength,12/sex/dose,FOB

* significantly different from control at p<0.05 (Dunnett=s test, raw data).
for clinical signs: * p<0.05; ** p<0.01; *** p<0.001 (Fisher=s exact test)

Table 20. Mean ChE inhibition in the SD rat after dermal methamidophos for 21 days[1/]

ChE Assay [2/]	0 mg/kg/day	1	15	50
Plasma ChE	(n=10)	(n=10)	(n=10)	(n=10)
male [3/]	0.49□0.06	0.48□0.10 (2%)	0.37□0.06* (2 4%)	0.20□0.04* (5 9%)
female [4/]	1.20□0.23	1.29□0.42 (+7%)	0.70□0.03 + (4 2%)	0.40□0.07 + (6 7%)
RBC ChE				
male [3/]	1.12□0.14	1.05□0.23 (6 %)	0.50□0.20* (5 5%)	0.28□0.10* (7 5%)
female [4/]	1.11□0.18	1.10□0.20 (1 %)	0.60□0.14* (46%)	0.27□0.11* (76%)
Brain ChE				
male [3/]	13.4□1.0	13.5□2.0 (1 %)	7.9□1.5* (4 1%)	4.5□0.8* (6 6%)
female [4/]	13.8□0.7	13.1□0.6 (5 %)	8.5□0.9* (3 8%)	5.3□0.7* (6 4%)

1/ from Sheets & Gastner, 1997; measured dosages were 0, 0.745, 11.2 or 36.5 mg/kg/day
2/ mean enzyme activity, IU/ml or IU/g (brain), and (% inhibition *vs.* control); n=9 or 10/sex/dose
3/ measured at 22 days
4/ measured at 21 days
* significantly different from control, p<0.05 (ANOVA + Dunnett=s test)
\+ sig. different from control, p<0.05 (Kruskall-Wallis Anova & Mann-Witney U test).

Inhibition of ChE (plasma, RBC, brain) was dose-dependent and averaged 53%, 23% and 47% (M) and 66%, 29% and 45% (F) at the HDT of 23.1 mg/m^3 (Table 21). At the mid-dose of 5.4 mg/m,^{3} which was the LOEL based on statistics, the corresponding mean inhibition was 38%, 14% and 28% (M) and 44%, 18% and 25% (F). At both doses the inhibition was significant at p<0.01. The mean inhibition of ChE (plasma, RBC, brain) at the NOEL of 1.1 mg/m^3 (0.26 mg/kg/day) was 26%, 2.5% and 7.9% (M) and 19%, 6.6% and 11% (F) and was not statistically significant. The ACh provocation test showed increased reactivity of the bronchial musculature to a challenge dose of ACh at the two highest doses, but without an alteration in lung function. Clinical signs of slight to moderate muscle tremors were observed only at the HDT. Tremors were observed in all rats during the dosing period but had reversed overnight. It was therefore concluded that the LOEL and NOEL values for the inhibition of ChE (plasma, RBC, brain), based on statistical significance, and associated functional changes in the ACh provocation test were 5.4 and 1.1 mg/m.^{3} RBC ChE may have been less sensitive to inhibition in males than females. The report was considered to be acceptable supplementary data.

Table 21. Cholinergic effects in the Wistar rat of methamidophos inhalation for 90d[1/]

ChE Assay	0 mg/m^3 0 mg/kg/day	1.1 0.26	5.4 1.28	23.1 5.46
Plasma ChE[2/] **Male:** 13 wks. **Female:**13 wks.	(n=10) 0.58 1.33	(n=10) 0.43 (26%) 1.08 (19%)	(n=10) 0.36** (3 8%) 0.75** (4 4%)	(n=10) 0.27** (5 3%) 0.45** (6 6%)
RBC ChE[2/] **Male:** 13 wks. **Female:**13 wks.	 2.35 2.86	 2.29 (2.5%) 2.67 (6.6%)	 2.03 (14%) 2.35** (1 8%)	 1.81 (23%) 2.04** (2 9%)
Brain ChE[3/] **Male:** 13 wks. **Female:**13 wks.	 1.39 1.30	 1.28 (7.9%) 1.16 (11%)	 0.99** (2 8%) 0.97** (2 5%)	 0.73** (4 7%) 0.72** (4 5%)
ACh provocation test (mean M, F)[4/]	0.07	0.15	0.25	0.27

1/ data from Pauluhn, 1988
2/ mean ChE activity expressed as kU/l and (% inhibition vs. control); n=10/sex/dose
3/ mean ChE activity expressed as U/g and (% inhibition vs. control); n=10/sex/dose
4/ units of cm H_2O/ml/sec.
** significantly different from control, p<0.01

Table 22. Mean ChE and NTE inhibition in the hen after oral methamidophos for 90d[1/]

ChE Assay	0 mg/kg/day	0.3	1	3
Plasma ChE[2/]				
time 0 (pretest)	2.38□0.49	2.84□0.72 (1 9%)	2.59□0.86 (9 %)	2.36□0.46 (1 %)
4 weeks	2.26□0.39	2.20□0.59 (3 %)	1.74□0.54 (2 3%)	1.18□0.39* (4 8%)
8 weeks	2.42□0.45	2.26□0.64 (7 %)	1.76□0.63* (2 7%)	1.19□0.39* (5 1%)
12 weeks	2.13□0.39	2.21□0.59 (4 %)	1.76□0.47 (1 7%)	1.19□0.28* (4 4%)
NTE 12 weeks[3/]				
Brain	5.3□0.5	5.8□0.4 (9 %)	5.2□0.5 (2 %)	4.4□0.4* (1 7%)
Spinal cord	4.1□0.4	3.8□0.5 (7 %)	3.2□0.5* (2 2%)	2.4□0.3* (4 1%)

1/ data from Sachsse *et al.*, 1987
2/ mean ChE activity expressed as m ol. -SH/ml/min. (BuChE); (%inhibition *vs.* control)
3/ mean NTE activity expressed as g phenol/ml reaction mixture; (%inhib. *vs.* control)
* significantly different from control, p<0.05 (Dunnett=s test)

Gavage-Hen

White Leghorn hens (16/dose level) were administered methamidophos (76% purity), at 0, 0.3, 1 and 3 mg/kg/day, by daily gavage, 5 days/week, for 3 months (Sachsse *et al.*, 1987). Measurements made included: motor activity, twice/week; plasma ChE every month (10 hens/dose); NTE in brain and spinal cord (6 hens/dose), plus neurohisto-pathology, at terminal sacrifice. The only treatment-related effects were, at the HDT:

slight clinical signs of somnolence, not associated with OPIDN; inhibition of brain NTE ($p<0.05$); lower body weight (*ca.*20%); at both the HDT and mid-dose, inhibition of plasma ChE and spinal cord NTE, $p<0.05$ (Table 22). It was concluded that there were no clinical signs of OPIDN because inhibition (of NTE) did not reach the required, critical level (45-65%), according to Johnson, 1982. The report was considered to be supplementary.

Dermal-Hen

Leghorn hens (15 - 25/dose level) were dermally exposed to methamidophos (76.3% purity), at 0, 0.5, 1.5 and 4.5 mg/kg/day, 5 days/week, for 13 weeks (Bomann *et al.*, 1993). Measurements made included: clinical appearance (daily); motor activity (weekly); plasma ChE (before treatment and 24h after the last treatment of weeks 3, 6, 13 and 17) for 10 hens/dose; NTE in brain and spinal cord (1 to 3 hens/dose, 24h after the last treatment of weeks 4 and 13) plus neurohistopathology (terminal sacrifice). An increase in clinical signs and effects was observed only at the HDT: apathy, ruffled feathers, staggering gait, reduced food intake and body weight, discolored feces and diarrhea. The only other systemic affects were an inhibition of (plasma) ChE at the mid and high doses and of NTE at the HDT only (Table 23). The LOEL for significant inhibition of plasma ChE was 4.5 and the NOEL was1.5 mg/kg/day. A loss of the uppermost layer of the skin was noted at the treatment site at the top two doses. The study was acceptable to DPR.

Table 23. Mean ChE and NTE inhibition in the hen: dermal methamidophos, 13 wk.[1/]

ChE Assay	0 mg/kg/day	0.5	1.5	4.5
Plasma ChE[2/] time 0 (pretest)	0.90±0.14	0.94±0.24	1.00±0.22	0.99±0.14
3 weeks	0.95±0.16	0.99±0.28	0.83±0.20 (⇓ 13%)	0.57±0.13* (⇓ 40%)
6 weeks	0.84±0.13	0.85±0.18	0.75±0.20 (⇓ 11%)	0.49±0.08* (⇓ 42%)
13 weeks	0.89±0.15	0.83±0.17 (⇓ 7%)	0.78±0.17 (⇓ 12%)	0.51±0.11* (⇓ 43%)
NTE 4 weeks[3/] Brain	2374 (n=3)	2786 (n=3)	2429 (n=3)	1867 (n=2) ⇓ 21%
Spinal cord	537 (n=3)	664 (n=3)	625 (n=3)	459 (n=2) (⇓ 15%)
NTE 13 weeks[3/] Brain	2319 (n=2)	2357 (n=1)	2461 (n=2)	2138 (n=3) (⇓ 8%)
Spinal cord	554 (n=2)	588 (n=1)	578 (n=2)	496 (n=3) (⇓ 10%)

1/ data from Bomann et al., 1993
2/ mean ChE activity as kU/L and (% inhibition vs. control) using 10 hens/dose/time
3/ mean NTE activity as nmol. phenyl valerate/min./g tissue; (% inhibition vs. control)
* significantly different from control @$p<0.05$ (Dunnett's test, log transformed)

Subchronic: Human

A subchronic toxicity study was conducted with human volunteers, subjected to

mixtures of methamidophos and acephate (1:4 or 1:9) for periods of 10 (1:4) or 21 (1:9) days (Garofalo, 1973). The insecticides were dissolved in corn oil and were administered orally in gelatin capsules three times per day, at doses of 0, 0.1 (M+F), 0.2 (M+F), 0.3 (M+F) or 0.4 (F) mg/kg/day. A total of 7 males and 7 females took part in the investigation. Blood samples were taken at 1, 3, 7, 14 or 16 and 21 days and ChE activity in RBC and plasma enzyme was recorded. The enzyme activity at each time point was compared with the pre-testing activity for each subject and the criterion for inhibition was satisfied if the activity fell more than 2 SDs below the pre-dosing level. No inhibition of RBC ChE was recorded during the study. For plasma ChE, however, all volunteers (2M+2F) dosed at 0.2 mg/kg/day of 1:4 showed inhibition after 16 days' dosing. Likewise, at 0.3 mg/kg/day of the 1:9 mixture, 3/3M and 0/3F showed inhibited plasma ChE and at 0.4 mg/kg/day of 1:9, at 10 days, 2/3F exhibited lowered ChE. None of the subjects had any clinical signs or symptoms during or after the study. Overall, the study indicates that humans may be no more susceptible than rodents to the toxic effects of methamidophos but several factors compromise the validity of the study for quantitative risk assessment: the study was conducted by IBT, an organization with a reputation for supplying ~~bogus~~ invalid reports to USEPA; mixtures of methamidophos and acephate were used for dosing; GLP standards were not in force, making it uncertain whether or not the subjects dosed themselves over the weekend periods during the study; inadequate number of replicates to show statistical significance. It was concluded by USEPA and DPR that the study was supplemental.

Literature Review - Delayed Neurotoxicity

A review of the literature was conducted to determine whether methamidophos caused OP-induced delayed polyneuropathy (OPIDP) in animals or man (Johnson and Lotti, 1989). This was based on several cases of poisoning (accidental and suicide attempts) in which patients survived the acute, cholinergic symptoms through the use of antidote therapy (atropine and oximes) but went on to develop neurological symptoms 2 - 3 weeks afterwards. Clinical signs included weakness in the feet, paresthesia, foot drop, absence of an ankle jerk and signs of denervation. Experiments in the hen were conducted to determine the ratio of a) the LD_{50} (without antidotes) to the minimal dose causing signs of OPIDP and b) the *in vitro* I_{50} for AChE inhibition to that for NTE inhibition. In each case, the ratio was <0.1, indicating that the dose of racemic methamidophos needed to cause OPIDP is >10x the dose needed to cause 50% mortality and also that the concentration needed to inhibit NTE is >10x that needed to inhibit AChE. Using human brain as a source of both enzymes gave a I_{50} AChE: I_{50} NTE ratio of 0.064, indicating that the hen is a good model and that the probability of methamidophos-induced OPIDP in humans is low, except at very large doses requiring vigorous antidotal therapy. Differences are apparent in the relative potencies of the D(+) and L(-) enantiomers of methamidophos as well as in the degree of aging of NTE (measured as the reactivation with KF). The D(+) isomer was more potent than the L(-) at inhibiting NTE and was reactivated (80%) with KF, whereas L(-) inhibited NTE appeared to be resistant to reactivation. Because the racemic mixture (as in Monitor7 end-products) was more like the D(+) isomer (*i.e.* showed reactivation), it is unlikely that methamidophos will result in problems of OPIDP under normal agricultural use.

Table 24. Summary of neurotoxicity studies with methamidophos.

Study	Toxicity endpoint	LOEL mg/kg/day	NOEL mg/kg/day	Ref [a/]
	ACUTE TOXICITY	**oral (except where stated)**		
Rat	ChE ↓ (RBC, plasma, brain); FOB effects	0.6 mg/kg/d	0.3	1[b/]
	B.Wt. ↓ clinical signs	-----	□0.6	
Rat	ChE ↓ (RBC, plasma, brain); FOB, clin. signs	0.9	<0.9	2,
	ALT, AST, cholesterol ↑	9.0	3.3	3[b/]
Rat	ChE ↓ (RBC, plasma) 24h	3.0	<3.0	4
dermal	ChE ↓ (brain) 72h	8.9	3.0[c/]	
Hen	Mortality (D+) isomer	400	200	5
	Clinical signs (D+) isomer	200	100	
	Clinical signs, mortality (±□ isomer	200	<200	
	Clinical signs, mortality (L□) isomer	400	<400	
Hen[d/]	OPIDN	-----	□50.6	6
	Mortality	30	<30	
Hen[d/]	NTE on Da y 1, normal by Day 38; chol. signs	25	<25	7
	OPIDN at □42 days	-----	□35	
Hen	NTE at 24 and 48 h	50	<50	8
	SUBCHRONIC TOXICITY -	**diet (except where stated)**		
	ChE (R BC, plasma, brain)	1 ppm[e/]	0.5 ppm	9
Rat	clinical signs	-----	□4	
8-wk.				
	FOB effects	60 ppm	12	10[b/]
Rat	ChE (R BC, plasma), clinical signs	12 ppm	1	
13-wk	AChE (b rain)	1 ppm	□1	
Rat	ChE (R BC, plasma, brain)			11
21-d.	clinical signs	11.2 mg/kg/d	0.75[f/]	
dermal		-----	□36.5	
	ChE (R BC, plasma, brain); ACh provoc. test			
Rat	clinical signs	1.28 mg/kg/d	0.26	12[b/]
3-mon.		0.26	□0.26	
Inhal.				
	ChE (p lasma)	1.5 mg/kg/d	0.5	
Hen	Clinical signs; B.Wt. ; NTE	4.5	1.5	13[b/]
13-wk	neuropathy	-----	□4.5	
dermal				
	ChE (p lasma); NTE (spinal cord)	1.0 mg/kg/d	0.3	
Hen	Clinical signs; B.Wt. ; NTE (b rain)	3.0	1.0	14
12-wk	neuropathy	-----	□3.0	
oral				

a/ References: 1. Sheets, 1994a; 2. Hamilton, 1993; 3. Sheets, 1993; 4. Easter & Rosenberg, 1986; 5. Bayer, 1990c; 6. Kruckenberg *et al*., 1979; 7. Thyssen & Eben, 1982; 8. Bayer,1990b; 9. Mobay, 1991; 10. Sheets, 1994b; 11. Sheets & Gastner, 1997; 12. Pauluhn, 1988; 13. Bomann *et al*., 1993; 14. Sachsse *et al*., 1987.

b/ studies were acceptable to DPR; all other studies were supplementary or unacceptable.

c/ equivalent to an absorbed dosage of 0.9 mg/kg/day

d/ atropine sulfate was given as an antidote of the cholinergic effects.

e/ see text.

f/ equivalent to an absorbed dosage of 0.22 mg/kg/day

IV RISK ASSESSMENT

A. HAZARD IDENTIFICATION

The Birth Defect Prevention Act of 1984 (SB 950) and the Food Safety Act (AB2161) require DPR to review the toxicological data for all active ingredients currently registered in California. DPR placed methamidophos in risk assessment based on low NOEL values identified in laboratory animal studies. In acute, sub-chronic and chronic studies, methamidophos consistently inhibited cholinesterase activity (plasma, RBC and brain), sometimes accompanied by clinical signs. The degree of inhibition was similar for each of these enzyme types. Cholinesterase inhibition was the most sensitive endpoint and, along with clinical signs, was used to characterize the human risk from potential acute, subchronic and chronic exposure. There was no evidence of developmental or reproductive toxicity in appropriate rat and rabbit toxicity tests. Gene mutations and chromosome aberrations were reported in CHO cells *in vitro*, but no increase in tumor incidence was observed in 2-year rodent dietary studies.

Acute Toxicity

Methamidophos and its formulations were acutely toxic to rodents and rabbits orally, (LD_{50} 13-16 mg/kg) and dermally, (LD_{50} 69-162 mg/kg) both Category I. Skin and eye irritation were both mild, Category IV. By inhalation, methamidophos was also toxic to the rat (LD_{50} 11-13 mg/kg), Category I. Formulated Monitor7-4 had reduced rat inhalation toxicity (LD_{50} 27-33 mg/kg), Category II, but remained highly toxic via the oral route (LD_{50} 16.5-21.3 mg/kg, for males and females, respectively), Category I. Several impurities and manufacturing intermediates, which may be present in the formulated products, also show significant oral toxicity to rodents (LD_{50} 112-708 mg/kg), Category II or III. However, this is □10-fold lower toxicity than the parent compound. Data describing the acute toxicity of metabolites are limited but, based in part on the lower toxicity of the impurities, it is anticipated that they would have lower acute toxicity than parent methamidophos.

In common with other organophosphate insecticides, the inhibition of ChE was the most sensitive endpoint in both acute and chronic toxicity tests. In acute, single dose, neurotoxicity tests in the rat, the NOEL for FOB effects and ChE inhibition (plasma, RBC, brain) was 0.3 mg/kg, with a LOEL of 0.6 mg/kg (Hamilton, 1993; Sheets, 1994a). In these studies, plasma, RBC and brain ChE showed similar degrees of inhibition (15% to 27%) at the LOEL and no differences between sexes. The increase in landing foot splay (23%, $p<0.05$), on the day of dosing, was observed only in males (Sheets, 1994a). It is concluded that the critical NOEL of 0.3 mg/kg/day, based on AChE inhibition and FOB effects, is appropriate for acute dietary risk characterization of methamidophos. For the characterization of risk from occupational exposure, where the great majority of the exposure is dermal, it is concluded that the rat acute dermal NOEL of 3.0 mg/kg/day is appropriate. This is equivalent to an absorbed dosage of 0.9 mg/kg/day, based on a measured human dermal absorption of 29% (Volume 2).

Subchronic Toxicity

Rat dietary studies of 8 and 13 weeks duration have been conducted, giving LOEL and

NOEL values of 0.06 and 0.03 mg/kg/day, respectively for the inhibition of RBC, plasma and brain ChE. In a 21-day rat dermal study, the same enzymes were inhibited with (nominal) LOEL and NOEL values of 15 and 1 mg/kg/day. A 3-month rat inhalation study with methamidophos gave LOEL and NOEL values of 1.28 and 0.26 mg/kg/day (1.1 and 5.4 mg/m^3) for the same enzymes and also for functional changes in the ACh provocation test. In dermal (13-wk.) and oral (12-wk.) studies in the hen, similar LOEL and NOEL values were obtained. For NTE inhibition, plasma ChE inhibition, clinical signs and body weight reduction, LOEL and NOEL values were 1 - 4.5 mg/kg/day and 0.3 - 1.5 mg/kg/day, respectively. Neuropathy was not reported. Therefore, for seasonal and chronic occupational risk characterization, the NOEL value of 0.75 mg/kg/day (measured) from the 21-day rat, dermal study (above) was used. This is equivalent to an absorbed dosage of 0.22 mg/kg/day, based on a measured human dermal absorption of 29% (Volume 2).

Chronic Toxicity

Reduced body weight, relative to controls, was observed in the rat and mouse, but not in the dog. Similarly, there was a significant increase in relative brain weight at the HDT (highest dose tested) in these rodents, in both sexes, but not in the dog, which could have been related to the body weight reduction. Only in the rat was there an increase in absolute brain weight, in both sexes, at the HDT. If the changes in brain weight were a secondary result of the inhibition of brain AChE, there was an absence of corollary histopathology. In all (3) species, there was clear evidence of inhibition of ChE in plasma and erythrocytes, and of AChE in brain. The LOEL for the inhibition of brain AChE was 2 ppm, equivalent to 0.1, 0.3 or 0.06 mg/kg/day in the rat, mouse and dog, respectively. There were few clinical signs at the doses employed in these studies.

Because there was no clear NOEL for brain AChE inhibition in the dog study (Hayes, 1984c), an estimated chronic NOEL was obtained by dividing the LOEL by an UF of 3 *i.e.* 0.02 mg/kg/day. Support for the use of a factor of 3 rather than 10 in estimating the NOEL from the LOEL was provided by the calculation of Benchmark Doses (BMDs). The mean and S.D. for brain AChE inhibition (Table 5) were analyzed using BMD software developed for USEPA (2002) by the National Centre for Environmental Assessment, using DPR guidelines. Four programs were run (Hill, Polynomial, Power and Linear models) and the BMD and BMDL (95% lower confidence limit of the BMD) were determined by each one, based on 10% enzyme inhibition. For male dogs, BMDLs were 0.025, 0.033, 0.11 and 0.11 mg/kg/day, for the four models, respectively. The AIC (Akaike Information Criteria) were -11.5, -15.1, 25.9 and 29.9, respectively. From the AIC values (the lower the better) and an inspection of the dose/response curves, it would appear that the Hill model provides the best analysis of the data, thus giving a BMDL of 0.025 mg/kg/day. For female dogs, the BMDLs were 0.035, 0.037, 0.11 and 0.11, respectively. The analogous AIC values were -8.0, -11.4, 21.9 and 17.9, respectively. It is therefore concluded that the use of 0.02 mg/kg/day as an estimated NOEL from this study should be relatively close to the "true" NOEL. This estimated NOEL of 0.02 mg/kg/day, based on 11-18% inhibition of brain AChE activity at 0.06 mg/kg/d (LOEL) in the 1-yr. dog study (Hayes, 1984c), was used as the critical value for chronic dietary risk characterization. The characterization of chronic occupational risk used the NOEL of 0.75 mg/kg/day from the 21-day rat dermal study, discussed above. This is equivalent to an absorbed dosage of 0.22 mg/kg/day, based

on human dermal absorption of 29% (Volume 2). It should be noted that dermal studies are preferred for occupational exposure risk assessment; the use of a sub-chronic rather than a chronic dermal NOEL is probably valid (without needing an additional uncertainty factor) since chronic and sub-chronic NOELs are usually very similar for OPs (in animal studies).

Oncogenicity

Methamidophos chronic feeding to rats or mice did not result in a dose-related increase in tumors in either sex, nor was there an earlier onset of tumors. Genotoxicity tests with methamidophos were generally negative. However, it did cause mutations at the HDT in one (of two) CHO/HGPRT tests *in vitro*, with metabolic activation. Chromosomal aberrations were also observed in CHO cells, *in vitro.*

B. EXPOSURE ASSESSMENT

1. Occupational Exposure (Volume 2)

Volume 2 of this RCD was prepared by the Worker Health & Safety Branch of DPR (Zhao & Formoli, 2005). Four types of workers associated with the application of methamidophos were considered, the mixer, loader, applicator, flagger (M/L/A/F). There are two formulations of methamidophos in California, both liquids containing 4 lbs/gallon. Because of the high acute toxicity of methamidophos dermally (Category I), PPE (Personal Protective Equipment) requirements are extensive. Applicators must wear coveralls over short-sleeved shirt or pants, chemical-resistant gloves, footwear and headgear, protective eyewear and a respirator of an approved design. In addition, the M/L and persons cleaning equipment should wear a chemical-resistant apron. Engineering controls required for methamidophos are also extensive, including a closed system for the M/L. For workers using a closed system and a closed cab (or cockpit), some of the PPE requirements are relaxed, but specific label directions must always be followed. Post-application workers are required to allow a REI (Restricted Entry Interval) of 48h according to the federal label. However, because annual rainfall is generally below 25 inches, the REI is 72h in California. Similarly, pre-harvest intervals (PHIs) for tomatoes are from 7 to 14 days, for fresh and processing fruit respectively, and 50 days for cotton. It was assumed that the PHI was 7 days for the calculations in Volume 2. Up to 5 applications per season may be made to tomatoes, at intervals of 7 to 10 days and for cotton twice per season.

The computer estimates of exposure were derived using PHED (Pesticide Handlers Exposure Database), using three methods of application (aerial, groundboom, chemigation), four types of work task (M/L/A/F) with the appropriate personal protective equipment and engineering controls for each separate task (Volume 2). Six types of post-application exposure have also been estimated (Table 25). Currently, the only crop uses of methamidophos in California are cotton, tomatoes and potatoes.

The (acute) ADD (Absorbed Daily Dosage) for M/L/As ranged from 20.0 µg/kg/day (groundboom M/L/A, 70 Acres/day) to 337 µg/kg/day (M/L, aerial 1200 A/day). Flaggers were estimated to have ADDs of 190 (350 A/day) to 653 µg/kg/day (1200A/day). The (seasonal) SADD values ranged from 5.0 µg/kg/day to 84.1

µg/kg/day. The AADD values ranged from 1.7 to 28.1 µg/kg/day. For each of these chronic exposure categories, the lowest anticipated exposure was experienced by the groundboom M/L/A (70A/day) on potatoes/tomatoes and the highest by the M/L, aerial (1200 A/day) on cotton.

For fieldworkers, the involvement in tasks such as scouting, irrigation, staking, pruning and harvesting resulted in ADD values ranging from 0.8 µg/kg/day (potato harvesting) to 4.4 µg/kg/day (tomato stake/tie or transplant/prune). The SADD values ranged from 0.3 µg/kg/day (cotton, scout) to 0.9 µg/kg/day (tomato stake/tie or transplant/ prune). Corresponding values for AADD were 0.07 µg/kg/day (tomato, stake/tie, transplant/ prune or cotton scout) to 0.2 µg/kg/day (tomato scout/irrigate).

Table 25. Occupational exposure estimates for methamidophos.[#/]

Job category	Exposure g/lb A.I./pers.	Acute ADD [f/] g/kg/day	SADD [g/] g/kg/day	AADD [a/] g/kg/day
M/L aerial [b/]				
350 A (p/t)	16.54	98.2	24.5	8.2
1200 A (c)	16.54	337	84.1	28.1
Groundboom				
80 A (p/t)	16.54	22.4	5.6	1.9
200 A (c)	16.54	56.1	14.0	4.7
Chemigation, 350 A (p/t)	16.54	98.2	24.5	8.2
Applicator aerial				
350 A (p/t)	12.16	75.0	17.8	5.9
1200 A (c)	12.16	257	61.0	20.3
Groundboom				
80 A (p/t)	16.83	23.0	5.7	1.9
200 A (c)	16.83	57.4	14.4	4.8
M/L/A [c/] Groundboom				
70 A (p/t)	16.91	20.0	5.0	1.7
180 A (c)	16.91	51.5	12.9	4.3
Flagger Aerial				
350 A (p/t)	32.63	190	47.6	15.9
1200 A (c)	32.63	653	163	54.4
Fieldworkers [d/ e/]	**g/person/d**	**g/person/**	**g/person/**	**g/person/d**
cotton: scout	846	**d**	**d**	0.07
tomatoes:		3.5	0.3	
scout/ irrigate	745			0.2
stake/tie	1064	3.1	0.6	0.07
transplant/ prune	1064	4.4	0.9	0.07
harvest	424	4.4	0.9	0.1
potatoes: harvest	200	1.8 0.8	0.4 ---	---

a/ AADD = SADD x potential exposure months per year/12 months

b/ calculated using PHED (Zhao & Formoli, 2005); p/t = potatoes/tomatoes, c = cotton.
c/ for the M/L/A, 10% of time performing M/L activities and 90% on A is assumed
d/ calculated from field studies in Fresno, CA (cotton and tomato) and Stilwell, KS (potato) (Zhao & Formoli, 2005)
e/ DFR of 0.007 to 0.027 based on 7 day REI or PHI.
f/ Acute ADD calculated as the upper CL on the 95th percentile exposure estimate
g/ Seasonal ADD calculated as the 90th CL on the mean ADD;
The data in this table are taken from Tables 8 and 11 in RCD Volume 2 (HS-1825).

Inhalation exposure was assessed by measuring air concentrations of methamidophos at 5 sites close to field applications near Fresno, CA, in 2002 (ARB, 2003). The highest concentration in ambient air, in 168 samples, was 16 ng/m.^{3} An off-site air-moniroring study was also conducted in San Joaquin County, CA.

2. Dietary Exposure

DPR evaluates the dietary exposure to an active ingredient in the diet using two processes: (1) use of residue levels detected in RACs (raw agricultural commodities) to estimate the exposure from all label uses, and (2) use of tolerance levels to estimate the exposure to individual commodities (see Section VI). For the evaluation of risk to detected residue levels, the total exposure in the diet is determined for all label-approved raw agricultural commodities, processed forms, and animal products (meat and milk) that have established U.S. EPA tolerances. Tolerances may be established for the parent compound and associated metabolites. DPR considers these metabolites and other degradation products that may be of toxicological concern in the dietary assessment.

The percentage of a commodity (crop) which is treated with a particular pesticide is often considered relevant for dietary exposure. For short-term (acute) dietary exposure, it is assumed that 100 percent of each commodity has been treated and therefore contains a residue. However, for long-term (chronic) dietary exposure, it is reasonable to suppose that only a proportion of any specific commodity has been treated with a particular pesticide. Therefore, a percentage crop-treated adjustment can be made for specific commodities.

Residue Data

Primary and Secondary Residues

Data for potential pesticide residues associated with U.S. EPA and California label-approved direct food uses with tolerances, and with any secondary residues in animal tissues, are necessary for estimating human dietary exposures. The sources of residue data for dietary exposure assessment include DPR and federal monitoring programs, field trials, and survey studies by registrants. Residue data obtained from the monitoring programs are often preferred because they represent a realistic estimate of potential exposure. When residues are at levels higher than established tolerances, they are not utilized in the dietary exposure assessments since they are illegal. Additionally, DPR evaluates the potential risk from consuming commodities with residues over tolerance levels using an expedited acute risk assessment process. In the absence of data, surrogate data are used from the same crop group as defined by U.S. EPA, or theoretical residues equal to U.S. EPA tolerances are used.

The U. S. Department of Agriculture (USDA) is responsible for the Pesticide Data

Program (PDP), a nationwide cooperative monitoring program. The PDP is designed to collect objective, comprehensive pesticide residue data for risk assessments. There have been no determinations of methamidophos residues in secondary animal products because there are no tolerances for such commodities. Because of its short persistence in the field, there is little likelihood of leaching into groundwater. Analysis was for parent only because the degradates are anticipated to have negligible toxicity. When no residue was detected in a sample, it was assumed that methamidophos was present at the limit of detection (LOD). Residue data in RACs for the determination of potential dietary exposure to methamidophos were obtained from (1) registrant field and processing studies and (2) USDA 1994-7 PDP monitoring program (Table 1).

Acute Exposure

Estimates of potential acute dietary exposure use the highest measured residue values at or below the tolerance for each commodity. The following assumptions are used to estimate potential acute dietary exposure from measured residues: (1) the residue does not change over time, (2) the concentration of residue does not decrease when the raw agricultural commodity is washed, (3) processing is assumed to result in a residue level equivalent to or higher than that in the raw agricultural commodity; an adjustment factor may be used and (4) all foods that are consumed will contain the highest reported residue. The default procedure assumed that "below detection limit" residues were equal to 100% of the LOD for each commodity.

Residue trials show that methamidophos (parent) residues would be anticipated on an acute basis in cotton (0.01 ppm), potato (0.0091 ppm) and tomato (0.082 ppm) (Table 1). Default residues of the LOD were used for each commodity for the estimation of potential acute dietary exposure when no residue was detected in a sample. It is considered inappropriate to use "percentage of crop-treated data" for addressing acute dietary exposure.

Chronic Exposure

Estimates of potential chronic dietary exposure used the average of measured and "below detection limit" residue values for each commodity. The default procedure assumed that "below detection limit" residues were equal to 50% of the LOD for each commodity. The following assumptions were used to estimate potential chronic dietary exposures from measured residues: (1) the residue level does not change over time, (2) residues are not reduced by washing the RAC, (3) processing is assumed to be at a level equivalent to the RAC residue level that may be multiplied by an adjustment factor (4) exposures to a commodity at all reported residue levels do occur, *i.e.* a commodity with the average calculated residue is consumed every day at an annual average level (dosage) and (5) except where stated, 100% of each crop was treated with a particular pesticide.

Field residue trials (Table 1) showed that methamidophos (parent) residues would be anticipated on an annual basis in cotton (0.005 ppm oil, 0.042 ppm meal), potato (0.0019 ppm) and tomato (0.013 ppm). Default residues of 50% of LOD were used for each commodity for the estimation of potential chronic (annual) dietary exposure when no residue was detected in a sample. Percentage of crop-treated data (Carr, 1998) indicates that approximately 15% of cotton, 30% of potatoes and 20 to 85% of tomatoes are treated with methamidophos in California (Appendix B).

Dietary Exposure Analysis

Acute Exposure

Acute dietary exposure analyses were conducted using the DEEM^{J} program (Novigen, 1998). This program estimates the distribution of user-day (consumer-day) exposure for the overall U.S. population and specific population subgroups. A user-day is any day in which at least one food from the specific commodity list is consumed. The analysis uses data from the USDA CSFII (Continuing Survey of Food Intakes of Individuals) from a 1994-1998 survey. The program was used to calculate the 95$^{th.}$ and 99.9$^{th.}$ percentile of user-day exposures. An acute dietary exposure analysis was conducted using a point estimate approach and also a Monte Carlo (probabilistic) method (Table 26). This was considered appropriate because the MOEs were only 460 to 1260 at the 95th percentile of exposure using the point estimate model.

The potential acute dietary exposure to methamidophos from all labeled uses at the 95$^{th.}$ percentile ranged from 0.238 to 0.646 g/kg-day (point estimate) and 0.048 to 0.129 g/kg-day (Monte Carlo) using the 1994-1998 CSFII survey data (Table 26). Seniors (55+ yrs.) and children, 1-6 yrs. were the low and high exposure groups, respectively. Potential acute dietary exposure to methamidophos from all labeled uses at the 99.9$^{th.}$ percentile ranged from 0.515 (seniors) to 1.410 g/kg-day (children, 1-6 yrs.) using Monte Carlo (Table 26). Appendix B gives the complete dietary analysis.

Chronic Exposure

The potential chronic dietary exposure was also calculated using DEEM^{J} software. The food consumption data for the chronic analysis was also based on the 1994-98 USDA Nationwide Food Consumption Survey. Calculations of annualized mean dietary exposure were made, adjusting for percentage of crop-treated with methamidophos in California (Appendix B), using the point estimate approach (Table 27).

All potential dietary exposure was pooled by combining methamidophos residues in all commodities on which methamidophos use is registered. The mean potential annual dietary exposure ranged from 0.001 (nursing infants) to 0.013 g/kg-day (children 1-6 yrs.) using the 1994-1998 CSFII survey data. Percentage of crop-treated adjustment factors were 15% for cottonseed (meal or oil), 30% potato and 85% for tomatoes. In the absence of PCT, mean annualized exposure ranged from 0.003 (nursing infants) to 0.027 g/kg-day (children 1-6 yrs.).

3. Combined Occupational and Dietary Exposure.

The potential acute combined exposure from occupational and dietary sources has been calculated for the US population, all-seasons sub-group (Tables 25, 26). The total was 20.3 - 337 µg/kg-d, using the point estimate approach for dietary exposure and 20.1 - 337 µg/kg-d using the Monte Carlo approach. Both used the 95th percentile for occupational (M/L/A) and dietary exposure. Thus, occupational exposure comprised ≥ 98% of total exposure.

Potential chronic combined exposure was 1.707 – 28.107 µg/kg-d *i.e.* occupational exposure comprised ≥ 99% of total exposure (Tables 25, 27).

Because DEEM[J] does not provide an estimate of seasonal, dietary exposure, it is not possible to calculate combined seasonal dietary and occupational exposure. However, because occupational exposure accounted for over 98% of total exposure for both acute and chronic combined exposure scenarios, it is probable that occupational exposure provided the vast majority of exposure for seasonal combined exposure also.

Table 26. Potential acute dietary exposure to methamidophos at the 95th. and 99.9th. percentile in all commodities with U.S. EPA tolerances.

Population subgroup	ACUTE EXPOSURE (g/kg -day)		
	95th. percentile		99.9th. percentile
	Point estimate	Monte Carlo	Monte Carlo
US Pop. all seasons	0.323[a/]	0.067[b/]	0.706[b/]
Western Region	0.355	0.071	0.749
Hispanics	0.394	0.083	0.877
Non-Hispanic Whites	0.314	0.065	0.670
Non-Hispanic Blacks	0.321	0.061	0.719
Non-Hispanic Other	0.353	0.088	0.816
All Infants	0.574	0.059	1.234
Infants (nursing)	0.366	0.059	0.822
Infants (non-nursing)	0.604	0.092	1.279
Children (1-6 yrs)	**0.646**[c/]	**0.129**[c/]	**1.410**[c/]
Children (7-12 yrs)	0.409	0.086	0.880
Females (13-19 yrs, not pregnant or nursing)	0.299	0.063	0.633
Females (13+ yrs, pregnant, not nursing)	0.292	0.061	0.567
Females (13+ yrs, nursing)	0.307	0.056	0.553
Females (20+ yrs, not pregnant or nursing)	0.248	0.051	0.519
Females (13-50 yrs.)	0.261	0.055	0.543
Males (13-19 yrs)	0.344	0.076	0.617
Males (20+ yrs)	0.279	0.059	0.568
Seniors (55+ yrs)	**0.238**[c/]	**0.048**[c/]	**0.515**[c/]

a/ DEEM[J] was used to calculate point estimates of acute dietary exposure (tomato, potato and cottonseed).

b/ DEEM[J] was used to calculate probabilistic (Monte Carlo) estimates of acute dietary exposure (tomato, potato and cottonseed).

c/ highest and lowest values are in bold type.

mg/kg/day, the amount absorbed in a rat acute dermal study) by the acute ADD (95th percentile). For the M/L/A, the MOEs ranged from 3 (M/L aerial, cotton) to 45 (M/L/A ground boom, potato/tomato). The seasonal MOE was calculated by dividing the sub-chronic NOEL (0.22 mg/kg/day, the amount absorbed in a rat subchronic dermal study) by the SADD (90th percentile). These MOEs ranged from 3 (M/L or A aerial, cotton) to 44 (M/L/A ground boom, potato/tomato). The annual MOE was determined by dividing this NOEL (0.22 mg/kg/day) by the AADD (the ADD amortized over 12 months). These MOEs ranged from 8 to 130 for the same groups of workers as for seasonal exposure. For flaggers, the MOEs were determined to be from 1 to 5 for all of these exposure periods. For fieldworkers, the MOE estimates ranged from 200 (tomato, stake/tie or transplant/prune) to 1100 (potato, harvest) at the acute exposure level. For seasonal exposure, MOEs ranged from 240 (tomato, stake/tie or transplant/prune) to 730 (cotton, scout). The annual MOEs ranged from 1100 (tomato, scout/irrigate) to 3100 (cotton, scout or tomato, stake/tie or transplant/prune).

Table 28. Margins of exposure for potential occupational exposure to methamidophos#

Job category	Acute MOE a/	Seasonal MOE b/	Annual MOE b/
M/L aerial			
350 A (p/t)	9c/	9c/	27c/
1200 A (c)	3	3	8
Groundboom			
80 A (p/t)	40	39	120
200 A (c)	16	16	47
Chemigation			
350 A (p/t)	9	9	27
Applicator aerial			
350 A (p/t)	12	12	37
1200 A (c)	4	4	11
Groundboom			
80 A (p/t)	39	39	120
200 A (c)	16	15	46
M/L/A			
Groundboom	45	44	130
70 A (p/t)	17	17	51
180 A (c)			
Flagger Aerial	5	5	14
350 A (p/t)	1	1	4
1200 A (c)			
Fieldworkers			
cotton: scout	260	730	3100
tomatoes: scout/ irrigate	290	370	1100
stake/tie	200	240	3100
transplant/ prune	200	240	3100
harvest	500	550	2200
potatoes: harvest	1100	---	---

a/ using a NOEL of 3.0 mg/kg/day, equivalent to an absorbed NOEL of 0.9 mg/kg/day (29% dermal absorption) from a rat acute dermal toxicity study (Easter & Rosenberg, 1986).

b/ using a NOEL of 0.75 mg/kg/day, equivalent to an absorbed NOEL of 0.22 mg/kg/day (29% dermal absorption) from a rat 21-day dermal toxicity study (Sheets & Gastner, 1997).

c/ numbers for MOE rounded to nearest whole number.

The occupational exposure data in this table are from Table 25. MOE = NOEL/Exposure.

Lifetime Exposure

The results of the chronic toxicity studies in rodents and in the genotoxicity tests (described in Section IIID and IIIE) suggest that there is little or no risk of cancer from the use of methamidophos. Therefore, lifetime exposure and risk are not considered relevant in the dietary assessment of the toxicology of methamidophos.

Table 27. Potential chronic dietary exposure to methamidophos in all commodities with U.S. EPA tolerances.

Population subgroup	CHRONIC EXPOSURE (annualized mean) g/kg -day	
	Percent Crop Treated (PCT)	**No PCT**
US Pop. all seasons	0.007 a/c/	0.014 a/c/
Western Region	0.007	0.015
Hispanics	0.009	0.017
Non-Hispanic Whites	0.007	0.014
Non-Hispanic Blacks	0.006	0.012
Non-Hispanic Other	0.007	0.014
All Infants	0.003	0.007
Infants (nursing)	**0.001** b/	**0.003** b/
Infants (non-nursing)	0.004	0.008
Children (1-6 yrs)	**0.013** b/	**0.027** b/
Children (7-12 yrs)	0.008	0.018
Females (13-19 yrs, NP NN)	0.006	0.013
Females (13+ yrs, P NN)	0.003	0.013
Females (13+ yrs, nursing)	0.007	0.012
Females (20+ yrs, NP NN)	0.006	0.011
Females (13-50 yrs.)	0.006	0.012
Males (13-19 yrs)	0.007	0.016
Males (20+ yrs)	0.006	0.012
Seniors (55+ yrs)	0.006	0.010

a/ DEEM[J] annual average dietary exposure (tomato, potato and cottonseed).
b/ highest and lowest values are in bold type.
c/ used 1994-1998 CSFII survey data for estimating dietary exposure.

C. RISK CHARACTERIZATION

The risk characterization process consists of calculating a margin of exposure (MOE) by dividing the critical acute, subchronic or chronic NOEL value for a specific toxicological endpoint (Section IV A) by an estimate of human exposure (Section IV B). Generally, a MOE of 100 is considered sufficient to protect human health when the critical NOEL is derived from laboratory animal studies or a MOE of 10, whenever those studies were conducted on humans. The critical NOEL values were derived from an acute dermal study in the rat (short-term occupational), a sub-chronic dermal study in the rat (seasonal and chronic occupational) an oral gavage study in the rat (acute dietary) and a dietary study in the dog (annual dietary). Dermal absorption of methamidophos in humans was estimated to be 29%, and this was used to estimate the absorbed dosages in rat dermal studies. Since oral toxicity studies were used to calculate MOEs for dietary exposure, no route-to-route extrapolation was necessary.

Occupational Exposure

The estimates of occupational exposure (Table 25) were used to calculate MOE values for various work tasks (Table 28). The acute MOE was derived by dividing the acute NOEL (0.9

The MOE for inhalation exposure, based on a measured maximum air concentration of 16 ng/m^3 and a 3-month rat inhalation toxicity NOEL of 1.1 mg/m^3 is likely to be ≥5 orders of magnitude for acute or seasonal inhalation exposure to methamidophos.

Dietary Exposure

Acute Exposure

The margin of exposure (MOE) for each population subgroup for potential acute dietary exposure to methamidophos is given in Table 29. These values were derived from the dietary exposure values (Table 26) for all registered commodities (cotton, potato, tomato). The MOE values, for exposure at the 95$^{th.}$ percentile, ranged from 460 for children, 1-6 yrs. to 1260 for seniors (55+ yrs.) using the point estimate approach. Using a Monte Carlo approach, the equivalent MOE figures were 2320 to 6230 for the same population subgroups. At the 99.9$^{th.}$ percentile of exposure, using Monte Carlo, the MOE ranges were 210 for children, 1-6 yrs. to 580 for Seniors, 55+. The dietary exposure and margin of exposure determinations are summarized in Table 31.

Chronic (Annual) Exposure

The margin of exposure for each population subgroup following potential chronic (annual, average) dietary exposure to methamidophos has been calculated, with DEEM[7] software, using point estimates (Table 30). These values were derived from the exposure values (Table 27) using all registered commodities, both with and without adjustment for percentage of crop-treated. The MOE values ranged from 1550, for children (1-6 yrs.), to 16,700 for nursing infants (<1 yr.) using PCT and 730 to 7950 for the same population subgroups without PCT. The dietary exposure and margin of exposure determinations are summarized in Table 31.

Combined Occupational and Dietary Exposure

The acute MOE following short-term exposure through occupational and dietary routes was 1 to 45. For chronic combined exposure, the range was <1 to 12, the same as for occupational exposure alone.

Table 29. Margins of exposure for potential acute dietary exposure to methamidophos at the 95th. and 99.9th. percentile in all commodities with U.S. EPA tolerances.[a,b/]

Population subgroup	MOE for ACUTE EXPOSURE[c/]		
	DEEM[7] [d/] 95th. percentile	DEEM[7] [e/] 95th. percentile	DEEM[7] [e/] 99.9h. percentile
US Pop. all seasons	930	4500	430
Western Region	840	4220	400
Hispanics	760	3600	340
Non-Hispanic Whites	960	4620	450
Non-Hispanic Blacks	930	4930	420
Non-Hispanic Other	850	4210	370
All Infants	520	3430	240
Infants (nursing)	820	5070	360
Infants (non-nursing)	500	3250	230
Children (1-6 yrs)	**460** [f/]	**2320** [f/]	**210** [f/]
Children (7-12 yrs)	730	3480	340
Females (13-19 yrs, not pregnant or nursing)	1000	4770	470
Females (13+ yrs, pregnant, not nursing)	1030	4910	530
Females (13+ yrs, nursing)	980	5380	540
Females (20+ yrs, not pregnant or nursing)	1210	5930	**580**
Females (13-50 yrs.)	1150	5430	550
Males (13-19 yrs)	870	3970	490
Males (20+ yrs)	1070	5120	530
Seniors (55+ yrs)	**1260** [f/]	**6230**[f/]	**580**[f/]

a/ from Carr, 1998 (Appendix 2).
b/ Residues on tomato, potato and cottonseed.
c/ MOE= NOEL / Acute Dietary intake
NOEL of 0.3 mg/kg/day based on brain and plasma AChE inhibition and FOB effects at 0.6 mg/kg/day in a rat neurotoxicity study (Sheets, 1994a).
d/ DEEM[J] point estimate of dietary exposure (Table 25).
e/ DEEM[J] probabilistic (Monte Carlo) estimate of dietary exposure (Table 25).
f/ highest and lowest values are in bold type.

Table 30 Margins of exposure for chronic dietary exposure to methamidophos residues in all commodities with U.S. EPA tolerances.[a/]

Population subgroup	MOE for CHRONIC EXPOSURE [b/]	
	Percent Crop Treated (PCT)	**No PCT**
US Pop. all seasons	2930	1440
Western Region	2690	1370
Hispanics	2160	1150
Non-Hispanic Whites	3010	1470
Non-Hispanic Blacks	3540	1620
Non-Hispanic Other	2690	1410
All Infants	6450	3010
Infants (nursing)	**16,700** [c/]	**7950**[c/]
Infants (non-nursing)	5230	2430
Children (1-6 yrs)	**1550**[c/]	**730**[c/]
Children (7-12 yrs)	2420	1080
Females (13-19 yrs, not pregnant or nursing)	3360	1490
Females (13+ yrs, pregnant, not nursing)	3200	1580
Females (13+ yrs, nursing)	2890	1620
Females (20+ yrs, not pregnant or nursing)	3490	1870
Females (13-50 yrs.)	3440	1730
Males (13-19 yrs)	2740	1280
Males (20+ yrs)	3250	1620
Seniors (55+ yrs)	3570	1970

a/ DEEM[7] annual average dietary exposure (tomato, potato and cottonseed), based on CSFII 1994-1998 (USDA, 1998).

b/ $\text{MOE} = \frac{\text{NOEL}}{\text{Chronic Dietary intake}}$

NOEL (estimated) of 0.02 mg/kg/day based on brain AChE inhibition in a dog 1-yr. toxicity study, with a LOEL of 0.06 mg/kg/day (Hayes, 1984c).

c/ highest and lowest values are in bold type.

Table 31. Summary of dietary exposure and margins of exposure associated with the use of methamidophos on cotton, potato and tomato, combined.

Type of calculation	95th. percentile acute	99.9th. percentile acute
ACUTE POINT ESTIMATE	0.238-0.646 g/ kg-d. [MOE=460[2/]-1,260[1/]]	
ACUTE DISTRIBUTIONAL (Monte Carlo)	0.048-0.129 g/ kg-d. [MOE=2,320[2/]-6,230[1/]]	0.515-1.410 g/ kg-d. [MOE=210[2/] - 580[1/]]
CHRONIC ANNUALIZED MEAN	**Percent-Crop-Treated** 0.001-0.013 g/ kg-d [MOE= 1,550[2/]-16,700[3/]]	**NO Percent-Crop-Treated** 0.003-0.027 g/ kg-d [MOE= 730[2/]-7,950[3/]]

1/ seniors (55+ yrs.)
2/ children (1-6 yrs.)
3/ nursing infants (<1 yr.)

V RISK APPRAISAL

A. Introduction

Risk assessment is the process that is used to evaluate the potential for exposure and the likelihood that the toxic effects of a substance will occur in humans under specific exposure conditions. Every risk assessment has inherent limitations and uncertainties in the application of existing data to estimate the potential risk to human health. Therefore, certain *a priori* assumptions are incorporated into the hazard identification, dose-response assessment and exposure assessment processes. These, in turn, result in uncertainty in the risk characterization, which integrates all of the information in these three processes. Qualitatively, risk assessment for all chemicals has similar types of uncertainty. However, the degree or magnitude of the uncertainty varies depending on the availability and quality of the data and the exposure scenarios being assessed. Varying degrees of uncertainty are involved in the estimation of these parameters, affecting the accuracy of the risk characterization. Specific areas of uncertainty associated with this risk assessment for methamidophos are delineated in the following discussion.

B. Hazard Identification

Acute toxicity tests measure the effects of a chemical after a single or brief period of exposure. Developmental toxicity tests, which are often used for acute risk assessment, did not show increased susceptibility of the developing organism to the effects of methamidophos relative to the dam. Maternal toxicity can also be used for acute risk assessment, for example, in cases where rapid body weight loss occurs during developmental toxicity tests. However, ChE inhibition in dams, which was determined at the study conclusion, is not considered an acute effect since it could have resulted from repeated dosings. Instead, the most sensitive acute endpoints were observed when methamidophos was evaluated in two acute neurotoxicity studies in the SD rat which, considered together, gave LOEL and NOEL values of 0.6 and 0.3 mg/kg/day, respectively. The latter value was used for acute dietary risk assessment for methamidophos. These values probably represent a fairly accurate determination of toxicity because they were based on both AChE inhibition (plasma, RBC and brain) and a FOB (behavioral) effect, (although the latter effect was only found in males). This helps to remove a lot of the uncertainty associated with the choice of a particular form of AChE for consideration as the endpoint for LOEL/NOEL determination. It should also be noted that AChE inhibition at the LOEL was □15%, for plasma, RBC and brain, was statistically significant and occurred in both sexes. However, it is unclear what level of inhibition of AChE should be considered adverse (see below). The rat reproductive toxicity and developmental neurotoxicity studies did not indicate a greater sensitivity of the pups than adults to methamidophos. In the latter study, it was considered by both the registrants and the DPR reviewer, that 8% inhibition ($p<0.05$) of brain AChE in dams was toxicologically significant at the LDT (lowest dose tested) of 1 ppm. However, in pups at 1 ppm, brain AChE was not inhibited at PND4, and by only 3% (M) and 2% (F) at PND21 (n.s.).

For acute, occupational risk assessment, where the majority of exposure is via the dermal route, it was considered appropriate to use a NOEL from an acute rat dermal toxicity study. In this study, the LOEL was 8.9 mg/kg/day and the NOEL was 3.0 mg/kg/day. The NOEL values at 72h were lower than those at 24h, the former being used for risk assessment in order to be health protective. However, it is possible that the 24h values are more appropriate for acute risk assessment. Another factor that may have lowered the NOEL is the use of a human (29%) rather than rat dermal absorption to calculate the absorbed dosage for this NOEL. Because dermal absorption in the rat is generally greater than in the human, by a factor of 5 to 10-fold according to Feldmann & Maibach, 1974 and Wester & Maibach, 1985, the rat NOEL (as absorbed dosage) could have been higher using rat dermal absorption. It should be remembered, however, that human dermal absorption may be greater during exposure under field conditions than in the laboratory.

In the evaluation of chronic toxicity, the most sensitive endpoint in the rat, mouse and dog, was the inhibition of AChE. A statistically significant level of inhibition was recorded in all species at the LDT of 2 ppm in the diet. Therefore, an estimated NOEL (from the dog study), equivalent to 0.02 mg/kg/day was calculated, by dividing the LOEL by a default UF of 3. This estimated NOEL was used for chronic, annual dietary risk characterization. The use of a default factor of 3 in estimating a NOEL from a LOEL is supported by BMD calculations (Section IV.A). The lower bound on the dose giving a 10% reduction of brain AChE activity was just above 0.02, regardless of the program used, indicating that this value would be close to the "true" chronic NOEL. It should also be noted that there is currently much uncertainty concerning the most appropriate degree of inhibition to use for regulatory purposes. For example, it has been suggested that inhibition of (brain) ChE of 20% should be used to establish the LOEL/NOEL (Carlock *et al.,* 1999) but current Medical Toxicology Branch policy considers 10% inhibition to be adverse.

It should also be noted that, owing to its high hydrophilicity (log K_{ow} -0.66), methamidophos would be anticipated to penetrate the blood brain barrier poorly, in the absence of a carrier-mediated specific uptake mechanism. Therefore, the brain AChE inhibition that was measured may have been predominantly localized in glial cells rather than having been synaptic. The presence of such extra-synaptic glial ChE has been demonstrated in the insect CNS using cytochemical methods, including electron microscopy (Smith and Treherne, 1965). The possible toxicological significance of the inhibition of brain, glial ChE is presently unclear, although it would not be anticipated to result in clinical signs to the same extent as would the inhibition of synaptic ChE. However, it may explain, at least in part, the relatively high inhibition of brain AChE that was reported in chronic and sub-chronic dietary studies in rodents and dogs, often as much as 90%, without any clinical signs. However, it has also been suggested that methamidophos requires activation *in vivo*, through an oxidation mechanism, prior to inhibiting ChE (Mahajna & Casida, 1998).

There is evidence that organophosphates may play a role in disrupting glial cell growth. It has been demonstrated that chlorpyrifos and diazinon inhibit DNA synthesis in nerve cells, *in vitro* (Qiao *et al.,* 2001). The effects were more pronounced in glial cells (C6) than in neuronal cells (C12). The disruption of DNA synthesis could, in turn, result in altered glial cell structure, with consequent changes in the properties of the blood-brain-barrier. However, counting against this theory to explain methamidophos' action is the finding that the parent OPs were more potent than their oxon metabolites, the form of methamidophos.

It is also possible that methamidophos interacts with P-Glycoprotein transporters (PGTs) in the rat brain, also known as the multi-drug-resistance or MDR-protein mechanism. Such PGTs remove a variety of molecules from the brain, including the carbamate insecticide thiodicarb (Lenning *et al.*, 1996). Disruption of the PGT system could result in higher levels of methamidophos in the brain being maintained than in the presence of an intact PGT system. However, in rodents such as the SD rat, the PGT system does not develop until the animal is 3 wks. of age (Lankas *et al.,*1989). The absence of the PGT system, which would be equivalent to its disruption, would therefore lead to greater levels of methamidophos in brain (for AChE inhibition) in neonatal rats than in adults. This is the opposite of the effects described in the DNT and reproductive toxicity studies, where the pups' brains appear to be less susceptible than adults,' reducing the likelihood of a PGT explanation.

However, it should be mentioned that pre-weaning rats, receiving all of their methamidophos via the dams' milk, would be anticipated to receive very little of the organophosphate. This is because a compound with such high aqueous solubility, coupled with such low lipid solubility, would not be anticipated to partition into milk at very high concentrations. The issue of the estimation of exposure is a critical one for the reproductive toxicity and DNT studies. As more research is conducted, it may be possible to amend the protocols for such studies to include estimations of the pups' exposure to the pesticide. This would allow a more precise measure of innate sensitivity of pups vs. dams for use in risk assessment

C. Exposure Assessment

Occupational Exposure

As mentioned in Section II.E., methamidophos application during the early 1990s was associated with a high probability of worker illness. It was third in likelihood, after mevinphos (since withdrawn) and methomyl. During the 5-year period 1996-2000, 14 cases were reported to DPR, but in every case, multiple pesticide applications obscured the identity of the causative agent(s). However, because the vast majority of the occupational exposure calculations gave MOE values well below 100 (many of them below 10), it is difficult not to consider methamidophos a risk factor in the development of illnesses following the application of methamidophos, even in the presence of competing risk factors. More recent occupational exposure data are provided in Zhao & Formoli, 2005.

Dietary Exposure

Methamidophos is an insecticide that is used on foliage and is therefore often detected in RACs (cotton and tomato) at harvest. Therefore, the residue values used for calculating possible dietary exposure are considered reasonable estimates rather than Aworst-case@ ones. For chronic exposure, the percentage of crop treated factor has been used, which will have the effect of reducing chronic dietary exposure and increasing the MOE values.

The two DEEM[7] programs used for calculating acute dietary exposure, point estimate and Monte Carlo, have resulted in slightly different dietary exposure estimates and corresponding MOE values. The Monte Carlo program generally yielded lower dietary exposure estimates than the point estimate, the former being generally 20% to 40% of the latter. It is often considered that the Monte Carlo probabilistic simulation of acute dietary exposure is more appropriate than the point estimate, deterministic approach. However, the use of MOE values from Monte Carlo simulations in risk assessment could result in underestimation (of dietary exposure) whenever point estimates are more appropriate. On the other hand, not using the percent crop-treated adjustment factor for acute exposure may have the effect of overestimating acute exposure in the present calculations.

The organophosphate insecticide acephate, which is the *N*-acetyl analog of methamidophos, is enzymatically converted to the latter, in both insects and mammals. Because acephate is inactive against AChE, it is considered to owe its toxicity to this conversion, *in vivo*. Acephate is widely used in California, on a range of ~20 crops, giving rise to potential indirect methamidophos exposure. It was also registered for home & garden uses, giving rise to additional potential exposure to methamidophos, but these uses have recently been canceled by the registrants. Because a risk assessment for acephate has not yet been completed, it has not yet been considered from the perspective of aggregate and/or combined exposure,

under FQPA (1996). However, it should be recognized that dietary exposure to methamidophos, calculated here from just the use of methamidophos, will probably underestimate total methamidophos exposure from all sources.

D. Issues Related to the Food Quality Protection Act

Introduction

The Food Quality Protection Act of 1996 mandated USA EPA to "upgrade its risk assessment process as part of the tolerance setting procedures" (US EPA, 1997a,b). The changes to risk assessment were based in part on recommendations from the National Academy of Sciences report, "Pesticides in the Diets of Infants and Children" (NRC, 1993). The act required an explicit determination that tolerances were safe to children. US EPA was required to use an extra 10-fold safety factor to take into account both pre-/post natal developmental toxicity and the completeness of the database, unless US EPA determined, based on reliable data, that a different margin would be safe. In addition, US EPA must consider available information on: 1/ aggregate exposure from all non-occupational sources; 2/ effects of cumulative exposure to the pesticide plus others with a common mechanism of toxicity; 3/ effects of *in utero* exposure; 4/ the potential for endocrine disrupting effects.

Aggregate Exposure(s)

This refers to the possibility that an individual might be exposed to a particular chemical by more than one route. In the case of methamidophos, exposure is likely to be entirely *via* the oral route. There are no home and garden registrations for methamidophos in California. Therefore, dietary exposure will be the only likely route; methamidophos is unlikely to be found in potable water. Home and garden uses of the insecticide acephate, which is bioactivated to methamidophos, have recently been canceled. Although not mandated under FQPA, DPR has previously conducted, and will continue to conduct, aggregate exposure and risk estimations based on dietary and occupational exposure pathways, where appropriate.

Cumulative Exposure(s)

There is a possibility that an individual could be exposed to multiple chemicals sharing the same mechanism of toxicity. An effort is to be made under FQPA to attempt to combine these "cumulative exposure(s)" to related chemicals. In the case of methamidophos, such multiple chemical exposure(s) will include exposure to acephate. The determination of cumulative risk (USEPA, 2002b) must await the completion of a risk assessment for acephate and other OPs by DPR.

Pre-/Post Natal Sensitivity

Seven developmental toxicity studies (four rat, three rabbit) failed to show fetal or embryonic toxicity at doses of methamidophos less than those affecting dams. No evidence was forthcoming from these experiments that there was an increase in sensitivity among fetal/embryonic animals compared with adults. It is therefore unlikely that an additional factor will be required to protect against increased pre-/post natal sensitivity to methamidophos. The recently completed developmental neurotoxicity study of methamidophos also indicates that fetal/young rats are not more sensitive than adults. However, there must remain a degree of uncertainty about the precise dosage received by the pups in the reproductive toxicity and developmental neurotoxicity studies. These issues have been discussed above (Section B).

In a 2-generation (SD) rat reproductive toxicity study, reduced body weight was reported in

adults and pups with the same LOEL and NOEL values. Because inhibition of AChE appeared to be more marked in adults than pups, it is therefore unlikely that methamidophos has adverse effects on reproduction.

Endocrine Effects

Endocrine effects caused by a pesticide are also to be addressed under FQPA. The main hormonal systems under consideration are male and female reproductive hormones and thyroid hormones. There are no indications that methamidophos may be toxic to any of these.

E. Comparison of the endpoints/NOELs used by DPR with those used by USEPA

Main points of comparison

Inhibition of brain AChE, usually accompanied by plasma and RBC ChE inhibition, is the endpoint chosen for risk assessment by both DPR and USEPA. The critical NOEL for acute dietary risk assessment (0.3 mg/kg/d), from a rat oral gavage study (Table 32, a) is agreed. DPR used an acute rat, dermal NOEL for acute occupational risk assessment (Table 32, b). USEPA used a subchronic (21-d) rat dermal study (Table 32, c) for both acute and seasonal occupational risk assessment, with a NOEL of 0.745 mg/kg/d. DPR used this study for seasonal and chronic occupational risk assessment. USEPA used a NOEL from a subchronic (8 wk) rat dietary study (Table 32, d), with a NOEL of 0.03 mg/kg/d, for chronic dietary risk assessment. DPR used an estimated NOEL of 0.02 mg/kg/d, from a 1-yr dog dietary study (Table 32, e), for chronic dietary and occupational risk assessment. USEPA does not conduct chronic occupational risk assessments.

FQPA considerations

USEPA added a FQPA safety factor of 3x in its dietary risk assessment of October 4, 1999, because of neurotoxicity concerns, in hens and humans.[6/] It was stated that these would be addressed in the DNT (developmental neurotoxicity) study, completed in February, 2002. However, the DNT study showed that immature rats were no more susceptible than adults (RCD, Section III.H). Nonetheless, USEPA continued to use a 3x FQPA safety factor in the IRED (April 7, 2002) based on literature evidence of delayed peripheral neuropathy (OPIDN) in hens and humans.[7/] The DNT study was not evaluated by USEPA at this time. OPIDN has been addressed by DPR as being a phenomenon that would only be of concern at very large (i.e. lethal) doses and would therefore not require a FQPA safety factor (RCD, Section III.I).

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[6]/ "The FQPA Safety Factor Committee retained a 3X factor because there is an indication of neurotoxic effects in hens and humans. A developmental neurotoxicity study is needed to properly evaluate the neurotoxicity of this chemical." on p. 5, paragraph 3.

[7]/ "In studies from the open scientific literature, ingestion of methamidophos has been shown to result in delayed peripheral neuropathy in humans" and "However, based on the evidence, the requirement of a developmental neurotoxicity study has been triggered. This study will in turn provide additional data. "

Table 32: Comparison of NOELs used by DPR and USEPA for conducting risk assessments for methamidophos.

Exposure type	DPR	USEPA	Study type
Acute, dietary	0.3 mg/kg/day[a/]	0.3 mg/kg/day[a/]	Rat, gavage[a/]
Acute, worker	3.0 mg/kg/day[b/]	0.745 mg/kg/day[c/]	Rat, dermal, 1-day[b/] Rat, dermal, 21-day[c/]
Seasonal, worker	0.75 mg/kg/day[c/]	0.745 mg/kg/day[c/]	Rat, dermal, 21-day[c/]
Chronic, dietary	0.02 mg/kg./day[e/]	0.03 mg/kg./day[d/]	Dog, diet, 1-yr.[e/]
Chronic, worker	0.75 mg/kg./day[c/]	Not applicable	Rat diet, 8-wk.[d/] Rat, dermal, 21-day[c/]

a/ Sheets, 1994.
b/ Easter & Rosenberg, 1986: a NOEL of 3.0 mg/kg/day is equivalent to an absorbed NOEL of 0.9 mg/kg/day (29% dermal absorption).
c/ Sheets & Gastner, 1997: a NOEL of 0.75 mg/kg/day is equivalent to an absorbed NOEL of 0.22 mg/kg/day (29% dermal absorption).
d/ Mobay, 1991.
e/ Hayes, 1984c.

VI TOLERANCE ASSESSMENT

A. INTRODUCTION

A tolerance is the maximum amount of pesticide residue that may remain in or on a food or animal feed (U.S. EPA, 1991). The U.S. EPA tolerance program was developed as an enforcement mechanism to identify illegal residue concentrations resulting from potential non-compliance with the product label requirements (e.g. improper application rates or methods, inadequate pre-harvest intervals, direct or indirect application to unapproved commodities). Tolerances are enforced by the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and state enforcement agencies (*e.g.* Pesticide Enforcement Branch of DPR).

The data requirements established by U.S. EPA for tolerances include: (1) residue chemistry which includes measured residue levels from field studies, (2) environmental fate studies, (3) toxicology studies which evaluate the hazards to humans, domestic animals, and non-target organisms, (4) product performance such as efficacy, and (5) product chemistry which includes physical-chemical characteristics and analytical method (Code of Federal Regulations, 1992). The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications, and formulations proposed (U.S. EPA, 1982).

Currently, the tolerances set by U.S. EPA are 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 (U.S. EPA, 1991). U.S. EPA uses the Reference Dose for non-cancer risks, and negligible risk level for cancer as guides to determine the appropriate levels for dietary exposure.

Assembly Bill 2161 (Bronzan and Jones, 1989) requires the DPR to "conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides". In the situation where "any pesticide use represents a dietary risk that is deleterious to the health of humans, the DPR shall prohibit or take action to modify that use or modify the tolerance. ... ". As part of the tolerance assessment, a theoretical dietary exposure for a specific commodity and specific population subgroups can be calculated from the product of the tolerance and the daily consumption rate.

For a pesticide allowed to be used on numerous commodities, tolerance assessments are conducted for selected fruits and vegetables. Generally, commodities are selected from all the uses based on the potential for high levels of dietary exposure. For methamidophos, the tolerances for the following commodities were evaluated: cottonseed, potato and tomato. These were selected because they constitute all registered commodities in the United States.

B. ACUTE EXPOSURE

An acute exposure assessment using the residue level equal to the tolerance was conducted for each individual label-approved commodity. The DEEM[7] software program and the USDA Continuing Survey of Food Intakes of Individuals (CSFII) 1994-1998 were used in this assessment. The acute tolerance assessment does not routinely address multiple

commodities at the tolerance levels since the probability of consuming multiple commodities at the tolerance decreases as the number of commodities included in the assessment increases.

The range of potential dietary exposure values at the 97.5$^{th.}$ percentile for each registered commodity is given in Table 30. In summary, the MOEs were all above 4780 for cottonseed, above 160 for potatoes and below 100 for tomatoes. The least dietary exposure was from cottonseed (0.007 to 0.063 g/kg-day) and the most, from tomato (3.93 to 11.3 g/kg-day). These theoretical acute dietary exposure levels would give MOE values of approximately 4,780-43,380 (cottonseed) to 26-76 (tomato). The sub-populations with the lowest MOE values were infants, non-nursing <1yr. for cottonseed and potato; children, 1-6 yrs. for tomato. The sub-populations with the highest MOE values were Seniors, 55+ yrs. for cottonseed and potato; females, 13+ yrs, pregnant, non-nursing for tomato. For potato, MOE values ranged from 160 to 710. The results of the (acute) tolerance assessment for tomatoes indicate that USEPA should review the current tolerance of 1 ppm since the MOEs for all population sub-groups are below 100. It is possible that the use of percent-crop-treated (PCT) adjustment, which is considered by DPR to be inappropriate for (acute) tolerance assessment, is responsible for USEPA's recent decision to *increase* rather than decrease the tolerance for methamidophos on tomatoes (USEPA, 2002c).

C. CHRONIC EXPOSURE

A chronic exposure assessment using residues equal to the established tolerances for individual or combinations of commodities was not conducted because it is highly improbable that an individual would habitually consume single or multiple commodities with pesticide residues at tolerance levels. This conclusion is supported by data from both federal and DPR pesticide monitoring programs which indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance (CDFA, 1990-1993).

Table 33. Margins of exposure after consumption of each commodity registered for methamidophos use with residues at U.S. EPA tolerances.[a/]

Population subgroup	(Acute) Margin of Exposure at 97.5th. Percentile [b/]		
	Cottonseed[d/]	Potato[e/]	Tomato[f/]
US Pop. all seasons	20,360	460	49
Western Region	14,500	430	46
Hispanics	15,620	390	43
Non-Hispanic Whites	23,210	480	51
Non-Hispanic Blacks	15,920	420	46
Non-Hispanic Other	8,890	410	40
All Infants	5,450	170	28
Infants (nursing, <1 yr.)	9,190	340	34
Infants (non-nursing, <1 yr.)	**4,780**[1/]	**160**[1/]	27
Children (1-6 yrs)	7,780	240	**26**[1/]
Children (7-12 yrs)	12,410	360	40
Females (13-19 yrs) (not pregnant, not nursing)	24,350	540	60
Females (13+ yrs) (pregnant, not nursing)	42,800	460[2/]	**76**[2/]
Females (13+ yrs) (nursing)	11,170	540	65
Females (20+ yrs) (not pregnant, not nursing)	36,310	670	67
Females (13-50 yrs)	31,850	610	65
Males (13-19 yrs)	24,350	420	52
Males (20+ yrs)	34,640	600	61
Seniors (55+ yrs)	**43,380**[2/]	**710**[1/]	68

a/ from Carr, 1998 (Appendix 2). Tolerances are: 0.1 ppm (cottonseed, potato), 1 ppm (tomato).

b/ $\text{MOE} = \frac{\text{NOEL}}{\text{Acute Dietary intake}}$

NOEL of 0.3 mg/kg/day based on brain, RBC and plasma AChE inhibition and FOB effects in a neurotoxicity study (Sheets, 1994a).

c/ determined using the DEEM[7] program, using the 1994-1998 CSFII data.

d/ 1/ highest exposure to methamidophos, 0.063 g/ kg/day; highest and lowest MOE in bold.
2/ lowest exposure to methamidophos, 0.007 g/ kg/day.

e/ 1/highest exposure to methamidophos, 1.870 g/ kg/day.
2/ lowest exposure to methamidophos, 0.424 g/ kg/day.

f/ 1/highest exposure to methamidophos, 11.30 g/ kg/day.
2/ lowest exposure to methamidophos, 3.93 g/ kg/day.

VII CONCLUSIONS

The toxicological risk from potential occupational and dietary exposure to methamidophos, as found in Monitor,[7] has been estimated. Residues in all three crops for which there are currently tolerances were considered *i.e.* cottonseed, potato and tomato. It is not anticipated that methamidophos will be a contaminant of potable water.

A MOE of at least 100 is generally considered adequate to protect people from the toxic effects of a chemical when the NOEL is based on toxicology data from animal studies. Such animal data for methamidophos indicated that the inhibition of AChE was likely to be the endpoint of toxicological concern. For occupational exposure, PHED exposure estimates resulted in MOEs below 100 for all M/L/A activities and flagging, suggesting that mitigation measures may be necessary; for reentry tasks, based on a field study, MOEs were above 100. Using crop residue data, dietary exposure levels resulted in MOE values above 100. All population sub-groups had MOE values above 100 for acute as well as for chronic dietary exposure situations. For combined occupational and dietary exposure, however, MOEs were all below 100.

The consumption of crops with residues at tolerance resulted in (acute) MOE values above 100 for cottonseed and potato but below 100 for tomato, for all population sub-groups. It is recommended that USEPA review the current tolerance for tomatoes.

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IX APPENDICES

APPENDIX A

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

METHAMIDOPHOS

Chemical Code # 1697, Tolerance # 315
SB 950 # 2

July 20, 1993
Revised: 6/16/94, 5/30/95, 2/6/96, 8/20/97, 6/22/98, 11/22/99, 9/30/02, 10/01/03 and 6/18/04

I. DATA GAP STATUS

Chronic toxicity, rat: No data gap, possible adverse effect

Chronic toxicity, dog: No data gap, possible adverse effect

Oncogenicity, rat: No data gap, no adverse effect

Oncogenicity, mouse: No data gap, possible adverse effect

Reproduction, rat: No data gap, possible adverse effect

Teratology, rat: No data gap, possible adverse effect indicated

Teratology, rabbit: No data gap, no adverse effect

Gene mutation: No data gap, possible adverse effect

Chromosome effects: No data gap, possible adverse effect

DNA damage: No data gap, no adverse effect

Neurotoxicity[1]: No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers through 211501 and 960217 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T040618.wpd
Revised by S. Morris, 11/22/99 and Gee, 9/30/02, 10/01/03 and 6/18/04

[1] Rat neurotoxicity studies are on file. A developmental neurotoxicity study is on file.

Note: 315-122; 089116; "SRA 5172 Study of the Subchronic Inhalation Toxicity to Rats in Accordance with OECD Guideline No. 413", Laboratory Project ID Report No. 98370; J. Pauluhn, Bayer AG, Wuppertal, Germany; 3/30/88. This study was not a required test type and was therefore not evaluated for acceptability and no worksheet was done (S. Morris, 1/5/93).

Note: 315-120; 089114: Supplemental data for doc. # 315-122, rec. # 089116. In the course of reviewing the recent genotoxicity studies and preparing the Summary of Toxicology Data, older studies were rereviewed. A number were upgraded as noted in the one-liners (S. Morris, 7/20/93).

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 315-060; 019914;** "Chronic Feeding/Oncogenicity Study of Technical methamidophos (Monitor®) to Rats", Study No. 81-271-01, Mobay No. 88687; R.H. Hayes, Mobay Chemical Corporation, Stilwell, KS, 11/13/84. Technical Methamidophos (Monitor, 70% stated purity, batch # 77-297-149) was fed in the diet to groups of 60 Fisher 344 rats/sex/dose for 106 weeks at 0, 2, 6, 18, or 54 ppm. Ten rats/sex/dose were sacrificed at 52 weeks. There were no treatment-related oncogenic effects. Treatment-related effects were: reduced group body weights in both sexes at 54 ppm with group mean body weights always being > 84% of controls and reduced group mean relative testicle weights in males at 18 and 54 ppm. Cholinesterase levels in brain, erythrocyte, and plasma were reduced in both sexes at 2, 6, 18, and 54 ppm (NOEL < 2 ppm). A **possible adverse effect** was indicated by approximately 10, 35, 64, and 77% depression of brain cholinesterase activity at respectively 2, 6, 18, and 54 ppm. The study was unacceptable (J. Schreider 1/29/85; H. Green and S. Morris, 11/17/92) but upgraded to acceptable by submission of adequate analytical data, individual clinical data, and rationale for the doses used (S. Morris, G. Patterson, and J. Gee; 5/30/95) .

315-065; 027092: Partial duplicate of doc. # 315-060, rec. # 019914.

315-106; 075900: This document contains gross and histopathology data for rats sacrificed at 12 months and historical control data for organ weights in Fisher 344 rats.

315-137; 130534: This document contains adequate analytical and individual clinical data (S. Morris, 5/30/95).

315-137; 130552: This document contains a 5-week pilot study in which 5 Fischer 344 rats/sex/dose were fed diets containing 0, 1, 2, 4, 8, 16, 32, and 64 ppm. There were no treatment-related clinical signs or pathological findings. There appeared to be a difference in group mean male body weights from controls at 64 ppm. The significance of this difference was obscured by the low number of animals and high variability within and between treatment groups. There were dose-related decreases in plasma, erythrocyte, and brain cholinesterase levels when compared to controls. Brain cholinesterase levels were not measured for the 32 and 64 ppm treatment groups. Evaluation of these data resulted in a change of study status to acceptable (S. Morris, G. Patterson, and J. Gee; 5/30/95).

Note: The possible adverse effect was listed under the Chronic Toxicity test type for rat.

CHRONIC TOXICITY, RAT

See COMBINED, RAT above.

315-013; 960209; "Two-year Chronic Oral Toxicity of RE 9006-III, SX-116 in Albino Rats", IBT No. B5485, 2/18/70; invalid IBT study; no worksheet (J. Schreider, 1/28/85; S. Morris, 10/16/92).

CHRONIC TOXICITY, DOG

**** 315-061; 019916;** "One-Year Feeding Study of Methamidophos (Monitor®) in Dogs", R. H.

Hayes, Mobay Chemical Corporation, Stilwell, Kansas, Study No. 81-174-01, Mobay No. 87474; 6/26/84. Technical methamidophos (Monitor, 70% stated purity, batch # 77-297-149) was fed in the diet of 6 beagle dogs/sex/group for 52 weeks at 0, 2, 8, or 32 ppm. There were no significant treatment-related effects on: clinical signs, feed consumption, body weight or ophthalmology, gross pathology, histopathology, hematology, and urology findings (chronic NOEL ≥ 32 ppm). Plasma, erythrocyte and brain cholinesterase activity were depressed at all doses. A **possible adverse effect** was indicated by a treatment-related depression of brain cholinesterase activity which was approximately 85, 50, and 30% of controls at respectively 2, 8, and 32 ppm (NOAEL = NOEL < 2 ppm). The study was unacceptable (J. Schreider, 1/25/85; S. Morris and H. Green, 10/15/92) but upgraded to acceptable by submission of adequate analytical data and rationale for the doses used (S. Morris, G. Patterson, and J. Gee; 5/30/95).

315-065; 027093: Partial duplicate of doc. # 315-061, rec. # 019916.

315-107; 075901: This document contains ophthalmology data for doc. # 315-061, rec. # 019916.

315-138; 130795: This document contains adequate analytical data and rationale for the doses used. Evaluation of this submission resulted in a change of study status to acceptable (S. Morris, G. Patterson, and J. Gee; 5/30/95).

315-013; 960208: "Two-year Chronic Oral Toxicity of RE9006-III, SX-116 in Beagle Dogs", IBT No. C5486, 10/20/69; invalid IBT study; no worksheet (J. Schreider, 1/28/85; S. Morris, 10/15/92).

ONCOGENICITY, RAT

See COMBINED, RAT above.

ONCOGENICITY, MOUSE

**** 315-059; 019913;** "Oncogenicity Study of Methamidophos Technical (Monitor®) on Mice." (Study No. 80-332-01, Mobay No. 87479, R. H. Hayes, Mobay Chemical Corporation, Stilwell, KS, 8/6/84). Technical methamidophos (Monitor, 70% stated purity, batch # 77-297-149) was fed in the diet of 60 CD1 albino mice/sex/group for 106 weeks at 0, 1, 5, or 25 ppm. Ten mice/sex/group were sacrificed at week 53. There were no treatment-related effects on survival or tumor incidence. Treatment-related effects were decreased body weight gains in both sexes after one year at 25 ppm with all treatment groups have group mean body weights > 86% of controls. A dose-related increase in diffuse interstitial pneumonia was seen in both sexes at 1, 5, and 25 ppm but not noted as a possible adverse effect because it was probably secondary to poor husbandry. **A possible adverse effect** was indicated by a treatment-related depression of brain cholinesterase activity in a pilot study (DPR doc. # 315-136, rec. # 130533). Compared to controls, brain cholinesterase activity was depressed approximately 25, 60, 87, and 90% at respectively 2, 10, 50, and 100 ppm. No evidence for an oncogenic effect was seen. The study was unacceptable (J. Schreider, 1/29/85; S. Morris and H. Green, 10/27/92) but upgraded to acceptable with submission of an adequate rationale for the doses used and adequate analytical data (S. Morris, G. Patterson, and J. Gee; 5/30/95).

315-065; 027094: Partial duplicate of doc. # 315-059, rec. # 019913.

315-107; 075902: Histopathology data for the 10 mice/sex/group that were sacrificed at week 53.

315-136; 130533: This document contains adequate analytical data (S. Morris, DPR Response,

1/12/95).

315-136; 130549: This document contains a 6-week pilot study in which at least 20 CD1 albino mice/sex/dose were fed diets containing 0, 2, 10, 50, and 100 ppm. There was 15% decrease in group mean body weight in males in the first week of treatment at 100 ppm. This was followed by normal body weight gain throughout the rest of the study. Depression of plasma, erythrocyte, and brain cholinesterase levels were treatment-related. Other possible signs of toxicity were seen at 100 ppm: two males had wet abdomens and one female had a black tarry-like substance around the anal region. Evaluation of these data resulted in a change of study status to acceptable (S. Morris, G. Patterson, and J. Gee; 5/30/95).

REPRODUCTION, RAT

****315-157; 159401**; "A Two-Generation Dietary Reproduction Study in Rats Using Technical Methamidophos." (Study No. 95-672-GJ; D.A. Eigenberg, K.J. Freshwater, and S.G. Lake; Bayer Corporation, Stilwell, KS; 1/5/98.) Groups of 30 Sprague-Dawley rats/sex were fed methamidophos (69.0% to 76.7% purity) in the diet at nominal concentrations of 0, 1.0, 10.0, and 30.0 ppm (analytical concentrations were 0,1.0, 9.7, 26.1 ppm). Exposures were continuous for the P and F1 adults. Starting at 7 weeks of age P adults were exposed for 10 weeks then mated twice to produce the F1a and F1b litters. Randomly-selected F1b weanling pups were exposed for 10 weeks then mated twice to produce the F2a and F2b litters. F1a, F2a, F2b, and unselected F1b pups were sacrificed at weaning. P and F1 males were sacrificed after the second breeding of each generation. Females were sacrificed at the respective F1b and F2b weanings. Adult animals were evaluated for compound-related effects on body weight, food consumption, clinical signs, estrous cycling, mating fertility, gestation length, litter size, and cholinesterase levels. The offspring were evaluated for effects on sex ratios, pup viability, body weight gain, clinical signs, cholinesterase activity. Gross necropsy evaluations were performed on all adults and pups. Histopathologic evaluations of the reproductive organs, the pituitary, and gross lesions were performed on all P and F1 adults. Treatment-related parental effects included: decreased body weight gain in P (30.0 ppm) and F1 (10.0, 30.0 ppm) males, F1 females (10.0, 30.0 ppm), and lactating females (10.0, 30.0 ppm); increased food consumption in P and F1 males (30.0 ppm); and decreased food consumption in lactating females (30.0 ppm) (parental NOEL = 1.0 ppm). A **possible adverse effect** was indicated by a treatment-related decrease in pup body weight gain seen at 10.0 and 30.0 ppm and increased pup cannibalism and decreased survival seen at 30.0 ppm (developmental NOEL = 1.0 ppm). Cholinesterase (ACh) inhibition was seen in adults in plasma, erythrocyte, and brain at 1.0, 10, and 30 ppm (adult ACh inhibition NOEL < 1.0 ppm). Cholinesterase inhibition was seen in pups in plasma, erythrocyte, and brain at 10 and 30 ppm (pup ACh inhibition NOEL = 1.0 ppm). The study is acceptable (S. Morris and J Gee, 4/9/98).

315-061; 019915; "Effect of Methamidophos (Monitor®) on Reproduction in Rats." (Study No. 82-671-01, E.J. Hixson, Mobay Chemical Corporation, Stilwell, KS, 11/8/84.) Methamidophos Technical (Monitor, 70.5% stated purity, batch # 77-297-149) was fed in the diet at nominal concentrations of 0, 3, 10, or 33 ppm to 26 CD adult rats/sex/group continuously through 2 generations beginning with at least 100 days of exposure for the adult F0 parents before mating then through gestation and lactation of a single F1 litter, during a 120-day growth phase of F1 rats and through gestation, lactation and one month rest period between mating for the F2a and F2b litters. Mean analytical concentrations were 0, 3.0, 9.1, and 29.9 ppm. There were no significant treatment-related effects on the parental animals (parental NOEL $\geq$ 33 ppm). A **possible adverse effect** was indicated by decreased mean live litter size and pup growth at 33 ppm and decreased live litters at 3, 10 and 33 ppm (reproductive NOEL < 3 ppm). The study is unacceptable and not upgradeable because there were less than 20 litters per treatment group, male reproductive performance could not be evaluated, inadequate rationale for high dose, inadequate necropsy and histopathology data, and no reproductive NOEL (J. Schreider, 1/28/85; H. Green and S. Morris, 10/2/92).

315-065; 027100: Partial duplicate of doc. # 315-061, rec. # 019915.

315-101; 072564: This document contains a rebuttal to EPA evaluations of doc. # 315-061, rec. # 019915 and additional data.

315-013; 960211; "Three-generation Reproduction Study in Albino Rats on SX-171 (Technical RE-9006-75%), Results Through Weaning of F1b Litters (First Generation), S-90", IBT No. P6255, 2/19/69; invalid IBT study; no worksheet (J. Schreider, 1/28/85; S. Morris, 11/12/92).

315-013; 960212; "Three-generation Reproduction Study in Albino Rats - SX-171 (Technical RE-9006-75%), Results Through Weaning of F2b Litters (Second Generation), Chevron Request No. S-90", IBT No. P6255, 9/12/69; invalid IBT study; no worksheet (J. Schreider, 1/28/85; S. Morris, 11/12/92).

315-013; 960214; "Three-generation Reproduction Study in Albino Rats on SX-171 (Technical RE-9006 75%), Results of All Three Generations, Chevron Request No. S-90", IBT No. P6255, 1/16/70; invalid IBT study; no worksheet (J. Schreider, 1/28/85; S. Morris, 11/12/92).

TERATOLOGY, RAT

**315-149; 144391; "Developmental Toxicity Study with Monitor® Technical in Sprague-Dawley Rat." (Study No. 96-612-EM; Bayer Report 107178; A.B. Astroff; Bayer Corporation, Agricultural Division, Toxicology, Stilwell, KA; 1/17/96.) Monitor Technical (batch no. # 0067009, 76.0% purity) was given to 36 mated female Sprague-Dawley rats/group by oral gavage at nominal doses of 0, 0.04, 0.1, or 4.0 (analytical 0, 0.05, 0.14, or 5.49) mg/kg/day on gestation days 6 through 15. Erythrocyte, plasma, and brain cholinesterase levels were determined on 6 rats/group that were sacrificed 90 minute after the last dose on gestation day 15. The remaining 30 animals/group were sacrificed on day 20, gross necropsy were performed, intact uteri were removed and weighed, fetuses sacrificed and weighed. Reproductive indices were measured and the fetuses examined for gross external malformations. One half of the fetuses were examined for visceral abnormalities and the other half cleared, stained and examined for skeletal abnormalities. Treatment-related maternal effects seen at 5.49 mg/kg/day were: increased incidence of tremors, muscle fasciculation, and salivation; decreased food consumption and body weight gain; and decreased plasma, erythrocyte, and brain cholinesterase activities (maternal NOEL = 0.14 mg/kg/day). Treatment-related fetal effects seen at 5.49 mg/kg/day were: decreased group mean fetal weight and an increased incidence of incomplete ossification of sacral arches and sternebra (developmental NOEL = 0.14 mg/kg/day). No adverse effect was indicated. The study was unacceptable but upgraded by an adequate rationale for dose selection. See doc. # 315-059, rec. # 20042 below and DPR Response, 11/22/99; S. Morris. 11/22/99).

315-155; 149039; "A Dose Range-Finding Developmental Toxicity Study with MONITOR Technical in the Sprague-Dawley Rat," study Number 94-612-ZA; A.B. Astroff; Bayer Corporation, Agricultural Division, Toxicology Department, Stilwell, KA. Nominal doses of 0.0, 0.04, 0.1, 1.0, or 4.0 mg/kg/day (analytical 0.0, 0.05, 0.15 1.41 or 6.04 mg/kg/day) were given by oral gavage to groups of 6 pregnant Sprague-Dawley rats on gestation days 6 through 20. Treatment-related maternal effects included: increased incidences of tremors, muscle fasciculation and decreased food consumption and body weight gain at 6.04 mg/kg/day and decreased plasma and brain cholinesterase levels at 0.15, 1.41, and 6.04 mg/kg/day and erythrocyte cholinesterase levels at 1.41, and 6.04 mg/kg/day. The only treatment-related developmental effect seen was reduced group mean fetal weight at 6.04 mg/kg/day. Evaluation of these data did change the study status of DPR doc. # 315-149, rec. # 144391 (Morris, DPR Response, 6/22/98).

315-163; 169761: The registrant submitted comments about dose analysis, rationale for dose selection, and correcting the NOEL based on dose analysis. Evaluation of this submission did not result in a study status change. No worksheet was done (see DPR Response, 11/22/99; S. Morris. 11/22/99).

315-059; 20042: Acute Oral Toxicity Study; Rat; Mobay Chemical Corporation, Corporate Toxicology Department, Stanley Research Center, Stilwell, KS; Report No. 68802; 7/1/80).

These data have been reviewed and found acceptable (T. Moore, 6/29/99; SRS 7/1/99). A formulated product containing 40% methamidophos had an acute oral LD50 for female rats of 21.3 mg/kg. The expected LD50 for monitor technical (76% methamidophos) would be approximately 10.8 mg/kg. The clinical signs and cholinesterase levels seen in the present study, the calculated LD50 and the expected presentation of organophosphorus toxicity indicate that the high dose (5.49 mg/kg) approached lethality. This is an adequate rationale for the dose selection in doc. # 315-149, rec. # 144391. The study is acceptable. No worksheet was done (see DPR Response, 11/22/99; S. Morris. 11/22/99).

315-061; 019917; "Embryotoxic and Teratogenic Effects of Methamidophos (Monitor®) in Rats." (Study No. 82-611-01, Mobay No. 87480, E. J. Hixson, Mobay Chemical Corporation, Stilwell, KS, 10/15/84.) Methamidophos (Monitor, 70.5% stated purity, batch # 77-297-149, water vehicle) was given by oral gavage to groups of 24 to 27 mated (sperm-positive, gestation day 0) female CD rats on gestation days 6 through 15 at 0, 0.3, 1.0, or 3.0 mg/kg/day. Sacrifice and Cesarean section were conducted on gestation day 21. Treatment-related maternal effects seen a 3.0 mg/kg were: decreased body weight gains with group mean body weights always > 88% of controls, decreased feed consumption, and increased clinical signs of cholinesterase inhibition (fasciculations, salivation, lacrimation, hyperactivity, and excessive urination; maternal NOEL = 1.0 mg/kg/day). There were no treatment-related effects on fecundity or skeletal or organ abnormalities. A **possible adverse effect** was indicated by decreased group mean fetal weights at 3.0 mg/kg in the main study and aborted litters in a preliminary study at 4.5 mg/kg/day (developmental NOEL = 1.0 mg/kg/day). The study was unacceptable but possibly upgradeable with adequate analytical data, submission of preliminary studies, and rationale for the doses used (J. Schreider, 1/29/85; H. Green and S. Morris, 11/06/92).

315-065; 027101: Partial duplicate of doc. # 315-061, rec. # 019917.

315-065; 027102; "A Pilot Teratology Study Using Technical Methamidophos in CD Rats", Study No. 80-611-01, Mobay No. 68765, Methamidophos (Monitor, 70% stated purity, batch # 77-297-149) was given by oral gavage to groups of 4 mated female rats at 0.0, 0.1, 0.3, 1.0, 3.3, or 10.0 mg/kg/day on gestation days 6 through 20. The only treatment-related effects reported were seen at 3.3 and 10 mg/kg/day: mild to severe signs of organophosphate toxicity, decreased mean maternal weight gain and decreased mean fetal birth weights. The report "recommended that the high dose level, for the definitive teratology study incorporating Methamidophos, not be higher than 10 mg/kg/day." No worksheet was done (S. Morris, 11/9/92).

TERATOLOGY, RABBIT

315-150; 145998; "Oral (Stomach Tube) Developmental Toxicity Study of MONITOR® Technical in Rabbits." (Argus # 222-001, Valent # VP-10143; A.M. Hoberman; Argus Research Laboratories, Inc., Horsham, PA; 3/8/89.) Groups of 23 New Zealand White pregnant female rabbits were given methamidophos (Monitor®, lot 0067009, 76% purity, water vehicle) by oral gavage at 0 (10 ml/kg water), 0.1, 0.5, or 2.5 (analytical 0, 0.2, 0.65, or 2.47) mg/kg/day on gestation days 6 through 18. All dams were sacrificed on gestation day 29, Caesarean-sectioned, examined grossly for internal lesions, corpora lutea counted, and uteri weighed and examined in detail. All fetuses were weighed, externally examined for alterations, and internally examined for visceral and skeletal alterations. Transient depression in body weight gain and food consumptions were seen at 0.65 and 2.47 mg/kg/day. Hyperactivity was observed at 2.47 mg/kg/day. Maternal NOEL = 0.2 mg/kg/day. There were no treatment-related effects on gestational observations, uterine weights, litter observations, fetal observations, and fetal malformations and abnormalities. Fetal NOEL □ 2.47 mg/kg/day. No adverse effect was indicated. The study was unacceptable and not upgradeable because the rationale for the doses used was inadequate (4/22/97, S. Morris and J. Gee).

315-150; 145998; pp. 181 - 316. Dose selection for the main study above was based on a preliminary pilot study: "Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of Monitor® in Rabbits," Argus # 222-001, Valent # VP-101143; A.M. Hoberman; Argus Research

Laboratories, Horsham, PA, 3/8/96. Groups of 5 New Zealand White pregnant female rabbits were given methamidophos (Monitor®, lot 0067009, 76% purity, water vehicle) by oral gavage at 0 (10 ml/kg water), 0.1, 0.5, 2.5, 5.0, or 7.5 (analytical 0, 0.2, 0.46, 2.46, 4.90, or 7.73) mg/kg/day on gestation days 6 through 18. Blood samples were taken on gestation day 18 to determine plasma (PChE) and erythrocyte (RChE) cholinesterase levels. All dams were sacrificed on gestation day 29, Caesarean-sectioned, and the uterine contents were examined. There were treatment-related maternal effects: death (2/5) at 7.73 mg/kg/day; rapid breathing, excess salivation, ataxia, abnormal breathing, and decreased food consumption at 4.90 and 7.73 mg/kg/day; decreased body weight gain a 2.46, 4.90, and 7.73 mg/kg/day; and decreased PChE and RChE levels at 0.46, 2.46, 4.90, and 7.73 mg/kg/day. The only treatment-related fetal effect was decreased group mean weight at 2.46, 4.90, and 7.73 mg/kg/day. These data did not adequately support a rationale for the doses used in the main study (4/22/97, S. Morris and J. Gee).

315-156; 159400: The registrant submitted comments about DPR's evaluation of the study at DPR doc. # 315-150, rec. # 145998; quotes of U.S. EPA policy, and two tables of cholinesterase inhibition in rats treated with methamidophos, and a table of similar data from rabbits that has already been reviewed by DPR. Evaluation of this submission did not result in a change in study status (S. Morris, DPR Response, 4/22/98).

315-162; 168533: The registrant submitted comments about DPR's evaluation of the study at DPR doc. # 315-150, rec. # 145998; and tables of data previously evaluated by DPR. Evaluation of this submission did not result in a change in study status (S. Morris, DPR Response, 11/22/99; J. Gee, DPR Meeting Memo, 2/18/99).

315-027; 001213 "SRA 5172 (Methamidophos), Studies of Embryotoxic and Teratogenic Effects on Rabbits Following Oral Administration." (Report No. 8410, L. Machemer, Bayer AG, Institut ~~fur~~ Toxikologie, Wuppertal-Elberfeld, Germany, 5/31/79.) Methamidophos (SRA 5172, 62% stated purity, suspended in 0.5% Cremophor emulsion) was given by oral gavage to groups of 15 naturally-inseminated (gestation day 0) female Himalayan rabbits on gestation days 6 through 18 at 0, 0.1, 0.5, or 2.5 mg/kg/day. Cesarean sections and sacrifices were performed on gestation day 29. There were biologically insignificant and non-dose related reductions in doe body weight gain in all treatment groups. There were no other treatment-related maternal or fetal effects (maternal and fetal NOELs ≥ 2.5 mg/kg/day). **No adverse effect** was indicated. The study is unacceptable but possibly upgradeable with submission of adequate analysis of the test and dosing materials, individual maternal and fetal data, and rationales for the doses and vehicle used (J. Schreider, 1/29/89; H. Green and S. Morris, 10/29/92).

315-001; 960210: Summary of doc. # 315-027, rec. # 001213.

315-029; 001214: Exact duplicate of doc. # 315-027, rec. # 001213.

315-050; 017047: Exact duplicate of doc. # 315-027, rec. # 001213.

Summary: The collective data for rabbit teratology studies with methamidophos (DPR doc. #'s 315-150, 315-156, 315-162, 315-027; rec. #'s 145998, 159400, 168533, 001213), have been reviewed. A pilot study that used a dose-range, marginally higher than the main study, that produced treatment-related effects on pregnant rabbits that included: death (2/5) at 7.73 mg/kg/day; decreased food consumption at 4.90 and 7.73 mg/kg/day, and decreased body weight gain a 2.46, 4.90, and 7.73 mg/kg/day death. The only treatment-related effect seen on uterine, fetal, or reproductive parameters appears to be a decrease in group mean fetal weights. The collective data are adequate to fill the data gap for a rabbit teratology study (see DPR Response, 11/22/99; S. Morris and J. Gee, 11/22/99).

GENE MUTATION

315-147; 141465; "CHO/HGPRT Mutation Assay," (Study No. TC865.332, Bayer No. 105076; C.A.H. Bigger and C. I. Sigler; Microbiological Associates, Inc. Rockville, MD; 5/27/93) Forward mutation of the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus of Chinese hamster ovary (CHO) cells was measured after exposures to Methamidophos (batch no. 0-06-7009) at 0, 0 (solvent) 1.0, 2.0, 3.0, 4.0, or 5.0 mg/ml with or without S-9 metabolic activation (9000 g supernatant of Aroclor-induced, male Sprague-Dawley rat liver homogenate). Duplicate flasks were seeded with 5 X 10^5 cells, grown for 18-24 hours, incubated with medium containing the test material with or without S-9 for 5 hours, washed, and re-incubated for 18-24 hours. Cytotoxicity was assessed by replating 1 replicate in triplicate at 100 cells/60 mm dish and incubating for 7-10 days. Expression of the mutant thioguanine-resistant phenotype was assessed by replating remaining replicates in duplicate and subculturing every 2-3 days for 7-9 days. Selection of the mutant phenotype was done by replating each duplicate into 5 flasks and incubating in the presence of 10 M 6-t hioguanine (TG) for 7-10 days. Colonies were fixed, stained, and counted for cloning efficiency and mutant selection. A **possible adverse effect** was indicated by increased TG resistant colonies seen at 5.0 mg/ml with metabolic activation. The study is unacceptable and not upgradeable because there was only one trial and the concentrations were inadequate (S. Morris and J. Gee, 4/10/97).

** 315-121; 089115; "CHO/HGPRT Mutation Assay." (Laboratory Study Number T5844.332008; J. W. Harbell and D. Jacobson-Kram, Microbiological Associates Inc., Rockville, Maryland, 1/12/90.) Methamidophos (Monitor Technical, # 77-297-149, 72.9% stated purity, DMSO solvent) for the ability to induce forward mutations at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus of Chinese hamster ovary (CHO) cells. CHO cells were plated at 5 x 105 cells/25 cm2 and incubated 18-24 hours. Duplicate flasks were incubated for 5 hours in medium containing the test material at 0.0, 0.2, 0.5, 1.0, 2.0, or 3.5 l/ ml and with or without S-9 metabolic activation system (9,000 x g supernatant of Aroclor-1254 induced, male Fisher 344 rat liver homogenates). Replicate cells were then harvested and pooled. To assess cytotoxicity cells were plated in triplicate at 100 cells/60 mm dish. For expression, pooled cells were subcultured every 2-3 days for 7 to 10 days at 106 cells/100 mm dish and finally harvested. For selection of the thioguanine (TG)-resistant phenotype, cells were plated in 4 dishes at 2 x 105 cells/100 mm dish in medium containing 10 mM TG. For cloning efficiency at selection, cells were plated in triplicate at 100 cells/60 mm dish. For cytotoxicity, selection, and cloning efficiency at selection the final incubation was 7 days after which colonies were fixed, stained and counted. No adverse effect was indicated by no treatment-related effect on TG-resistant colony count. The study is acceptable (J. Gee and S. Morris, 12/9/92).

315-143; 137332; "SRA 5172: Salmonella/Microsome Test," (Bayer Report No. 106392; B. Herbold; B. Bayer AG Department of Toxicology, Wuppertal, Germany; 9/14/94.) The frequency of reversion of histidine auxotrophic strains of *Salmonella typhimurium* (TA 1535, TA 1537, TA 100, and TA 98) to prototrophy was measured after exposures to methamidophos (SRA 5172, batch number 278167052, 73.4% purity, water vehicle) for 48 hours at 0, 16, 50, 158, 500, 1581, or 5000 g per plate without or with S9 metabolic activation system (9000 g supernatant of homogenized livers from Aroclor-1254-induced male Sprague-Dawley rats). There were 4 replicates per dose per strain. Exposure time was for forty-eight hours. There were 3 trials with S9 and 2 without. Controls were adequate. No treatment related increase in reversion rate or bacteriotoxic activity was seen. No adverse effect was indicated. The study was unacceptable but possibly upgradeable with submission of adequate analysis of the exposure solutions (J. Kishiyama and S. Morris, 4/1/97).

315-061; 019920; "Salmonella/Microsome Test to Evaluate for Point Mutation." (Report No. 9175, B. Herbold, Bayer AG, Wuppertal-Elberfeld, 5/20/80.) SRA 5172 Methamidophos (SRA 5172, 62.6% stated purity, DMSO solvent) was tested in a bacterial assay that measured the rate of mutation of a histidine auxotrophic strains of Salmonella typhimurium (tester strains TA98, TA100, TA1535, and TA1537) to prototrophy. Four plates/strain/dose were exposed to 0, 20, 50, 100, 200, 500, 2500 or 12500 g/ plate, in the presence or absence of metabolic activation system (S9 fraction of Aroclor 1254-induced, male Sprague-Dawley rat liver homogenates). Colonies per plate and total bacteria counts were measured. Treatment-related increased mutation frequency was not seen. **No adverse effect** was indicated. The study is unacceptable and not upgradeable because: repeat trials did not include all dose levels and strains, inadequate rationale for the doses and vehicle, lack of experimental details in the report, and no analytical data (J. Schreider, 1/27/85; H. Green and S. Morris, 11/24/92).

315-065; 027099: Exact duplicate of doc. # 315-061, rec. # 019920.

315-061; 019921; "Salmonella/Mammalian Microsome Mutagenicity Test (Ames Test) with Monitor Technical." (SOCAL 1711; M.L. Machado, J.A. Parker and Z.A. Wong; Chevron Environmental Health Center, Richmond, CA; 2/3/82.) Methamidophos (Monitor Technical, purity not stated, Mobay 77-297-149) was tested in a bacterial assay that measured the rate of mutation of a histidine auxotrophic strains of Salmonella typhimurium (tester strains TA98, TA100, TA1535, TA1537, and TA1538) to prototrophy. Three plates/strain/dose were exposed to 0, 0.1, 0.5, 1.0, 5.0, or 10 g/ plate, in the presence or absence of metabolic activation system (liver homogenate S-9 fraction, no other details). Colonies per plate were measured. Treatment-related increased mutation frequency was not seen. **No adverse effect** was indicated. The study is unacceptable and not upgradeable because: no repeat trials, lack of experimental details in the report, inadequate rationale for the doses, inadequate analytical data, and no cytotoxicity data (J. Schreider, 1/25/85; H. Green and S. Morris, 11/25/92)

315-018; 960216: Exact duplicate of doc. # 315-061, rec. # 019921.

315-040; 960217: Exact duplicate of doc. # 315-061, rec. # 019921.

CHROMOSOME EFFECTS

** **315-110; 090583;** "Mutagenicity Test on SRA 5172 In An In Vitro Cytogenetic Assay Measuring Chromosomal Aberration frequencies in Chinese Hamster Ovary (CHO) Cells." (HLA Study No. 10972-0-437; M. Hemalatha; Hazleton Laboratories America, Inc., Kensington, MD; 1/19/90.) Methamidophos (SRA 5172, 74.5% stated purity) was tested in vitro for induction of chromosome aberrations in cultured Chinese hamster ovary (CHO) Cells. Exponentially-growing monolayers were treated in duplicate for varying times with the test material at 0, 1870, 2500, 2570, 3150, 3850, 4200, 5140, or 5250 g/ ml without or with S-9 metabolic activation system (9000 x g supernatant of Aroclor 1254 induced, male Sprague-Dawley rat liver homogenates) at 0, 1250, 3750, or 4990 g/ ml. The cells were washed 2.5 hours before harvest and re-incubated in medium with 0.1 mg/ml Colcemid. A **possible adverse effect** was indicated by treatment-related increases in chromosome aberrations with or without activation. The study is acceptable (H. Green and S. Morris, 12/30/92)

315-061; 019923 "In Vivo Cytogenetics Study in Mice, Methamidophos Technical (SX-1244)." (MRI-176-CCC-82-36; H.J. Esber, EG&G/Mason Research Institute, Worcester, MA; 11/18/83.) Methamidophos Technical (SX-1244, batch # 77-297-149, 73.5% stated purity) was given in water by single oral gavage at 0.0, 0.8, 2.7, 8.1, 12.1, or 16.1 mg/kg to 12 CD1 mice/sex/group. Mice were given colchicine ip at 1.2 mg/kg 2 hours prior to sacrifice. At 6, 24, or 48 hours after dosing, 4 mice/sex/dose were sacrificed and femoral bone marrow samples were fixed and stained and 50 metaphase cells/mouse were analyzed microscopically for chromosome aberrations. There were no treatment-related effects on chromosome aberrations. No adverse effect was indicated. A NOEL for anticholinesterase activity of < 4.1 mg/kg was based on clinical signs in a preliminary acute mortality studies. The study was unacceptable because of inadequate rationales for doses and sampling intervals and no analysis of dosing solutions and not upgradeable because there were inadequate mice/sex/dose/time point (J. Schreider, 1/30/85; H. Green and S. Morris, 12/21/92).

315-045; 020163: Exact duplicate of doc. # 315-061, rec. # 019923.

315-045; 020164: Protocol for study at doc. # 315-061, rec. # 019923.

315-061; 019919 "Dominant Lethal Study of Methamidophos Technical in Mice." (SOCAL 1783; G.H. Eisenlord, J.H. Carver and Z.A. Wong; Chevron Environmental Health Center, Inc., Richmond, CA; 3/23/84.) Methamidophos Technical (Mobay Reference No. 77-297-149, 74.3% stated purity) was fed in the diet of groups of 12 CD-1 male mice for 5 days at 0, 5, 50, or 150 ppm followed by an 8-week mating period in which each male was paired with 2 new females every week for a total of 16 females per male. Eight days after each 1-week mating period, the females were sacrificed and their uteri were

examined for the numbers of implants, live fetuses and early and late fetal deaths. At the end of the 8-week mating period, the males were sacrificed and necropsied. Group mean food consumption for the 5 treatment days and body weight on day 5 were reduced in the 150 ppm males to respectively 53% and 88% of controls (subacute NOEL = 4.6 mg/kg/day). There were no other treatment-related effects reported on males or uterine variables. No adverse effect was indicated. The study is unacceptable because of an inadequate rationale for the doses used and not upgradeable because of an inadequate number of pregnant females (J. Schreider, 1/29/85; H. Green and S. Morris 12/16/92)

315-065; 027097: Partial duplicate of doc. # 315-061, rec. # 019919.

315-061; 019918; "Dominant Lethal Test on Male Mouse to Evaluate SRA 5172 for Mutagenic Potential." (Report No. 9583; Dr. B. Herbold, Bayer AG, Institut Für Toxikologie, Wuppertal, Germany; 11/26/80.) Methamidophos (SRA 5172, 62.6% stated purity) was emulsified in 0.5% Cremophor and given by a single oral gavage to groups of 50 male NMRI/ORIG Kissleg mice at 0 or 5 mg/kg on day 1. Starting on day 1 each male mouse was paired with a new female mouse every 4 days for 48 days for a total of 12 females/male mouse. The females were sacrificed 12 days after the pairing interval and their uteri were examined for total implants, viable implants, dead implants, and Corpora lutea. There were no treatment-related effects on the males' body weight, appetite, physical appearance, motor activity, or survival. There were no treatment-related effects on uterine variables. No adverse effect was indicated. The study is unacceptable because the rationales for the doses and vehicle were inadequate and there was no analysis of dosing material. The study is not upgradeable because there was no positive control (J. Schreider, 1/29/85; H. Green and S. Morris, 12/11/92).

315-065; 027098: Partial duplicate of doc. # 315-061, rec. # 019918.

315-061; 019922 "Micronucleus Test on the Mouse to Evaluate for Mutagenic Effect." (Report No. 9707; B. Herbold; Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany; 1/22/81) Methamidophos (SRA 5172, 62.6% stated purity) was given by oral gavage (0.5% Cremophor suspension) to five NMRI/W 77 mice/sex/group at 0, 5, or 10 mg/kg. Two doses were given 24 hours apart and femoral bone marrow samples were taken 6 hours after the second dose. For each mouse, 1,000 polychromatic erythrocytes were scored for micronuclei and the ratio of normo/poly chromatic erythrocytes was determined. Convulsions were observed in one mouse/sex at the high dose. There were no other treatment-related effects. No adverse effect was indicated. The study is unacceptable but possibly upgradeable with adequate submissions of analysis of the dosing material and rationales for the dose levels, timing, and vehicle (J. Schreider, 1/30/85; H. Green and S. Morris, 12/1/92).

315-065; 027096: Exact duplicate of doc. # 315-061, rec. # 019922.

DNA DAMAGE

**315-153;149102; "SRA 5172 Micronucleus Test on the Mouse," (Study No. T 9060076, Bayer Report No. 107443; B. Herbold; Bayer AG, Wuppertal, Germany; 5/23/96.) Groups of 5 Hsd/Win:NMRI mice / sex / time point were given single intraperitoneal injections of methamidophos (SRA 5172, batch # 278467030, 75% analytical purity, saline vehicle, 10 ml/kg) at 8 mg/kg. Femoral marrow samples were taken 16, 24, or 48 hours later. Marrow smears were dried and stained. One thousand polychromatic erythrocytes / animal were microscopically evaluated for micronuclei, and the number of normochromatic erythrocytes / 1000 polychromatic erythrocytes and the number of normochromatic erythrocytes with micronuclei were determined. There was no treatment-related effect on the micronuclei incidence. No adverse effect was indicated. The positive controls were adequate. The study was acceptable (S. Morris and J. Gee, 5/6/97).

315-153; 149102; p. 13. A brief abstract of a pilot study was included in the main report above. Groups of both sexes of 5 mice/dose were given intraperitoneal injections of methamidophos at 8,10, or 50 mg/kg. Animals at all doses exhibited apathy, roughened fur, sternal recumbency, spasm, palmospasm, difficulty in breathing, eyelids stuck together, lachrymation, and salivation. One of 5 and 5 of 5 mice died at 10 and 50 mg/kg, respectively. These data are an adequate rationale for the dose used in the main study.

315-061; 019924; "Pol Test on E. Coli to Evaluate for DNA Damage." (Report No. 12318; Dr. B. Herbold, Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld; 12/19/83.) Methamidophos (SRA 5172, batch 808319101, 71.2% stated purity) was tested for genotoxic activity in an assay that compared the inhibition of growth of two strains of the bacterium Escherichia coli. One strain was deficient ((K12)p 3478) while the other was proficient (W 3110) in DNA repair. The assay was conducted with or without metabolic activation (S-9 fraction of Aroclor-1254-induced, male rat liver homogenates) at 0, 625, 1250, 2500, 5000, or 10000 g/ plate. The plate diffusion method was used with 4 plates/dose/ strain being incubated for 24 hours. No adverse effect was indicated. The study is unacceptable because there was no rationale for the doses used, no individual plate data, no viability data, no concentration or rationale for the vehicle, and the report did not adequately describe the protocol. The study is not upgradeable because there was no positive control for metabolic activation and the 2 strains were not equally sensitive to the negative control agent (J. Schreider, 1/30/85; (H. Green and S. Morris 12/4/92).

315-065; 027095: Exact duplicate of doc. # 315-061 rec. # 019924.

315-105; 075732; "Unscheduled DNA Synthesis in Rat Primary Hepatocytes." (MBA Study No. T5844.380; R.D. Curren, Microbiological Associates, Inc., Rockville, MD; 10/24/88.) Methamidophos (Monitor Technical, Reference No. 77-297-149, 71.2% stated purity, DMSO solvent) was tested in an unscheduled DNA synthesis (UDS) assay. Triplicate plates with primary male Sprague-Dawley rat hepatocytes attached to coverslips were incubated for 18-20 hours in medium containing the test material at 0, 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1.0, 3.0, or 10.0 l/ ml and 3H-thymidine. The cells were fixed, developed for autoradiography and stained for cellular material. Nuclear grains counts were made for 50 cells/plate. There was no treatment-related effect on net nuclear grain counts. No adverse effect was indicated. The study is unacceptable but possibly upgradeable with submissions of adequate cytotoxicity data, protocol for the LDH assay, rationales for the doses and solvent, raw grain counts, specific activity of 3H-thymidine, and the morphological criteria and rationale for excluding cells from nuclear grain counts (H. Green and S. Morris 1/5/93).

NEUROTOXICITY, HENS

**315-146; 141419; “Subchronic Dermal Neurotoxicity Study (Ninety-Day Hen Study),” (Study No. T1033771, Bayer No. 105085; W. Bomann, G. Kaliner and H. Mager; Bayer AG, Wuppertal, Germany; 6/25/93.) Groups of 15 to 25 leghorn hens were dermally exposed to methamidophos (SRA 5172, analytical No. 31192, Fs 23280, 76.3% analytical purity, isopropanol solvent, 0.02 ml/kg b.w.), once a day, 5 days per week for 13 weeks at 0, 0.5, 1.5, or 4.5 mg/kg/day. Neuropathy target esterase (NTE) level was determined in brain and spinal cord homogenates from 1 to 3 hens per group, 24 hours after the last treatments of weeks 4 and 13. Clinical appearance and behavior were monitored once daily and forced activity and ladder climbing tests were performed weekly for all groups during treatment and 4 weeks post treatment for the 0 and 4.5 mg/kg/day groups. Plasma cholinesterase levels (ChE) were measured on 10 birds/group 1 week prior to treatment and 24 hours after the last treatments of weeks 3, 6, and 13 and week 17 (4 weeks post treatment, 0 and 4.5 mg/kg/day only). All birds were sacrificed at the end of their treatment or post-treatment observation period. Sciatic nerve, brain and spinal cord were examine histologically. TOCP was the positive control. Treatment-related effects seen at 4.5 mg/kg/day were apathy, ruffled feathers, staggering gait, reduced feed intake, transient decrease in body weight, discolored feces, and diarrhea. Detachment of the uppermost layer of skin at the treatment site was seen at 1.5 and 4.5 mg/kg/day. One animal in each treatment group either died or was sacrificed moribund. There were no treatment-related effects on forced activity or ladder climbing. At 4 and 13 weeks, brain and spinal cord NTE were decreased at 4.5 mg/kg/day. At weeks 3, 6, and 13, plasma ChE was decreased at 1.5 and 4.5 mg/kg/day. There were no treatment-related histopathology findings. The positive control was adequate. There was no treatment-related neuropathy. No adverse effect was indicated. The study was acceptable (S. Morris and J. Gee, 4/7/97).

315-013; 960205; "Neurotoxicity Study - Chickens Monitor RE 9006, 75 Percent Technical"; IBT No.

J6480; 11/12/68. Invalid IBT study (J. Schreider, 1/28/85).

315-115; 095393; Acute Delayed Neurotoxicity; 817; Hen; Bayer AG, Dept. of Toxicology, Wuppertal, Germany; Mobay Report No. 100281; 4/10/90; 3 test articles: #1. (±) Methamidophos, #2. (+) Methamidophos, #3. (-) Methamidophos; Study No. T3029958: #2,(100 and 200 mg/kg)-5 hens/dose; T2029722: Control-11 hens; #2, #3 (400 mg/kg)-13 hens; TOCP (100 mg/kg)-2 hens; T2029957: #3 (400 mg/kg)-10 hens; T1029956: #1 (200 and 400 mg/kg)-10 hens/dose; Mortalities: T3029958: #2-0/10; T2029722: Control-0/11, #2-3/13, #3-6/13, TOCP-0/2; T2029957: #3-9/10; T1029956: #1-2/10 (200 mg/kg), 7/10 (400 mg/kg), all deaths within 6 days post-dosing, except for 1 hen which died day 28 (T1029956, 200 mg/kg); Clinical signs: acute phase (common to three test compounds, all dose groups)-apathy, ruffled feathers, staggering gait, diarrhea, rapid shallow breathing, some cases of flat, lateral prostration, spasms, (in addition for #3) salivation, labored breathing, dry and limp comb; OPIDP: T3029958-100 mg/kg, no signs, 200 mg/kg-abnormal gait, reversible; T2029722-#2 (400 mg/kg) 2 totally paralyzed by day 18, 1 marked ataxia, 1 ataxic, disturbed motor coordination; #3 (400 mg/kg) no signs (1 hen); TOCP-treated not observed; T2029957-#3 (400 mg/kg) no signs (1 hen); T1029956-#1 (200 mg/kg) no signs (9 hens), (400 mg/kg) 1 disturbed motor coordination, 2 slightly abnormal gait; Necropsy: (animals which survived the acute phase) pale, sometimes lobulated liver ((±)-Methamidophos, 200 and 400 mg/kg, 7/11 hens); No histopathology performed. Unacceptable and not upgradeable (No histopathological evaluation of the target tissues was performed.) (T. Moore, 11/28/90).

315-027; 000046. This document contains a brief summary of a study in which an unspecified number of full-grown hens were injected ip with PAM (0.1 g/kg) and atropine sulphate (0.05 g/kg) followed by oral (50 or 100 mg/kg) or ip (25, 50 or 100 mg/kg) exposure to the active ingredient and observed for 42 days. No neurotoxic effects were reported. No worksheet was done (S. Morris, 9/16/92).

315-027; 001212 "Acute Delayed Neurotoxicity Study on Monitor Technical." (Study No. ANHO1, Mobay No. 68037, S.M. Kruckenberg et al., Department of Pathology, College of Veterinary Medicine, Kansas State University, Manhattan, KS, 7/29/79.) Adult White Leghorn hens were simultaneously given im injections of atropine sulfate at 50 mg/kg and Methamidophos (Monitor Technical, 74% stated purity, batch no. 9030005, analysis not stated, water vehicle) by oral gavage at 0.00 (8 hens), 30.00 (10 hens), or 50.63 (12 hens) mg/kg on days 0 and 21 and observed for 42 days. There were 2/10 and 4/12 lethalities at 30.00 and 50.63 mg/kg respectively. There were no clinical signs or histological evidence in spinal cord and sciatic nerve of delayed neuropathy. The rationale for dosing was adequately based on a preliminary lethality study. The positive controls were adequate. No adverse effect was indicated. The study was unacceptable but possibly upgradeable by submission of adequate analysis of the test material (J. Schreider, 1/29/85; H. Green and S. Morris, 9/18/92).

315-029; 001215: Partial duplicate of doc. # 315-027, rec. # 001212.

315-050; 017046: Exact duplicate of doc. # 315-027, rec. # 001212.

315-067; 028429: Exact duplicate of doc. # 315-027, rec. # 001212.

315-001; 960201: Partial duplicate of doc. # 315-027, rec. # 001212.

315-031; 960202: Partial duplicate of doc. # 315-027, rec. # 001212.

315-061; 019925; "Methamidophos (Tamaron Active Ingredient) and Tamaron, Sri Lanka Formulation, Special Study for Neurotoxic Effects on the Chicken." (J. Thyssen and A. Eben, Bayer AG Institute of Toxicology, Report No. 10815, 4/20/82.) Two formulations of Methamidophos (Tamaron technical BR, batch 808018244, 74.6% stated purity and Tamaron Fl. 1376/476, Sri Lanka formulation, 52.4% stated purity) were tested. There were 4 protocols that differed in: test material, dose, dosing schedule, numbers of hens, post-treatment clinical observation period, serial sacrifice schedule, and testing for neurotoxic esterase activity (NTE). Groups of 5 to 30 adult white Leghorn hens were treated on 5 consecutive days by oral gavage with test material at 25, 30, or 35 mg/kg (water vehicle, doses corrected for purity) and simultaneous im injections of atropine sulphate at 50 mg/kg. All protocols

produced acute mortality and all hens displayed clinical cholinergic signs for up to 15 days post-treatment. Brain, spinal cord and sciatic nerve levels of NTE were severely depressed on post-treatment day 1 but gradually recovered on days 2, 3 and 5 to normal levels on day 38. Delayed neurotoxicity was not observed at 42 days post-treatment. No adverse effect was indicated. The study was not a standard neurotoxicity protocol, was therefore considered supplemental information and no updated worksheet was done (J. Schreider, 1/30/85; S. Morris and H. Green, 10/6/92).

315-064; 027091: Exact duplicate of doc. # 315-061, rec. # 019925.

315-067; 028431: Exact duplicate of doc. # 315-061, rec. # 019925.

315-013; 960205; "Neurotoxicity Study - Chickens Monitor RE 9006, 75 Percent Technical", IBT No. J6480; Invalid IBT study; no worksheet (J. Schreider, 1/28/85; S. Morris, 10/9/92).

315-115; 095394; NTE Assay after Oral Administration; Hen; Bayer AG, Dept. of Toxicology, Wuppertal, Germany; Mobay Report No. 100280; 5/29/90; 3 test articles: #1. (±)-Methamidophos, #2. (+)-Methamidophos, #3. (-)-Methamidophos; Study No. T3027743: Control (6 hens), #1 (50 mg/kg) (6), TOCP (300 mg/kg) (4), NTE assayed 24, 48 hrs post-dosing, lymphocyte, brain, spinal cord, sciatic nerve; T3029543: Control (6), #2 (50 mg/kg) (6), #3 (50 mg/kg) (6), TOCP (100 mg/kg) (2), NTE assayed 24, 48 hours post-dosing, brain; T2029722: Control (6), #2 (400 mg/kg) (6), #3 (400 mg/kg) (6), TOCP (300 mg/kg) (2), NTE assayed 24, 48 hrs post-dosing, brain; T4030335: Control (3), #2 (400 mg/kg) (6), NTE assayed 24 hrs, brain; T6032001: Control (8), #2 (100 mg/kg) (9), #3 (200 mg/kg) (9), NTE assayed 24, 48 hrs and 7 days, lymphocyte, brain, spinal cord, and sciatic nerve; Results: #2 and #3-dose-dependent % inhibition of brain NTE; % inhibition (50 mg/kg)-#1=#2>#3; spinal cord, sciatic nerve % inhibition equal to brain; lymphocyte-activity more quickly recovered; reactivation of NTE-#1=#2>#3; TOCP (positive control)-90 to 100% inhibition, minimal reactivation. Supplemental (T. Moore, 11/29/90)

315-102; 070877; "3-Month Subchronic Delayed Neurotoxicity Study with SRA 5172 (C.N. Methamidophos)" K. Sachsse et al.; KFM Kleintierfarm Madoerin AG, Fuellinsdorf, Switzerland; RCC Research and Consulting Company AG, Itingen, Switzerland; and RCC Umweltchemie AG, Itingen, Switzerland; Laboratory Project ID 94213/064293; 5/15/87. Methamidophos (SRA 5172, batch 808 526 298, 76% stated purity) was given 5 days/week for 3 months by oral gavage (water vehicle) at 0, 0.3, 1.0, or 3.0 mg/kg/day to groups of 16 White Leghorn hens per dose. Motor activity of each hen was measured twice weekly. Plasma cholinesterase levels were measured after 4, 8, and 12 weeks of treatment and central and peripheral neuro-histopathology done at termination on 10 hens/ dose. Terminal brain and spinal cord neurotoxic esterase (NTE) was measured on the remaining 6 hens/dose. Mortalities, 2 each at 0 and 3.0 mg/kg, were not treatment-related. Treatment-related effects were: somnolence and terminal group mean body weight was 80% controls at 3.0 mg/kg, 12-week plasma cholinesterase levels were 83 and 56% of controls respectively at 1.0 and 3.0 mg/kg, brain NTE was 83% of controls at 3.0 mg/kg, and spinal cord NTE was 78 and 59% of controls respectively at 1.0 and 3.0 mg/kg. There were no behavioral or histopathological indications of delayed neurotoxicity. No adverse effect was indicated. This study was not a required test type and was therefore not evaluated for acceptability and no worksheet was done (H. Green and S. Morris, 10/8/92).

SUPPLEMENTAL (RATS, HUMANS)

**315-122; 089116; "SRA 5172 Study of the Subchronic Inhalation Toxicity to Rats in Accordance with OECD Guideline No. 413." (Laboratory Project ID Report No. 98370; J. Pauluhn, Bayer AG, Wuppertal, Germany; 3/30/88.) Groups of 10 Wistar rats/sex were head/nose exposed 6 hours/day, 5 days/week for 3 months to methamidophos (SRA 5172, batch # TOX 1767-00, 73.4%) at mean analytical concentrations of 0 (air only), 0 (vehicle), 0 (vehicle, recovery group), 1.1, 5.4, 23.1 (recovery group), or 23.1 mg/m^3. After the 3 month exposure period, the two recovery groups (vehicle and 23.1 mg/m^3) were allowed a 6-week
exposure -free period. Treatment-related effects were seen in both sexes at 23.1 mg/m^3: slight to moderate tremors on the day of exposure but not prior to exposure the next day; decreased body weight gain, decreased relative spleen weights and increased relative adrenal weights. There were

treatment-related, noncumulative decreases in cholinesterase activity in plasma and brain, and increased sensitivity to the acetylcholine provocation test in both sexes at 5.4 and 23.1 mg/m^3. The NOEL = 1.1 mg/m^3 (0.3 mg/kg body weight/day) based on decreases in brain cholinesterase ant the mid and high doses and tremors at the high dose. **No adverse effect** was indicated. The study is acceptable as supplemental data (S. Morris and J. Gee, 1/19/99).

315-120; 089114: Supplemental data for doc. # 315-122, rec. # 089116.

315-125; 89440; "Technical Grade Methamidophos (Monitor): An Eight-Week Subchronic Cholinesterase Study in Fischer 344 Rats" 855; Rat; Mobay Corporation, Health, Environment, Safety and Plant Management, Corporate Toxicology Department, Stilwell, KS; Project# 100667; 3/19/91; Methamidophos; Batch No. 0067009; Doses: (nominal-0, 0.5, 1, 2, 4 ppm), 0 (vehicle-corn oil (1% w/w of diet), 0.49, 0.97, 2.12, 4.30 ppm; (M): 0.028, 0.055, 0.122, 0.244 mg/kg/day, respectively; (F): 0.033, 0.065, 0.143, 0.284 mg/kg/day, respectively; 25 animals/sex/group; No mortality; Observations: no treatment-related signs; Cholinesterase Assays: Dose-related inhibition of plasma butyrylcholinesterase (PBChE), red blood cell acetylcholinesterase (RChE), and brain acetylcholinesterase (BChE), > 30% inhibition (4.30 ppm) F: PBChE-days 14, 42, BChE-day 56; M: PBChE-day 42; NOEL can not be determined; study unacceptable, but may be upgradeable with the submission of a more detailed analysis of the test article. (Moore, 6/18/91).

** 315-131 127242 Hamilton, B. "An Acute Oral Neurotoxicity Screening Study with Technical Grade Methamidophos (Monitor®)in Rats",(Miles, Inc., Agriculture Division, Toxicology, Stilwell, KS. Miles, Inc. Report # 105053, 11/5/93). Methamidophos technical (purity 75.6%, Batch 0-06-7009) was administered by single oral gavage to 24 Sprague-Dawley (Sas:CD(SD)BR) rats/sex/group at 0, 0.9, 3.3 and 9.0 mg/kg. Daily clinical observations (e.g. muscle fasciculations, ataxia, urine stain, and nasal stain) and FOB observations (e.g. gait incoordination, muscle fasciculations, salivation, urine stains, tremors, reduced rearing and reduced reflex reactions) were reflective of acute cholinesterase inhibition. Motor and locomotor activity was decreased in all dose groups at day 0; only high-dose males showed reduction in motor activity by day 7. **NOEL (clinical signs, FOB and motor activity test) < 0.9 mg/kg.** Serum aspartate amino- transferase (AST), serum alanine aminotransferase (ALT) and cholesterol values were increased in high-dose males and females. Plasma, RBC and brain cholinesterase (ChE) activity was significantly depressed at all dosage levels (up to 92% inhibition in the high-dose group) two hours after treatment. **NOEL (ChE inhibition) < 0.9 mg/kg.** No histopathological lesions; **No Adverse Neurotoxic Effects.** Originally UNACCEPTABLE; upgradeable with submission of analytical data for the test compound and positive (historical) control data (Green, Kellner and Gee, 5/6/94). This study was upgraded to **ACCEPTABLE** after review of historical positive control data in 374-087:122985. Kellner, 6/5/95.

374-087:122985: Historical positive control data used as a supplement to 315-131:127242; Sheets L.P., "Historical control and method validation studies in rats for the acute and subchronic neurotoxicity screening battery", Miles Inc., Agricultural Division, Toxicology, Stilwell, Kansas, Miles Report No. 103979, 3/31/93. This volume contains verification of the test procedures used for motor activity, FOB and neuropathology using positive control substances with known neurobehavioral and neuropathological effects. Animals were treated with chlorpromazine and triadimefon for the motor activity tests, with acrylamide and carbaryl for the Functional Observational Battery (FOB) and with acrylamide or trimethyltin for neuropathology. These data allow an upgrade of study 315-131:127242 to ACCEPTABLE. Another review of these data is contained in a worksheet by C. Aldous, appearing under 374-087:122985. Kellner, 6/5/95.

** 315-139 132008 Sheets, L. P. "An Acute Oral Neurotoxicity Screening Study with Technical Grade Methamidophos (Monitor®)in Rats", (Miles, Inc., Agriculture Division, Toxicology, Stilwell, KS. Miles, Inc. Report # 105053-1, 8/12/94). Methamidophos technical (purity 75.6%, Batch 0-06-7009) was administered by single oral gavage to 18 Sprague-Dawley (Sas:CD(SD)BR) rats/sex/group at 0, 0.3 and 0.6 mg/kg. There were no treatment-related effects on motor activity, body weights or daily clinical signs. Possible treatment-related FOB observations included increased landing footsplay in high-dose males. **NOEL (for neurobehavioral effects) = 0.3 mg/kg.** Gross pathological or micropathology

examinations were not performed. Significant reductions in RBC, plasma and brain cholinesterase (ChE) activity in males and RBC and brain ChE in females were noted at the high-dose level. **NOEL (ChE inhibition) = 0.3 mg/kg. No Adverse Neurotoxic Effects.** ACCEPTABLE. Kellner and Gee, 6/5/95.

315-148 142828. This document contains data supplemental to the study at DPR doc. # 315-139, rec # 132008. This document contained supplemental information on the stability, homogeneity, and purity of the test material and dosing solutions and method for measuring ChE activity. No worksheet was done (S. Morris, 2/6/96).

315-135 129816 Sheets, L. "A Subchronic Dietary Neurotoxicity Screening Study with Technical Grade Methamidophos (Monitor®) in Fischer 344 Rats", (Miles, Inc., Agriculture Division, Toxicology, Stilwell, KS. Miles, Inc. Report # 106351, 4/13/94). Methamidophos technical (purity 75.6%, Batch 0-6-7009) was administered in the diet for 13 weeks to 18 Fischer 344 rats/sex/group at nominal concentrations of 0, 1.0, 12 and 60 ppm (mean intake males: 0.067, 0.787 and 4.26 mg/kg/day; females: 0.074, 0.899 and 4.94 mg/kg/day). Daily clinical observations (e.g. muscle fasciculations, increased reactivity, perianal stain, urine stain and lacrimation), FOB observations (e.g. muscle fasciculations, salivation, urine stains, tremors, decreased forelimb grip strength) and decreased motor and locomotor activity were noted in the mid- and high-dose rats. High-dose rats showed reduced motor activity during weeks 4, 8 and 13 (reductions in the mid-dose females during week 4 only). **NOEL (clinical signs, FOB and motor activity test) = 1.0 ppm. Plasma, RBC and brain cholinesterase (ChE) activity was significantly depressed in the mid- and high-dose groups (up to 97%RBC ChE inhibition by week 13 in the high-dose males) **NOEL (ChE inhibition) = 1.0 ppm.** No histopathological lesions; **No Adverse Neurotoxic Effects.** Unacceptable (Kellner and Gee, 6/5/94) but upgraded to acceptable with clarification of active ingredient content of test feed (i.e. if correction made for 75.6% purity of technical methamidophos) and submission of positive (historical) control data (S. Morris and J. Gee, 5/8/97)

315-152; 149098: This document contained clarification of the active ingredient content of test feed and positive (historical) control data. Evaluation of these data resulted in upgrading the study status to adequate.

7-067; 028430. This document contains a brief review of some acute human poisonings with the test material and related animal data. A worksheet was not done (S. Morris, 10/7/92).

315-061; 028430: Exact duplicate of doc. # 315-067, rec # 028430.

8-061; 020053; N. Senanayake and M.K. Johnson (1982), "Acute Polyneuropathy after Poisoning by a New Organophosphate Insecticide", *The New England Journal of Medicine* 306:155-157, 1/27/82. This article discusses 10 human exposures (7 suicide attempts and 3 accidental poisonings) to toxic levels of methamidophos in Sri Lanka. Acute symptoms of toxicity described include unconsciousness, pupillary constriction, muscular fasciculations, and profuse sweating. A **possible adverse effect** was reported: delayed neuropathy (muscle weakness). This study was not a required test type and was therefore not evaluated for acceptability and no worksheet was done (H. Green and S. Morris, 1/6/93).

315-115; 095397; "Can Methamidophos Cause Delayed Polyneuropathy in Man or in Test Animals?"; Literature review; M.K. Johnson and M. Lotti; The authors assessed the potential of methamidophos to induce OPIDP in humans. Several instances have been reported of accidental overdoses to methamidophos in Nicaragua and Sri Lanka. OPIDP-like symptoms were observed in these patients 2 to 3 weeks after an episode of severe cholinergic poisoning. They required a period of 6 weeks to 2 years to recover from the neuropathy. Researchers have been able to reproduce in hens a similar response with a single dose of the racemate (400 mg/kg) or a multiple dose regimen of 130 + 50 + 50 mg/kg given over a 4 day period. These doses are well in excess of the LD50 value of 25 mg/kg for the racemate and the hens required vigorous antidotal therapy. Inhibition of the target tissues in these hens was > 86%. The authors compared the in vitro I50 AChE/I50 NTE ratio for hens to the

LD50/OPIDP value. The former ratio had a range of 0.022 to 0.064 in comparison to 0.083 for the latter value. These values indicate that more than a 10 fold concentration of methamidophos is required to inhibit 50% of the NTE activity than that of AChE and that a greater than 10 fold dose is required to induce OPIDP than to achieve the LD50. Treatment with the D-(+) isomer (200 mg/kg) was sufficient to produce signs of OPIDP that were reversible. In contrast treatment with the L-(-) isomer (400 mg/kg) was insufficient to produce any signs of OPIDP in the surviving birds (2/17). Reactivation studies revealed that > 80% of the NTE activity inhibited with the racemate and the D-(+) isomer could be reactivated by KF. These results indicated that the enzyme had not aged, a step considered necessary for the induction of OPIDP. NTE inhibited by the L-(-) isomer could not be reactivated. The I50 AChE/I50 NTE ratio (racemate) for human brain tissue is 0.064. This value taken in conjunction with clinical observations obtained from patients suffering from an overdose of methamidophos confirms that humans are only susceptible to the induction of OPIDP at a dose quite in excess of the LD50 value. (T. Moore, 4/26/91).

315-126; 089467: Exact duplicate of doc. # 315-115, rec. # 095397.
315-102; 070878; "The Cholinesterase Inhibition Potential of Analytical Grade Methamidophos (SX-1672) and Methamidophos Technical (SX-1490) Following Topical Application of a Single Dose to Male and Female Rats." Study No, S-2284; M.D. Easter and D.W. Rosenberg; Chevron Environmental Health Center, Inc., Richmond, CA; 6/27/86. Groups of 5 Sprague-Dawley rats/sex were given analytical (SX-1672, 99.1% purity) or technical (SX-1490, 74.7% purity) grade Methamidophos by single dermal applications to shaved dorsal skin at 0, 1.00, 2.50, 6.25, and 15.60 mg/rat. Animals were sacrificed 24 or 72 hours later and brain, red blood cell (RBC), and plasma cholinesterase levels (ChE) were measured. With the analytical grade, RBC, plasma, and brain ChE were inhibited at 1.00 mg/rat in females at 24 hours and in both sexes at 2.50 mg/rat after 72 hours. With the technical grade RBC, plasma, or brain ChE were inhibited in both sexes at 2.50 mg/rat at 24 and 72 hours. No adverse effect was indicated. This study was not a required test type and was therefore not evaluated for acceptability and no worksheet was done (H. Green and S. Morris, 1/5/93).

315-158; 160096 "Repeated-Dose 21-Day Dermal Toxicity Study with Technical Grade Methamidophos (Monitor®) in Rats," (L.P. Sheets and M.E. Gastner; Bayer Corporation, Stilwell, KA; Study Number 96-122-KQ, Report Number 107635, 12/10/97.) Methamidophos (batch #703-0001, 76.9 to 80.5% purity) was applied as aqueous solutions (1 ml/kg) daily for 6 hours to the shorn backs of groups of 9 or 10 Sprague-Dawley rats/sex/dose for 18 of 22 days (males) or 17 of 21 days (females) at nominal doses of 0, 1, 15, or 50 mg/kg/day (analytical doses were 0, 1, 15, 47 mg/kg/day). Observations and measurements were made: detailed clinical observations, body weight, food consumption, ophthalmology, brain, erythrocyte (RBC) and plasma cholinesterase (ChE) activity, organ weights, gross necropsy findings and micropathology. Brain, RBC, and plasma ChE activities were decreased at 15 at 50 mg/kg/day (ChE inhibition NOEL = 1 mg/kg/day). Males had the greatest depression of brain ChE which was 34% of controls. There were no other treatment-related effects reported. No adverse effect was indicated. The study is unacceptable but possibly upgradeable with adequate submissions of analytical data for the test material and dosing solutions; hematology, serum chemistry, and an adequate rationale for the highest dose (S. Morris and J Gee, 4/15/98). See record 206823 in 315-169 for adequate analytical data for record 160096, satisfying that deficiency. The study remains unacceptable based on the lack of hematology and clinical chemistry. (Gee, 10/1/03)

315-169 206823 Supplemental to 160096. Moore, K. D., 9/28/98, Report Number 107635-1. This supplement presents the analytical data for the dermal study. The active ingredient content of the dose preparations was actually 0.749, 11.2 and 36.5 mg of methamidophos per ml. The dose preparations were stable in the refrigerator for 21 days.
In addition, five batches of technical material were analyzed and 30 compounds identified in each batch. The average content of methamidophos was 76 - 77% of the 98% total identified. No worksheet. (Gee, 10/1/03)

315-169 206824 Duplicate of 160096 in 315-158.
315 - 0167 200767 " A developmental neurotoxicity screening study with technical grade methamidophos (Monitor) in Wistar rats." (Sheets, L. P., Pathology Report by S. G. Lake, Bayer Corp., Agriculture Division, KS, Study No. 00-D72-A1, Report No. 110924, February 11, 2002). Female Wistar

Crl:W(HAN)BR rats, 30/group, were mated with untreated males, 1:1. Beginning on GD 0, females were exposed to feed containing methamidophos (batch 803-0182, 72.3 to 74.2% active ingredient) at 0, 1.0, 10 or 30 ppm (analytical concentrations were 0, 0.851, 9.77 and 27.2 ppm, adjusted for purity). Exposure continued until lactation day 21 with selected pups continuing on control diet until approximately 75 days of age. Average consumption of test article for dams during gestation: 0, 0.1, 0.9 and 2.5 mg/kg/day; during lactation: 0, 0.2, 2.4 and 7.9 mg/kg/day. Dams: There were no effects on reproduction parameters, no deaths, no treatment-related findings in the observational battery for dams on GD 6, GD 20, LD 11 and LD 21. For offspring, preputial separation was delayed at 30 ppm, body weights were lower at 30 ppm for both sexes and at 10 ppm for females. Motor activity was reduced at 10 and 30 ppm on PND 13 relative to controls but not at later times (days 17, 21 and 60). There were no treatment-related findings for acoustic startle habituation, water maze, ophthalmology, brain weight or brain morphometry or micropathology of brain or neural tissues. Brain weights were not affected. The most significant findings concerned inhibition of cholinesterase. Plasma, RBC and brain cholinesterase inhibition were determined on lactation day 21 for the dams, PND 4 for pups (males and females combined) and PND 21, sexes separate. There was a significant inhibition of brain ChE (8%) in dams at 1.0 ppm, and in all three cholinesterase activities at 10 ppm and 30 ppm, with slightly greater inhibition at 30 ppm. For pups, day 4, at 10 ppm, RBC cholinesterase was inhibited 20% compared with controls and at 30 ppm, all three activities were significantly lower than controls. At postnatal day 21, there was no significant inhibition at 1.0 ppm for any measurement. At 10 ppm, for male pups, both plasma (-22%) and brain (- 13%) ChE were significantly lower and for female pups, only brain was inhibited (-17%). At 30 ppm, all three cholinesterase activities were significantly lower in both sexes, with inhibition being slightly greater in female pups. The percent inhibition, however, for the pups was considerably less than for the dams. NOEL for dams was < 1.0 ppm (inhibition of brain ChE). NOEL for pups = 1.0 ppm (cholinesterase inhibition, lower body weight in females at 10 ppm - the only measured effect that persisted to termination). Unacceptable but upgradeable (identification and/or submission of the cited positive control studies.) No evidence of neuropathology. (Gee, 9/27/02)

315 - 0281 211501 “A study of the effects of Orthene and Monitor on plasma and erythrocyte cholinesterase activity in human subjects during subacute oral administration.” (Garofalo, M., Industrial Bio-Test Laboratories, Inc., IBT No. 636-02498, Report No. 98473, March 7, 1973) Note: This study has been evaluated by US EPA as “S” for supplementary and not as “I”, invalid. Pages 49 and following contain evaluations of the study made in 1977/1978, comparing the report with the available raw data. The major problem was the lack of some raw data to support the values in the IBT report, especially for the 0.4 mg/kg/day females.

Study: The test materials were mixtures of methamidophos (Monitor) and acephate (Orthene) in ratios of either 1:9 or 1:4 parts of Monitor/Orthene. The materials were taken three times daily in corn oil in gelatin capsules for daily doses of 0.1, 0.2, 0.3 or 0.4 (females only) mg/kg/day. The subjects were seven male and seven female volunteers with 2/sex in the control and 1:4 groups and 3/sex in the 1:9 group. Ages ranged from 21 to 48 years. Exposure was for a total of 21 consecutive days for 0.1, 0.2 and 0.3 mg/kg/day and 10 (?) days for 0.4 mg/kg/day in females. Baseline plasma and erythrocyte cholinesterase activities were determined 5 times during the 2 weeks preceding exposure. ChE activities were determined on days 1, 3, 7, 14 and 21 during the test period. Each subject was given increasing doses of the test materials, same ratio, in sequence of increasing dose. After exposure to 0.3 mg/kg/day, there was a 7-day rest period with evaluation of ChE activities. ChE was determined by an AutoAnalyzer using the procedure of Levine, J. B. *et. al.* Limited hematology parameters were also evaluated pretest and at the end of the exposure period. Additional observations included blood pressure, muscle tone, pulse rate, pupil size, light reflex, eye accommodation, knee jerk, tongue tremor and finger tremor. Subjects were also to report any abnormal symptoms. Results There was no effect on erythrocyte ChE in any group. There was no effect on ChE at 0.1 mg/kg/day with either ratio. At 1:4, 0.2 mg/kg, plasma ChE was depressed in both sexes (considered to be the minimum effect level by the author) but not at 1:9 ratio. At 1:9, 0.3 mg/kg/day caused depression in plasma ChE in males [1:4 was not tested at this dose]. At 0.4 mg/kg/day,1:9, in three females, plasma, but not erythrocyte, ChE was depressed. ChE was considered affected if there were two consecutive measurements with depression greater than 2 standard deviations below the mean pretest value. The report states that there were no significant effects on hematology or the other parameters evaluated. Individual data were presented for hematology and clinical chemistry. Corrected pages, based on raw data, are

included in the reevaluation pages. Supplemental study. No worksheet. (Gee, 6/18/04)

APPENDIX B

METHAMIDOPHOS
(Monitor ®)

DIETARY EXPOSURE ASSESSMENT SUMMARY

Wesley C. Carr, Jr.

HEALTH ASSESSMENT SECTION

MEDICAL TOXICOLOGY BRANCH

CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

Dietary Analysis Completed: October 18, 2001
Chronic Dietary Exposure Updated: March 12, 2003

I. Methamidophos Introduction

Acute and chronic dietary exposure assessments and an acute tolerance assessment were conducted for the pesticide active ingredient methamidophos (40 CFR #180.315). All available methamidophos raw agricultural commodity (RAC) residue data were evaluated (Table 1). The 40 CFR 180.315 tolerance is characterized as methamidophos (Code of Federal Regulations, 2000).

The federal and state regulatory pesticide residue monitoring programs can analyze for methamidophos. The detections are reported as parent methamidophos and does not include the oxon degradate. The Food and Drug Administration (FDA) monitoring program analyzes for parent methamidophos only . The United States Department of Agriculture (USDA) Food Safety Inspection Service (FSIS) and the Pesticide Data Program (PDP) monitor for the same pesticide form. The California Department of Pesticide Regulation (DPR) organophosphate residue screen can also identify methamidophos.

Residues analyzed by the FDA regulatory monitoring surveillance program (statistically based commodity survey) from July 1, 1992 through June 30, 1993 for domestic and imported tomatoes were considered for use in the DPR dietary exposure analysis. The FDA multiple residue screen minimum quantification level (LQ) for methamidophos in the statistical survey for tomatoes is 0.02 ppm (Roy *et al.*, 1995). The USDA PDP data were used in preference to the FDA residue data.

The DPR market basket surveillance program methamidophos limit of detection (LOD) during the years 1993 - 1995 was 0.02 ppm for potato and 0.01 ppm for tomato. There were extensive multiple residue screens analyses made which included detected methamidophos residues (DPR, 1994, 1995a, 1997). The USDA PDP program data were used in preference to the DPR residue data. The lower LODs and greater number of analyzed total samples within the PDP program better represented the commodity residue profiles.

The USDA monitors for methamidophos with their multi- residue screen analytical program and the results are reported in two different annual surveys, the Pesticide Data Program (PDP) and the Food Safety Inspection Service (FSIS). The PDP program targets raw and processed commodities that are likely to be heavily consumed by infants and children. The FSIS looks for residues on various commercial meat animals such as cattle, sheep and poultry. Since there are no meat tolerances listed for methamidophos, the FSIS data were not reported.

The USDA Pesticide Data Program (PDP), established May 1991, has monitored for methamidophos using the multi residue methods (MRMs) since 1992. The 1994, 1995, 1996 and 1997 PDP data were used as these data are the most recent available for two of the assessed RACs.

The PDP methamidophos residue limits of detection (LOD) range for potatoes tested during 1994 and 1995 is between 0.002 ppm and 0.015 ppm. The specific LODs by state are 0.002 ppm (New York), 0.003 ppm (California and Michigan), 0.004 ppm (Texas), 0.005 ppm (Florida) and 0.015 ppm (Washington) for each laboratory (USDA, 1995a, 1996b and 1997b).

The USDA - PDP LOD range for tomatoes tested during 1996 and 1997 is between 0.001 ppm and 0.015 ppm. The specific LODs are 0.001 ppm (California), 0.003 ppm (New York and Michigan), 0.005 ppm (Florida lab 1), 0.006 ppm (Ohio) and 0.015 ppm (Florida lab 2) for each state laboratory (USDA, 1998 b,c).

The 0.015 ppm detection limits for potatoes and tomatoes did not constitute a significant number of the total samples but were still included together with the other LOD values. The individual non detect LOD values for each state's commodity analysis program were reported for all acute samples without any detected methamidophos residues instead of reporting a zero value (½ LOD for chronic) in the DPR dietary exposure analyses. The following RACs used the PDP annual data; potato (1994 and 1995) and tomato (1996 and 1997).

The Bayer Corp. pesticide name used in the submitted field residue studies is methamidophos (Monitor ®): (O,S-dimethyl-phosphoramidothioate). The potential dietary exposure from residues of methamidophos was evaluated by Bayer (= Mobay Corp.) and

reported in submitted field studies. The registrant limit of quantification (LOQ) for methamidophos was 0.01 ppm for cottonseed (Leslie, 1989, Russo, 1998), potato (Koch, 1988) and tomato (Morris & Olson, 1974) based on the most recent submitted field studies.

Currently there are just 2 active registrations of methamidophos approved for use in California. Both registrations are exclusively for agricultural use. These agricultural use products are for general insect pest control on raw agricultural commodities. The active ingredient formulations are both 40% crop sprays. The crop pre-harvest intervals (PHI) range from a minimum of 7 days for tomatoes to a maximum of 50 days for cottonseed.

California Annual Pesticide Use

There were 312,070 lbs. of methamidophos used in California during 1997 (DPR, 1999). There were 244,270 lbs. applied during 1998 and for 1999, 138,988 lbs. (DPR, 2000a, 2000b). A total of 76,865 lbs. was applied during 2000 and for 2001, 46,615 lbs. (DPR, 2001, 2002). The California 5 year (1997-2001) average annual use is 163,760 lbs. of methamidophos active ingredient (DPR, 2002). Average annual California use (163,760 lbs. a.i.) represents about 28 percent of the total national annual average. The average amount of methamidophos applied per year in the United States is about 600,000 lbs. of a.i. (U.S. EPA, 2000). Methamidophos use on California crops has declined every year since 1997.

The 4 commodities receiving the most methamidophos applications in California are alfalfa, cotton, tomato (fresh and processing), and potato. These 4 crops comprise about 90% of the total methamidophos used in California.

II. Residue Database

All of the commodity residue data used for the DPR methamidophos dietary exposure assessment were obtained from the following sources: a) registrant commodity field residue studies or b) USDA 1994 - 1997 PDP residue monitoring program data. A U.S. EPA tolerance was assigned in the acute dietary exposure analysis for one agricultural commodity. The tomato tolerance value was used to represent dried tomato because the default dietary program concentration factor when multiplied by the PDP acute residue value exceeded the U.S. EPA tolerance. All available methamidophos raw agricultural commodity residue data, expressed as methamidophos parent, were used to conduct the DPR dietary analyses are presented in Table 1.

Table 1. Summary of Methamidophos Residues (October, 2001)

RAC	Source [a] (Reference)	Toler [b] (ppm)	Acute Residue (ppm) [c] Point	Monte Carlo	Chronic Residue	N [d]	Additional Information	PCT [e]
Cottonseed, meal	REG-fp	0.1(N)[f]	0.044	N.A.	0.042	32	acute average (mixture).	15%
Cottonseed, oil	REG-fp	0.1(N)	0.01	N.A.	0.005	4	processing = non detect (ND)	15%
Potato	USDA (PDP)	0.1(N)	0.0091	monitor	0.0019	1401	acute pt est = 95th%,LOD for ND	30%
Tomato	USDA (PDP)	1.0	0.082	potato.rdf monitor	0.013	879	PDP range of state LODs	20%
				toma.rdf			Fresh tomato:	85%

a/ **USDA** = U.S. Department of Food and Agriculture, **PDP** = U.S. Department of Agriculture Pesticide Data Program residue monitoring program, **REG-f & REG-fp**= Registrant supplied field or field and processing residue studies.
b/ **U.S. EPA** = Tolerances for U.S. EPA 40 CFR 180.315 (methamidophos).
c/ **Point** = Point Estimate acute residue value. **Monte Carlo** = Distributional analysis of the acute residue values.
d/ **N** = The number of RAC composite samples analyzed from the selected submitted studies or monitoring programs.
e/ **PCT** = Percent of the crop treated adjustment made to chronic dietary residues when sufficient use data are available.
f/ (N) = U.S. EPA determined that the commodity is expected to be a negligible residue (as defined).

III. Residue Adjustments

A. Percent of the Crop Treated

The current DPR chronic dietary exposure analysis default assumption is that 100% of any crop is treated with the pesticide under consideration. When quality data are available that indicate that less than 100% of a commodity is treated with a specific pesticide, then on an individual commodity by pesticide combination basis, exceptions to the default assumptions can be made.

The assumption that people under normal eating conditions would be continuously exposed to the averaged residue level of a pesticide for every labeled commodity for either for 1 year (chronic) or 70 years (lifetime) is unrealistic based on available substantial dietary information. This assumption does not take into account the fact that a significant amount of a commodity is often untreated with the pesticide under consideration. This is not reflective of actual practices and is borne out by the lower residue levels encountered in various market basket surveys versus the registrant field studies. The actual percentage of the crop treated with a specific pesticide varies from year to year depending upon biotic and abiotic factors. Using the existing percent crop treated data, it is reasonable to revise the 100% treated assumption downward using more realistic pesticide treatment rates and use patterns. Commodities that used residues obtained from registrant field trial or state and federal monitoring data in the chronic dietary exposure assessment were considered for percent crop treated adjustments.

The percent of the crop treated (%CT) adjustment method has been employed as a comparison to the standard chronic dietary exposure assessment using 3 commodities that have methamidophos tolerances. The following commodities have reported methamidophos applications at the federal and state levels and have comprehensive use data: cottonseed, potato and tomato. DPR Pesticide Use Reports and CDFA crop statistics together with USDA Ag Field Crops Summary annuals were used. Conservative, but realistic, assumptions were made when setting the percentage of crop treated adjustment factors for the chronic dietary exposure section for each commodity. Multiple years of methamidophos use and acreage harvested data were evaluated at the federal and state levels.

1. Cottonseed (meal and oil)

The total planted California cotton acreage during 1995 was 1,170,000, for 1996 it was about 1,000,000 and for 1997 it was 880,000 acres (USDA, 1997a,b, 1998a). The California cotton acreage represents, on average, approximately 10% of the total annual U.S. cotton production (USDA, 1997a,b, 1998a). Methamidophos was applied to an average of about 120,000 acres of cotton nationally during 1995, 1996 and 1997 growing seasons. The USDA agricultural statistics information indicates that methamidophos was applied to an average of 11% (13% single year peak) of the California cotton acreage. The United States cotton acreage is primarily from seven major states; Alabama, Arkansas, California, Georgia, Louisiana, Mississippi, and Texas, which produced a harvest during 1995 of 11,650,000 acres, 1996 from 11,915,000 acres and 13,075,000 acres during 1997 (USDA, 1997a,b, 1998a). Based on USDA Agriculture Marketing Statistics data, methamidophos was applied, on average, to no more than 2% of the 1995, 1996 and 1997 acreage in the 7 major production states. The higher methamidophos use in the California acreage, 13% highest year, will be used for the percent crop treated adjustment rather than the less than 2% national average. Derived from this California cotton use data, a 15% crop adjustment factor (13% rounded up to next highest even 5% value) will be used for cotton in the chronic dietary residue file. The 15% crop adjustment factor means that the DPR chronic dietary exposure analysis will assume that at least 85% of the U.S. cotton crop is not treated with methamidophos. The actual USDA use data indicates, on average, that less than 5% of the U.S. cotton crop is treated, however the 15% adjustment value takes into consideration the greater amount of methamidophos that is applied on average to California cotton and not the average national levels.

2. Potato

Potatoes were planted to an average of about 963,000 acres during the 1995, 1995 and 1997 seasons (3 year range: 797,000 - 1.147,000 acres) in the major production states (USDA, 1997a,b, 1998a). The United States primary national acreage originates from 10 states; Colorado, Idaho, Maine, Michigan, Minnesota, North Dakota, Oregon, Pennsylvania, Washington and Wisconsin (USDA, 1997a,b, 1998a). California is not a significant potato production state and was not included in the USDA NASS survey results. Methamidophos was applied to about 26% of the 1995, 1996 and 1997 national acreage (USDA, 1997a,b, 1998a). Based on the 3 year average of 26% (highest year; 1996 and 29%) for the national data, a 26% crop adjustment factor will be used to represent domestic methamidophos applications on potatoes. There are also some imported potato crop data available from the USDA. The most recent year of data, 1992, showed that 7 million hundred weight (cwt.) of potatoes were imported into the United States versus domestic production of around 425 million hundred weight (cwt.) annually (USDA, 1994). The imported potatoes represent about 2% (actual; 1.6%) of the total U.S. potato market. All of the imported potatoes are assumed to have been treated with methamidophos for ease of calculation. Based on the combined USDA domestic use (26%) and the imported potato data (2%), a combined 30% crop adjustment factor (28% rounded to 30%) to represent the chronic annual potato treatment with methamidophos will be used.

3. Tomatoes (fresh market and processed)

The United States fresh market acreage originates from eight main states; California, Florida, Georgia, Michigan, New Jersey, New York, North Carolina, and Texas which during 1992 produced tomatoes from 105,000 acres, 1994 from 104,000 acres and 89,000 acres during 1996 (USDA, 1993, 1995b, 1997c). The USDA methamidophos fresh market tomato records indicate that there was use on about 50% of the acres in 1992 and 1996 and 60% of the acres during 1994 (USDA, 1993, 1995b, 1997c). The California fresh market tomato acreage totaled 37,000 acres during 1992 and 1994 and 33,000 acres during 1996 (USDA, 1993, 1995b, 1997c). The 1992, 1994 and 1996 California acreage represented approximately 36% of the total U.S. fresh market tomato crop. Methamidophos was applied to between 50 - 65% of the California fresh market tomatoes during the 1992, 1994 and 1996 seasons (DPR, 1996a,b, USDA, 1993, 1995b, 1997c). Therefore for the fresh market component of tomatoes, 60% (actual = 57%) representing the three year average (1992, 1994 and 1996) of California use will be added to the fresh market tomatoes portion of methamidophos use.

The California processed tomato acreage totaled 242,000 acres in 1992 and about 318,000 acres in each of the 1994 and 1996 seasons (USDA, 1993, 1995b, 1997c). The 1992, 1994 and 1996 California

tomato acreage represented more than 94% of the total U.S. processed tomato harvest. The DPR and USDA processed tomato records for California indicate that methamidophos was applied to between 9 - 30% of the California processing tomatoes during the 1992, 1994 and 1996 seasons (DPR, 1996a,b, (DPR, 1996a,b, USDA, 1993, 1995b, 1997c). A three year average (1992, 1994 and 1996) representing methamidophos use on California processing tomatoes of 20% (actual = 17%) will be added to the processing tomatoes portion of use.

The total U.S. domestic tomato production (fresh and processed combined) amounted to 11,451,490 tons during 1993 (USDA, 1994b). Foreign imports as fresh, canned and pureed tomatoes, during 1993, amounted to about 100,000 tons which constitutes less than 1% of the total (fresh and processed) U.S. market (USDA, 1994b). The food form codes for processed tomatoes (juice, paste and puree) included no significant imported processed tomato adjustment. Therefore, the percent crop treated adjustment for the processed tomato food codes with be 20% (domestic 17% rounded up) in the chronic dietary exposure. There are data that suggest that as much as 25% of the U.S. fresh tomato market are imports (Roy *et al.*, 1995). This FDA tomato import estimate (DPR default assumption is that 100% of imports are treated) will be combined with domestic methamidophos use to modify the percent of the crop treated adjustment factor for U.S. fresh tomatoes. Based on the U.S. domestic fresh tomato methamidophos treatment rate average value of 60% (California use) plus the 25% imported fresh market tomatoes value results in a combined total of 85% to represent whole tomato food forms in the chronic dietary exposure analysis.

B. Commercial Processing

The were two Registrant processing studies reviewed for methamidophos residues in cottonseed and processed tomato products. The cottonseed processing study of meal, crude and refined oil however, did not provide any specific residue reduction factors data relevant to the fate of methamidophos residues other than the determination that there is no concentration in these processed fractions (Leslie, 1989). The more recent processing study in tomatoes is discussed in more detail since residue reduction data were quantified and these processing reduction factors were used to modify the default adjustment factor.

Tomato (Processed)

A registrant methamidophos residue concentration study using commercial tomato processing methods was included in a magnitude of the residues study (Morris and Olson, 1974). The study showed that the commercial preparation of tomatoes (washing, peeling and cooking) did not concentrate methamidophos residues in the processed portions (tomato juice, catsup, puree or paste) (Morris and Olson, 1974). This was demonstrated by the normal processing of whole tomatoes after fortification with 1.52 ppm of methamidophos. The analysis of the processed fractions (juice, etc.) showed that all processed portions (except pomace and pulp) had recovered residues less than the 1.52 ppm contained in the whole tomato. The recovered residues and processed fractions were: pasteurized juice, 1.36 ppm, canning tomatoes (to represent puree), 1.11 ppm and catsup (also representing tomato paste), 1.04 ppm. While there is not enough information to apply specific reduction factors to the tomato products, there is enough data so that the tomato default concentration values can be changed to 1.0X from their higher values (range 1.5X to 5.4X). Therefore, the DEEM® program food form adjustment factor #1 for tomato juice, puree, catsup and paste were set to 1.0X and then combined with the USDA PDP monitoring program residues in the acute and chronic dietary exposure analyses.

IV. Dietary Exposure (Summary)

A. Acute Dietary Exposure

The acute dietary exposure was estimated based on residue data from market place surveillance

and registrant field trials together with the 1994-1998 Continuing Survey of Food Intakes by Individuals (CSFII) consumption data. The acute dietary values resulting from the calculated exposure using the methamidophos no-observed-effect-level (NOEL) of 0.3 mg/kg/day (rat neurotoxicity study, brain ChE inhibition), commodity consumption, and anticipated methamidophos residues were examined and the results are presented in Table 2 (Novigen, 2001, USDA, 1994-98).

There were two acute dietary exposure scenarios calculated. The first scenario consisted of dietary exposure data based on point estimates for all of the commodity residue values. The second scenario had the point estimate residue values for the commodities potatoes and tomatoes replaced by Monte Carlo (probabilistic estimates) data sets derived from the USDA PDP monitoring data. The point estimate 95 th percentile acute dietary margins of exposure(MOEs) ranged from 0.000238 mg/kg/day, seniors 55^{+} years (methamidophos MOE: 1,260) to 0.000646 mg/kg/day, children 1-6 years (methamidophos MOE: 460). The Monte Carlo acute dietary analysis MOEs reported at the 95 th percentile level of exposure ranged from 0.000048 mg/kg/day, seniors 55^{+} years (methamidophos MOE: 6,230) to 0.000129 mg/kg/day, children 1-6 years (methamidophos MOE: 2,320). The 99.9 th percentile Monte Carlo level of exposure MOEs ranged from 0.000515 mg/kg/day, seniors 55^{+} years (MOE: 580) to 0.001410 mg/kg/day, children 1-6 years (MOE: 210). None of the population subgroups, using either the point estimate or Monte Carlo scenarios, had margins of exposure values of less the 100 when the 0.3 mg/kg/day NOEL was used. The acute dietary exposure analyses include all the current U.S. EPA label approved methamidophos uses.

B. Seasonal Dietary Exposure for California Workers

Methamidophos, because of its pervasive year around utilization on California crops, does not present a clearly defined sub-chronic use season for workers applying the pesticide. The Worker Health and Safety branch therefore has not calculated a seasonal California worker occupational exposure. The Health Assessment Section (HAS) of the Medical Toxicology branch has also determined that no seasonal exposure by workers would result in a sub-chronic dietary exposure. Therefore, none was calculated.

C. Chronic Dietary Exposure

The chronic non-oncogenic dietary exposure values obtained by using an estimated NOEL (ENEL) of 0.02 mg/kg/day derived from a 1 year dog study were examined (Novigen, 2001, USDA, 1994-98) (Table 3). Both percent of the crop treated (%CT) adjustments and non-modified with %CT scenarios were calculated. The chronic dietary exposure scenario with %CT adjustments had each of the three commodities modified. The %CT values were derived from the average weighted methamidophos use information from the DPR, U.S. EPA BEAD and USDA marketing and use data. The %CT chronic dietary exposure ranged from 0.000001 mg/kg/day (nursing infants) to 0.000013 mg/kg/day (children 1-6 years) (Table 3). The chronic dietary exposure unmodified by %CT adjustments ranged from 0.000003 mg/kg/day (nursing infants) to 0.000027 mg/kg/day, (children 1-6 years) (Table 3).

D. Lifetime (Oncogenic) Dietary Exposure

There is no calculated oncogenic potency factor for methamidophos. Therefore, no cancer risk from lifetime (chronic) dietary exposure to methamidophos or any of its degradation products was determined.

Table 2. Acute Dietary Margins of Exposure [a] from Anticipated Methamidophos Residues on Raw Agricultural Commodities Using Point and Monte Carlo Estimates.

	Point Estimate Dietary Exposure [b]	Monte Carlo (M.C.) Dietary Exposure [b]	
	95 th % Point MOEs [c]	95 th % M.C. MOEs	99.9 th% M.C. MOEs
Population Subgroups	(Exposure in mg/kg/day) [c]	(Exposure) [d]	(Exposure)
US Pop. all seasons	930 (0.000323)	4,500 (0.000067)	430 (0.000706 mg/kg/day)
Western Region	840 (0.000355)	4,220 (0.000071)	400 (0.000749)
Hispanics	760 (0.000394)	3,600 (0.000083)	340 (0.000877)
Non-Hispanic Whites	960 (0.000314)	4,620 (0.000065)	450 (0.000670)
Non-Hispanic Blacks	930 (0.000321)	4,930 (0.000061)	420 (0.000719)
Non-Hispanic Other	850 (0.000353)	4,210 (0.000071)	370 (0.000816)
All infants	520 (0.000574)	3,430 (0.000088)	240 (0.001234)
Infants (nursing, < 1 year)	820 (0.000366)	5,070 (0.000059)	360 (0.000822)
Infants (non-nursing, < 1year)	500 (0.000604)	3,250 (0.000092)	230 (0.001279)
Children (1-6 years)	460 (0.000646)	2,320 (0.000129)	210 (0.001410)
Children (7-12 years)	730 (0.000409)	3,480 (0.000086)	340 (0.000880)
Females (13-19 years) (not pregnant, not nursing)	1,000 (0.000299)	4,770 (0.000063)	470 (0.000633)
Females (20+ years) (not pregnant, not nursing)	1,210 (0.000248)	5,830 (0.000051)	580 (0.000519)
Females (13-50 years)	1,150 (0.000261)	5,430 (0.000055)	550 (0.000543)
Females (13+ years) (pregnant, not nursing)	1,030 (0.000292)	4,910 (0.000061)	530 (0.000567)
Females (13+ years) (nursing)	980 (0.000307)	5,380 (0.000056)	540 (0.000553)
Males (13-19 years)	870 (0.000344)	3,970 (0.000076)	490 (0.000617)
Males (20+ years)	1,070 (0.000279)	5,120 (0.000059)	530 (0.000568)
Seniors (55+ years)	1,260 (0.000238) mg/kg/day)	6,230 (0.000048)	580 (0.000515

a/ MOEs based on all label approved commodities. Exposure levels have been rounded off to 3 significant figures and are based on the 1994-1998 Continuing Survey of Food Intakes of Individuals (CSFII).

b/ The acute residue files used anticipated residue values for the commodities.

c/ Both the Point Estimate and Monte Carlo scenarios exposure results use percent user days values and not per capita.

d/ MOE = NOEL ÷ Exposure. A MOE of at least 100 is generally considered to be protective of human health when the NOEL (non-oncogenic) is based on animal data. The acute NOEL value of 0.3 mg/kg/day was used (rat: brain ChE inhibition).

Table 3. Chronic Dietary Margins of Exposure [a] from Anticipated Methamidophos Residues on Raw Agricultural Commodities.

Population Subgroups	Chronic Exposure [b] Annualized Average (Margins of Exposure) [c] Percent Crop Treated (%CT) [d]	No %CT
US Pop. all seasons	2,927 (0.000007 mg/kg/day)	1,443 (0.000014 mg/kg/day)
Western Region	2,690 (0.000007)	1,370 (0.000015)
Hispanics	2,160 (0.000009)	1,150 (0.000017)
Non-Hispanic Whites	3,010 (0.000007)	1,470 (0.000014)
Non-Hispanic Blacks	3,540 (0.000006)	1,620 (0.000012)
Non-Hispanic Other	2,690 (0.000007)	1,410 (0.000014)
All infants	6,450 (0.000003)	3,010 (0.000007)
Infants (nursing, < 1 year)	16,720 (0.000001)	7,950 (0.000003)
Infants (non-nursing, < 1 yr)	5,230 (0.000004)	2,430 (0.000008)
Children (1-6 years)	1,550 (0.000013)	730 (0.000027)
Children (7-12 years)	2,420 (0.000008)	1,080 (0.000018)
Females (13-19 years) (not pregnant, not nursing)	3,360 (0.000006)	1,490 (0.000013)
Females (20+ years) (not pregnant, not nursing)	3,490 (0.000006)	1,870 (0.000011)
Females (13-50 years)	3,440 (0.000006)	1,730 (0.000012)
Females (13+ years) (pregnant, not nursing)	3,200 (0.000006)	1,580 (0.000013)
Females (13+ years) (nursing)	2,890 (0.000007)	1,620 (0.000012)
Males (13-19 years)	2,740 (0.000007)	1,280 (0.000016)
Males (20+ years)	3,250 (0.000006)	1,620 (0.000012)
Seniors (55+ years)	3,570 (0.000006)	1,970 (0.000010)

a/ MOEs based on all label approved commodities. Exposure levels have been rounded off to 3 significant figures and are based on the 1994-1998 Continuing Survey of Food Intakes of Individuals (CSFII).
b/ The chronic residue files used anticipated residue values for the commodities.
c/ MOE = NOEL ÷ Exposure. A MOE of at least 100 is generally considered to be protective of human health when the NOEL (non-oncogenic) is based on animal data. The chronic NOEL value of 0.02 mg/kg/day was used (dog: 1 year; LOEL of 0.06 mg/kg/d, brain ChE inhibition).
d/ %CT = percent of the crop treated. The modification is made to adjustment factor 2 in the chronic residue file.

V. Acute Tolerance Assessment

An acute tolerance assessment was performed for methamidophos using the current U.S. EPA tolerances (U.S.EPA, 2001). The methamidophos acute NOEL of 0.3 mg/kg-body wt/day was used to calculate dietary margins of exposure based on a rat neurotoxicity study (brain ChE inhibition). There are currently 3 human consumption RACs that have United States methamidophos tolerances (CFR, 2001). The individual commodities were analyzed at the tolerance level maximum residue contribution (MRC) for acute dietary exposure using the NOEL of 0.3 mg/kg-body wt/day. The commodities and their tolerances are: cottonseed (0.1 ppm tolerance), potato (0.1 ppm), and tomato (1.0 ppm). The MOE ranges for each commodity are reported at the 97.5th percentile of MRC dietary consumption (Table 4).

Two of the three commodities evaluated had MOE values greater than 100 at the 97.5th percentile of dietary exposure for each population subgroup while 1 commodity did not. The two commodities with MOE values greater than 100 for all population subgroups are; cottonseed and potato. The RAC cottonseed tolerance MOE range is non nursing infants <1 year; 4,780 (0.000063 mg/kg-bw) - seniors 55^{+} years; 43,380 (0.000007 mg/kg-bw). The MOE range for the potato tolerance assessment is non-nursing infants < 1 year; 160 (0.001871 mg/kg-bw) - seniors 55^{+} years; 710 (0.000424 mg/kg-bw).

Margins of exposure (MOE) were less than 100 at the 97.5th percentile of dietary exposure for all of the population subgroups for the commodity tomato at tolerance when using the methamidophos acute NOEL value of 0.3 mg/kg-body wt/day. The tomato tolerance MOE range is children 1-6 years; 26 (0.011313 mg/kg-bw) - female 13+ -pregnant/not nursing; 76 (0.003933 mg/kg-bw).

The highest acute tolerance residue contribution exposure (lowest MOE) was 0.011313 mg/kg-bw (MOE: 26) which occurred in the children 1-6 years population subgroup from tomato (all food forms) consumption at tolerance level. The lowest exposure (highest MOE) was obtained from the cottonseed tolerance assessment of the population subgroup seniors 55^{+} years with a value of 0.000007 mg/kg-bw (MOE: 56,900). Additionally, the three commodities cottonseed, potato and tomato are listed separately (Table 4) with each of the individual population subgroup's MOEs.

Table 4. Margins of Exposure [a] for Population Subgroups From Three Individual Commodities With Tolerance Level Methamidophos.

Commodity:	Acute 97.5 th Percentile Margins of Exposure [b] Cottonseed	Potato	Tomato
Population Subgroup			
US Pop. all seasons	20,360	460	49
Western Region	14,500	430	46
Hispanics	15,620	390	43
Non-Hispanic Whites	23,210	480	51
Non-Hispanic Blacks	15,920	420	46
Non-Hispanic Other	8,890	410	40
All Infants	5,450	170	28
Infants (nursing, < 1 year)	9,190	340	34
Infants (non-nursing, < 1 year)	4,780	160	27
Children (1-6 years)	7,780	240	26
Children (7-12 years)	12,410	360	40
Females (13-19 years) (not pregnant, not nursing)	24,350	540	60
Females (20+ years) (not pregnant, not nursing)	36,310	670	67
Females (13-50 years)	31,850	610	65
Females (13+ years) (pregnant, not nursing)	42,800	460	76
Females (13+ years) (nursing)	11,170	540	65
Males (13-19 years)	24,350	420	52
Males (20+ years)	34,640	600	61
Seniors (55+ years)	43,380	710	68

a/ MOEs based on label approved commodities. Exposure levels have been rounded off to 3 significant figures and were based on the 1994-1998 Continuing Survey of Food Intakes of Individuals.

b/ The residue files used tolerance level values for the commodities. The number of user days from the 1994-98 CSFII database are acceptable for each commodity.

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ATTACHMENT A

Acute Dietary Exposure Assessment

(Monte Carlo and Point Estimate Runs)

California Department of Pesticide Regulation Ver. 7.73
DEEM Acute analysis for METHAMIDOPHOS
Residue file name: D:\deem\Resi-files\monitoracute.R96
Analysis Date 10-16-2001 Residue file dated: 01-31-2000
DPR Reference dose (NOEL) = 0.3 mg/kg bw/day
Comment: Dietary exposure analysis for 180.315 using REG & monitoring residue data.

RDL indices and parameters for Monte Carlo Analysis:

Index	Dist	Parameter #1	Param #2	Param #3	Comment #	Code
1:	6	monitortoma.rdf.	2:	6	monitorpotato.rdf	

Food Code	Crop Grp	Food Name	Residue (ppm)	Adj.Factors #1	#2	RDF Index
159	8	Tomatoes-whole	0.082000	1.000	1.000	1
		Full comment: PDP 1996 & 97. N= 879 samples				
160	8	Tomatoes-juice	0.082000	1.000	1.000	1
		Full comment: REG study: processed residues < 1X conc.				
161	8	Tomatoes-puree	0.082000	1.000	1.000	1
		Full comment: therefore use 1X conc. factor exposure				
162	8	Tomatoes-paste	0.082000	1.000	1.000	1
		Full comment: for processed tomatoes				
163	8	Tomatoes-catsup	0.082000	1.000	1.000	1
207	1C	Potatoes/white-whole	0.009100	1.000	1.000	2
		Full comment: PDP 1994/95 data. 95th% UB value				
208	1C	Potatoes/white-unspecified	0.009100	1.000	1.000	2
209	1C	Potatoes/white-peeled	0.009100	1.000	1.000	2
210	1C	Potatoes/white-dry	0.009100	6.500	1.000	2
211	1C	Potatoes/white-peel only	0.009100	1.000	1.000	2
290	O	Cottonseed-oil	0.010000	1.000	1.000	
		Full comment: REG LOD (0.01 ppm)				
291	O	Cottonseed-meal	0.044000	1.000	1.000	
		Full comment: REG: acute average (mixture)				
423	8	Tomatoes-dried	1.000000	1.000	1.000	1
		Full comment: Use tolerance since residue X conc. > tolerance				

Summary of Residue Distribution Files (RDF) listed in D:\deem\Resi-files\monitoracute.R96

RDF #	File Name	N residues w freq's	N residues w/o freq's	N LODs Value	LOD	Number Of Zeros
1	monitortoma.rdf	0	879	0	0	0
2	monitorpotato.rdf	0	1401	0	0	0

PDPpotato RDF for DPR monitor acute residue file (in ppm)
Methamidophos, 10-16-2001
TotalNZ= 1401 TotalLOD= 0
TotalZ= 0

0.038 0.026 0.022 0.015 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006

0.006 0.006 0.006 0.005 0.005 0.005 0.004 0.015 0.015 0.015 0.015 0.015

0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015

0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015

0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015

0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015

0.015

Plus the following Frequencies:

0.005 ppm x 78

0.004 ppm x 243

0.003 ppm x 620

0.002 ppm x 387

PDP Tomato, RDF for DPR monitor acute residue (in ppm)
Methamidophos,10-16-2001
TotalNZ= 879 TotalLOD= 0
TotalZ= 0

0.35 0.32 0.29 0.29 0.25 0.22 0.2 0.18 0.18 0.16 0.16 0.15

0.14 0.13 0.13 0.12 0.12 0.12 0.12 0.12 0.12 0.12 0.11 0.11

0.1 0.1 0.098 0.095 0.092 0.091 0.091 0.09 0.089 0.089 0.084 0.082

0.08 0.08 0.079 0.074 0.07 0.069 0.069 0.069 0.068 0.068 0.065 0.065

0.065 0.06 0.058 0.057 0.055 0.055 0.054 0.053 0.051 0.051 0.05 0.05

0.05 0.049 0.049 0.049 0.048 0.048 0.046 0.044 0.044 0.043 0.043 0.043

0.043 0.042 0.041 0.039 0.038 0.037 0.037 0.037 0.036 0.035 0.035 0.034

0.033 0.033 0.033 0.033 0.032 0.031 0.031 0.03 0.03 0.029 0.028 0.028

0.027 0.027 0.026 0.026 0.026 0.025 0.025 0.025 0.025 0.025 0.025 0.025

0.025 0.025 0.025 0.025 0.025 0.025 0.025 0.025 0.025 0.025 0.025 0.025

0.024 0.023 0.023 0.023 0.023 0.023 0.022 0.022 0.022 0.022 0.021 0.021

0.02 0.02 0.02 0.02 0.019 0.019 0.019 0.019 0.019 0.018 0.018 0.018

0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.017 0.017 0.017 0.016 0.016

0.016 0.016 0.016 0.016 0.015 0.015 0.015 0.014 0.014 0.014 0.013 0.013

0.013 0.013 0.013 0.012 0.012 0.012 0.012 0.011

Plus the following Frequencies:

0.01ppm x 22 0.006 x 90 0.0015 x 60

0.009 ppm x 3 0.005 x 141 0.001 x 151

0.008 ppm x 12 0.003 x 200 0.007 ppm x 3 0.002 x 21

CDPR ACUTE Analysis: METHAMIDOPHOS. DEEM Ver. 7.73 (1994-98 CSFII data)
Residue file: monitoracute.R96. Adj. factor #2 NOT used. **Monte Carlo Analysis**
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.3 mg/kg body-wt/day, MC iterations = 500, MC seed = 1
Dietary exposure analysis for 180.315 using REG & monitoring residue data.
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Summary calculations (per capita):

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	MOE	Exposure	MOE	Exposure	MOE
U.S. Population:	0.000065	4605	0.000207	1448	0.000696	430
Western region:	0.000069	4339	0.000221	1354	0.000739	406
Hispanics:	0.000081	3716	0.000254	1180	0.000859	349
Non-hispanic whites:	0.000064	4702	0.000201	1492	0.000663	452
Non-hispanic blacks:	0.000059	5073	0.000195	1541	0.000708	423
Non-hisp/non-white/non-black:	0.000067	4480	0.000222	1352	0.000792	378
All infants:	0.000036	8393	0.000144	2088	0.000734	408
Nursing infants (<1 yr old):	0.000013	22722	0.000058	5177	0.000336	893
Non-nursing infants (<1 yr old):	0.000043	6901	0.000171	1754	0.000849	353
Children 1-6 yrs:	0.000128	2350	0.000416	721	0.001397	214
Children 7-12 yrs:	0.000086	3503	0.000264	1134	0.000876	342
Females 13+ (preg/not nursing):	0.000060	5005	0.000189	1587	0.000563	532
Females 13+ (nursing):	0.000056	5378	0.000183	1640	0.000553	542
Females 13-19 (not preg or nursing):	0.000062	4835	0.000188	1597	0.000629	476
Females 20+ (not preg or nursing):	0.000050	5942	0.000164	1832	0.000515	582
Females 13-50 yrs:	0.000054	5535	0.000170	1765	0.000538	557
Males 13-19 yrs:	0.000074	4035	0.000213	1407	0.000611	490
Males 20+ yrs:	0.000058	5190	0.000178	1683	0.000564	531
Seniors 55+:	0.000047	6321	0.000161	1860	0.000512	586

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001/14:15:58 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

U.S. Population	Daily Exposure Analysis /a (mg/kg body-weight/day)	
	per Capita	per User
Mean	0.000017	0.000018
Standard Deviation	0.000057	0.000058
Margin of Exposure 2/	17,351	16,867

Percent of Person-Days that are User-Days = 97.21%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000037	8,146
20.00	0.000001	405,911	95.00	0.000067	4,499
30.00	0.000002	134,431	97.50	0.000114	2,639
40.00	0.000004	77,621	99.00	0.000211	1,423
50.00	0.000006	52,170	99.50	0.000317	947
60.00	0.000008	36,493	99.75	0.000458	655
70.00	0.000012	25,137	99.90	0.000706	425
80.00	0.000019	16,044			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000036	8,356
20.00	0.000001	572,242	95.00	0.000065	4,605
30.00	0.000002	157,632	97.50	0.000111	2,695
40.00	0.000004	84,086	99.00	0.000207	1,448
50.00	0.000005	55,056	99.50	0.000311	963
60.00	0.000008	37,997	99.75	0.000451	664
70.00	0.000012	25,993	99.90	0.000696	430
80.00	0.000018	16,531			

a/ Analysis based on all two-day participant records in CSFII 1994-98 survey.
2/ Margin of Exposure = NOEL/ Dietary Exposure.

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001/14:15:58 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Western region	Daily Exposure Analysis (mg/kg body-weight/day)	
	per Capita	per User
Mean	0.000018	0.000019
Standard Deviation	0.000061	0.000062
Margin of Exposure	16,548	15,973

Percent of Person-Days that are User-Days = 96.53%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE

10.00	0.000000	>1,000,000	90.00	0.000039	7,682
20.00	0.000001	415,710	95.00	0.000071	4,216
30.00	0.000002	140,316	97.50	0.000122	2,464
40.00	0.000004	79,009	99.00	0.000226	1,325
50.00	0.000006	51,938	99.50	0.000340	883
60.00	0.000008	35,684	99.75	0.000486	617
70.00	0.000012	24,126	99.90	0.000749	400
80.00	0.000020	15,183			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000038	7,936
20.00	0.000000	630,584	95.00	0.000069	4,339
30.00	0.000002	172,038	97.50	0.000119	2,527
40.00	0.000003	87,907	99.00	0.000221	1,354
50.00	0.000005	55,881	99.50	0.000333	900
60.00	0.000008	37,680	99.75	0.000478	627
70.00	0.000012	25,188	99.90	0.000739	406
80.00	0.000019	15,796			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001/14:15:58 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Hispanics — Daily Exposure Analysis

	(mg/kg body-weight/day) per Capita	per User
Mean	0.000021	0.000022
Standard Deviation	0.000071	0.000072
Margin of Exposure	14,041	13,497

Percent of Person-Days that are User-Days = 96.12%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000046	6,494
20.00	0.000001	232,574	95.00	0.000083	3,600
30.00	0.000003	99,619	97.50	0.000141	2,126
40.00	0.000005	61,585	99.00	0.000260	1,154
50.00	0.000007	42,139	99.50	0.000388	773
60.00	0.000010	29,573	99.75	0.000559	536
70.00	0.000015	20,269	99.90	0.000877	342
80.00	0.000024	12,758			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000045	6,736
20.00	0.000001	360,481	95.00	0.000081	3,716
30.00	0.000003	119,065	97.50	0.000137	2,183
40.00	0.000004	68,172	99.00	0.000254	1,180
50.00	0.000007	45,373	99.50	0.000380	789
60.00	0.000010	31,248	99.75	0.000545	550

70.00	0.000014	21,303	99.90	0.000859	349
80.00	0.000023	13,310			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001/14:15:58 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Non-hispanic whites — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000017	0.000017
Standard Deviation	0.000053	0.000053
Margin of Exposure	17,659	17,266

Percent of Person-Days that are User-Days = 97.77%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000036	8,343
20.00	0.000001	348,291	95.00	0.000065	4,620
30.00	0.000002	125,611	97.50	0.000110	2,720
40.00	0.000004	74,962	99.00	0.000204	1,470
50.00	0.000006	51,287	99.50	0.000305	984
60.00	0.000008	36,328	99.75	0.000439	684
70.00	0.000012	25,293	99.90	0.000670	448
80.00	0.000018	16,333			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000035	8,518
20.00	0.000001	457,707	95.00	0.000064	4,702
30.00	0.000002	140,104	97.50	0.000109	2,764
40.00	0.000004	79,623	99.00	0.000201	1,492
50.00	0.000006	53,422	99.50	0.000301	997
60.00	0.000008	37,450	99.75	0.000434	691
70.00	0.000012	25,946	99.90	0.000663	452
80.00	0.000018	16,714			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001/14:15:58 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Non-hispanic blacks — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000015	0.000016
Standard Deviation	0.000060	0.000061
Margin of Exposure	19,406	18,719

Percent of Person-Days that are User-Days = 96.46%

Estimated percentile of user-days falling below calculated exposure

in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000033	9,003
20.00	0.000000	>1,000,000	95.00	0.000061	4,932
30.00	0.000001	305,285	97.50	0.000105	2,858
40.00	0.000002	125,276	99.00	0.000200	1,502
50.00	0.000004	72,480	99.50	0.000306	980
60.00	0.000006	46,495	99.75	0.000453	661
70.00	0.000010	30,180	99.90	0.000719	416
80.00	0.000016	18,216			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000032	9,323
20.00	0.000000	>1,000,000	95.00	0.000059	5,073
30.00	0.000001	432,948	97.50	0.000102	2,934
40.00	0.000002	147,182	99.00	0.000195	1,541
50.00	0.000004	78,847	99.50	0.000300	998
60.00	0.000006	49,543	99.75	0.000445	674
70.00	0.000009	31,747	99.90	0.000708	423
80.00	0.000016	19,009			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001/14:15:58 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Non-hisp/non-white/non-black Daily Exposure Analysis

	(mg/kg body-weight/day) per Capita	per User
Mean	0.000018	0.000019
Standard Deviation	0.000071	0.000074
Margin of Exposure	16,959	15,726

Percent of Person-Days that are User-Days = 92.73%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000039	7,705
20.00	0.000000	766,241	95.00	0.000071	4,214
30.00	0.000002	169,410	97.50	0.000125	2,406
40.00	0.000003	86,808	99.00	0.000232	1,292
50.00	0.000006	54,367	99.50	0.000354	846
60.00	0.000008	36,026	99.75	0.000520	576
70.00	0.000012	24,254	99.90	0.000816	367
80.00	0.000020	15,295			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000036	8,266
20.00	0.000000	>1,000,000	95.00	0.000067	4,480

30.00	0.000001	374,397	97.50	0.000118	2,540
40.00	0.000003	109,823	99.00	0.000222	1,352
50.00	0.000005	64,341	99.50	0.000340	882
60.00	0.000007	41,106	99.75	0.000500	599
70.00	0.000011	26,975	99.90	0.000792	378
80.00	0.000018	16,553			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001/14:15:58 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

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All infants

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000009	0.000025
Standard Deviation	0.000057	0.000092
Margin of Exposure	33,351	12,143

Percent of Person-Days that are User-Days = 36.41%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000047	6,329
20.00	0.000001	416,917	95.00	0.000088	3,425
30.00	0.000002	138,821	97.50	0.000153	1,957
40.00	0.000004	76,091	99.00	0.000311	964
50.00	0.000007	44,889	99.50	0.000508	590
60.00	0.000010	28,993	99.75	0.000767	390
70.00	0.000016	18,815	99.90	0.001234	243
80.00	0.000025	11,981			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000018	16,841
20.00	0.000000	>1,000,000	95.00	0.000036	8,393
30.00	0.000000	>1,000,000	97.50	0.000066	4,536
40.00	0.000000	>1,000,000	99.00	0.000144	2,088
50.00	0.000000	>1,000,000	99.50	0.000249	1,202
60.00	0.000000	>1,000,000	99.75	0.000413	726
70.00	0.000001	518,118	99.90	0.000734	408
80.00	0.000005	57,813			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

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Nursing infants (<1 yr old) Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000003	0.000017
Standard Deviation	0.000028	0.000061
Margin of Exposure	91,211	17,865

Percent of Person-Days that are User-Days = 19.59%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000034	8,831
20.00	0.000000	767,952	95.00	0.000059	5,065
30.00	0.000001	240,054	97.50	0.000106	2,826
40.00	0.000003	108,777	99.00	0.000213	1,405
50.00	0.000004	72,659	99.50	0.000341	879
60.00	0.000006	47,773	99.75	0.000502	597
70.00	0.000010	29,670	99.90	0.000822	364
80.00	0.000018	16,763			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000004	76,023
20.00	0.000000	>1,000,000	95.00	0.000013	22,722
30.00	0.000000	>1,000,000	97.50	0.000029	10,518
40.00	0.000000	>1,000,000	99.00	0.000058	5,177
50.00	0.000000	>1,000,000	99.50	0.000104	2,870
60.00	0.000000	>1,000,000	99.75	0.000176	1,703
70.00	0.000000	>1,000,000	99.90	0.000336	893
80.00	0.000000	>1,000,000			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

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Non-nursing infants (<1 yr old) Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000011	0.000026
Standard Deviation	0.000064	0.000097
Margin of Exposure	26,878	11,503

Percent of Person-Days that are User-Days = 42.80%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000050	5,988
20.00	0.000001	373,050	95.00	0.000092	3,249
30.00	0.000002	126,619	97.50	0.000162	1,857
40.00	0.000004	68,704	99.00	0.000330	910
50.00	0.000007	40,623	99.50	0.000545	550
60.00	0.000011	26,769	99.75	0.000818	366
70.00	0.000017	17,669	99.90	0.001279	234
80.00	0.000026	11,454			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000022	13,390
20.00	0.000000	>1,000,000	95.00	0.000043	6,901
30.00	0.000000	>1,000,000	97.50	0.000080	3,762
40.00	0.000000	>1,000,000	99.00	0.000171	1,754
50.00	0.000000	>1,000,000	99.50	0.000298	1,006
60.00	0.000000	>1,000,000	99.75	0.000487	615
70.00	0.000002	127,585	99.90	0.000849	353
80.00	0.000008	36,166			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Children 1-6 yrs — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000034	0.000035
Standard Deviation	0.000109	0.000110
Margin of Exposure	8,707	8,540

Percent of Person-Days that are User-Days = 98.09%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	643,301	90.00	0.000072	4,184
20.00	0.000002	191,641	95.00	0.000129	2,316
30.00	0.000004	70,740	97.50	0.000223	1,345
40.00	0.000008	39,597	99.00	0.000421	712
50.00	0.000012	25,910	99.50	0.000638	470
60.00	0.000017	17,986	99.75	0.000924	324
70.00	0.000024	12,486	99.90	0.001410	212
80.00	0.000037	8,054			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	840,114	90.00	0.000070	4,259
20.00	0.000001	234,613	95.00	0.000128	2,350
30.00	0.000004	77,895	97.50	0.000220	1,364
40.00	0.000007	41,977	99.00	0.000416	721
50.00	0.000011	26,885	99.50	0.000631	475
60.00	0.000016	18,483	99.75	0.000915	327
70.00	0.000023	12,779	99.90	0.001397	214
80.00	0.000037	8,213			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

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Children 7-12 yrs

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000023	0.000023
Standard Deviation	0.000070	0.000070
Margin of Exposure	12,928	12,834

Percent of Person-Days that are User-Days = 99.27%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	775,912	90.00	0.000048	6,227
20.00	0.000001	200,639	95.00	0.000086	3,481
30.00	0.000003	88,059	97.50	0.000145	2,075
40.00	0.000006	52,363	99.00	0.000266	1,129
50.00	0.000008	36,234	99.50	0.000399	751
60.00	0.000012	25,998	99.75	0.000579	517
70.00	0.000016	18,210	99.90	0.000880	341
80.00	0.000025	11,806			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	843,721	90.00	0.000048	6,268
20.00	0.000001	214,884	95.00	0.000086	3,503
30.00	0.000003	90,994	97.50	0.000144	2,085
40.00	0.000006	53,274	99.00	0.000264	1,134
50.00	0.000008	36,678	99.50	0.000397	754
60.00	0.000011	26,248	99.75	0.000577	520
70.00	0.000016	18,360	99.90	0.000876	342
80.00	0.000025	11,892			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Females 13+ (preg/not nursing) Daily Exposure Analysis

	(mg/kg body-weight/day) per Capita	per User
Mean	0.000016	0.000016
Standard Deviation	0.000045	0.000045
Margin of Exposure	19,251	18,763

Percent of Person-Days that are User-Days = 97.47%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000033	9,005
20.00	0.000001	403,616	95.00	0.000061	4,905
30.00	0.000002	133,527	97.50	0.000103	2,907
40.00	0.000004	80,581	99.00	0.000192	1,562
50.00	0.000005	57,465	99.50	0.000285	1,053
60.00	0.000007	41,100	99.75	0.000398	753
70.00	0.000010	28,604	99.90	0.000567	529
80.00	0.000017	17,231			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000033	9,225
20.00	0.000001	578,040	95.00	0.000060	5,005
30.00	0.000002	154,155	97.50	0.000102	2,944
40.00	0.000004	85,128	99.00	0.000189	1,587
50.00	0.000005	59,810	99.50	0.000281	1,068
60.00	0.000007	42,700	99.75	0.000391	766
70.00	0.000010	29,282	99.90	0.000563	532
80.00	0.000017	17,777			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Females 13+ (nursing) Daily Exposure Analysis
(mg/kg body-weight/day)
per Capita per User

Mean	0.000015	0.000015
Standard Deviation	0.000042	0.000042
Margin of Exposure	19,728	19,728

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)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000032	9,517
20.00	0.000001	524,465	95.00	0.000056	5,378
30.00	0.000002	153,881	97.50	0.000097	3,098
40.00	0.000003	86,971	99.00	0.000183	1,640
50.00	0.000006	54,270	99.50	0.000266	1,125
60.00	0.000008	38,916	99.75	0.000374	802
70.00	0.000011	27,986	99.90	0.000553	542
80.00	0.000017	17,437			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000032	9,517
20.00	0.000001	524,465	95.00	0.000056	5,378
30.00	0.000002	153,881	97.50	0.000097	3,098
40.00	0.000003	86,971	99.00	0.000183	1,640
50.00	0.000006	54,270	99.50	0.000266	1,125
60.00	0.000008	38,916	99.75	0.000374	802
70.00	0.000011	27,986	99.90	0.000553	542
80.00	0.000017	17,437			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Females 13-19 (not preg or nursing)

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000017	0.000017
Standard Deviation	0.000059	0.000059
Margin of Exposure	17,906	17,586

Percent of Person-Days that are User-Days = 98.21%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000035	8,456
20.00	0.000001	335,131	95.00	0.000063	4,766
30.00	0.000002	121,273	97.50	0.000105	2,855
40.00	0.000004	72,456	99.00	0.000190	1,581
50.00	0.000006	50,381	99.50	0.000285	1,051
60.00	0.000008	36,280	99.75	0.000408	735
70.00	0.000012	25,477	99.90	0.000633	474
80.00	0.000018	16,503			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000035	8,604
20.00	0.000001	416,692	95.00	0.000062	4,835
30.00	0.000002	132,514	97.50	0.000104	2,892
40.00	0.000004	75,611	99.00	0.000188	1,597
50.00	0.000006	52,325	99.50	0.000283	1,060
60.00	0.000008	37,159	99.75	0.000405	740
70.00	0.000012	26,066	99.90	0.000629	476
80.00	0.000018	16,824			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

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Females 20+ (not preg or nursing) Daily Exposure Analysis

	(mg/kg body-weight/day) per Capita	per User
Mean	0.000013	0.000014
Standard Deviation	0.000041	0.000041
Margin of Exposure	22,540	22,042

Percent of Person-Days that are User-Days = 97.79%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000028	10,699
20.00	0.000000	677,380	95.00	0.000051	5,831
30.00	0.000002	187,635	97.50	0.000089	3,364
40.00	0.000003	100,341	99.00	0.000166	1,807
50.00	0.000005	66,596	99.50	0.000246	1,219
60.00	0.000006	46,713	99.75	0.000348	861
70.00	0.000009	32,639	99.90	0.000519	577
80.00	0.000014	21,108			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000027	10,926
20.00	0.000000	865,462	95.00	0.000050	5,942
30.00	0.000001	216,584	97.50	0.000088	3,423
40.00	0.000003	107,303	99.00	0.000164	1,832
50.00	0.000004	69,351	99.50	0.000243	1,232
60.00	0.000006	48,145	99.75	0.000345	870
70.00	0.000009	33,517	99.90	0.000515	582
80.00	0.000014	21,580			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Females 13-50 yrs

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000014	0.000015
Standard Deviation	0.000045	0.000046
Margin of Exposure	20,961	20,457

Percent of Person-Days that are User-Days = 97.60%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000031	9,784
20.00	0.000001	525,312	95.00	0.000055	5,426
30.00	0.000002	164,488	97.50	0.000094	3,185
40.00	0.000003	91,510	99.00	0.000172	1,742
50.00	0.000005	60,817	99.50	0.000255	1,178
60.00	0.000007	42,496	99.75	0.000362	829
70.00	0.000010	29,659	99.90	0.000543	552
80.00	0.000016	19,218			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000030	10,005
20.00	0.000000	711,278	95.00	0.000054	5,535
30.00	0.000002	189,752	97.50	0.000093	3,242
40.00	0.000003	98,122	99.00	0.000170	1,765
50.00	0.000005	63,747	99.50	0.000252	1,191
60.00	0.000007	43,969	99.75	0.000357	839
70.00	0.000010	30,483	99.90	0.000538	557
80.00	0.000015	19,699			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Males 13-19 yrs

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User

Mean	0.000019	0.000020
Standard Deviation	0.000052	0.000053
Margin of Exposure	15,427	15,077

Percent of Person-Days that are User-Days = 97.73%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000043	6,919
20.00	0.000001	228,672	95.00	0.000076	3,966
30.00	0.000003	93,829	97.50	0.000122	2,467
40.00	0.000005	58,301	99.00	0.000216	1,387
50.00	0.000007	40,025	99.50	0.000313	957
60.00	0.000011	28,367	99.75	0.000433	693
70.00	0.000015	20,031	99.90	0.000617	486
80.00	0.000023	13,269			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000042	7,059
20.00	0.000001	304,956	95.00	0.000074	4,035
30.00	0.000003	103,503	97.50	0.000120	2,506
40.00	0.000005	61,741	99.00	0.000213	1,407
50.00	0.000007	41,794	99.50	0.000310	967
60.00	0.000010	29,268	99.75	0.000429	698
70.00	0.000015	20,551	99.90	0.000611	490
80.00	0.000022	13,515			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Males 20+ yrs

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000015	0.000016
Standard Deviation	0.000044	0.000045
Margin of Exposure	19,564	19,208

Percent of Person-Days that are User-Days = 98.18%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000032	9,231
20.00	0.000001	407,566	95.00	0.000059	5,118
30.00	0.000002	132,589	97.50	0.000099	3,037
40.00	0.000004	78,032	99.00	0.000180	1,664
50.00	0.000006	53,815	99.50	0.000267	1,123
60.00	0.000008	38,375	99.75	0.000379	791
70.00	0.000011	27,055	99.90	0.000568	527
80.00	0.000017	17,771			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000032	9,387
20.00	0.000001	520,067	95.00	0.000058	5,190
30.00	0.000002	146,154	97.50	0.000097	3,078
40.00	0.000004	81,957	99.00	0.000178	1,683
50.00	0.000005	55,600	99.50	0.000264	1,134
60.00	0.000008	39,309	99.75	0.000376	798
70.00	0.000011	27,621	99.90	0.000564	531
80.00	0.000017	18,081			

DEEM ACUTE MC Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

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Seniors 55+ Daily Exposure Analysis

	(mg/kg body-weight/day) per Capita	per User
Mean	0.000013	0.000013
Standard Deviation	0.000040	0.000040
Margin of Exposure	23,533	23,156

Percent of Person-Days that are User-Days = 98.40%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000026	11,663
20.00	0.000000	799,084	95.00	0.000048	6,233
30.00	0.000002	198,893	97.50	0.000085	3,536
40.00	0.000003	102,446	99.00	0.000163	1,841
50.00	0.000004	68,558	99.50	0.000245	1,223
60.00	0.000006	49,228	99.75	0.000346	866
70.00	0.000009	34,869	99.90	0.000515	582
80.00	0.000013	22,819			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000025	11,853
20.00	0.000000	956,328	95.00	0.000047	6,321
30.00	0.000001	223,816	97.50	0.000084	3,581
40.00	0.000003	107,356	99.00	0.000161	1,860
50.00	0.000004	70,458	99.50	0.000243	1,233
60.00	0.000006	50,295	99.75	0.000344	872
70.00	0.000008	35,479	99.90	0.000512	586
80.00	0.000013	23,158			

California Department of Pesticide Regulation Ver. 7.73
DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Point Estimate Analysis. Residue file: monitoracute.R96. Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001/14:15:58 Residue file dated: 01-31-2000/15:50:20/14
NOEL (Acute) = 0.3 mg/kg body-wt/day. Daily totals for food & foodform consumption used.
Comment: "Dietary exposure analysis for 180.315 using REG & monitoring residue data."

Summary calculations (per capita):

	95th Percentile Exposure	95th Percentile MOE	99th Percentile Exposure	99th Percentile MOE	99.9th Percentile Exposure	99.9th Percentile MOE
U.S. Population:	0.000319	938	0.000605	496	0.001208	248
Western region:	0.000351	854	0.000631	475	0.001253	239
Hispanics:	0.000385	778	0.000699	429	0.001786	167
Non-hispanic whites:	0.000311	964	0.000577	520	0.001083	276
Non-hispanic blacks:	0.000316	948	0.000626	478	0.001303	230
Non-hisp/non-white/non-black:	0.000342	876	0.000690	434	0.001056	284
All infants:	0.000209	1434	0.000680	441	0.001292	232
Nursing infants (<1 yr old):	0.000075	4014	0.000366	820	0.000731	410
Non-nursing infants (<1 yr old):	0.000263	1139	0.000723	414	0.001302	230
Children 1-6 yrs:	0.000640	468	0.001117	268	0.002054	146
Children 7-12 yrs:	0.000407	736	0.000739	405	0.001220	245
Females 13+ (preg/not nursing):	0.000291	1030	0.000414	724	0.000493	607
Females 13+ (nursing):	0.000307	976	0.000397	756	0.000483	620
Females 13-19 (not preg or nursing):	0.000299	1003	0.000484	619	0.001412	212
Females 20+ (not preg or nursing):	0.000246	1217	0.000418	717	0.000663	452
Females 13-50 yrs:	0.000257	1169	0.000424	708	0.000681	440
Males 13-19 yrs:	0.000339	885	0.000616	487	0.000914	328
Males 20+ yrs:	0.000277	1081	0.000464	647	0.000884	339
Seniors 55+:	0.000237	1264	0.000402	745	0.000733	409

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

U.S. Population — Daily Exposure Analysis /a (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000084	0.000086
Standard Deviation	0.000132	0.000133
Standard Error of mean	0.000001	0.000001
Margin of Exposure 2/	3,569	3,469

Percent of Person-Days that are User-Days = 97.21%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE[2]
10.00	0.000001	566,438	90.00	0.000224	1,339
20.00	0.000003	85,802	95.00	0.000323	928
30.00	0.000014	21,914	97.50	0.000430	697
40.00	0.000025	11,802	99.00	0.000608	493
50.00	0.000041	7,280	99.50	0.000760	394
60.00	0.000062	4,821	99.75	0.000925	324
70.00	0.000091	3,279	99.90	0.001213	247
80.00	0.000136	2,206			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	763,691	90.00	0.000220	1,361
20.00	0.000002	182,084	95.00	0.000319	938
30.00	0.000012	25,351	97.50	0.000427	703
40.00	0.000023	12,971	99.00	0.000605	496
50.00	0.000039	7,713	99.50	0.000753	398
60.00	0.000060	5,039	99.75	0.000919	326
70.00	0.000088	3,394	99.90	0.001208	248
80.00	0.000133	2,261			

a/ Analysis based on all two-day participant records in CSFII 1994-98 survey.
2/ Margin of Exposure = NOEL/ Dietary Exposure.

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Western region — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000089	0.000092
Standard Deviation	0.000140	0.000141
Standard Error of mean	0.000001	0.000001
Margin of Exposure	3,364	3,247

Percent of Person-Days that are User-Days = 96.53%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE

10.00	0.000001	541,122	90.00	0.000237	1,264
20.00	0.000003	94,240	95.00	0.000355	844
30.00	0.000014	21,679	97.50	0.000441	681
40.00	0.000027	10,924	99.00	0.000639	469
50.00	0.000046	6,545	99.50	0.000781	384
60.00	0.000068	4,420	99.75	0.000914	328
70.00	0.000098	3,057	99.90	0.001260	238
80.00	0.000147	2,034			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	800,424	90.00	0.000232	1,293
20.00	0.000001	252,945	95.00	0.000351	854
30.00	0.000011	26,661	97.50	0.000438	684
40.00	0.000024	12,362	99.00	0.000631	475
50.00	0.000042	7,101	99.50	0.000777	385
60.00	0.000065	4,631	99.75	0.000909	330
70.00	0.000095	3,145	99.90	0.001253	239
80.00	0.000143	2,099			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

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Hispanics — Daily Exposure Analysis

	(mg/kg body-weight/day) per Capita	per User
Mean	0.000106	0.000110
Standard Deviation	0.000159	0.000161
Standard Error of mean	0.000002	0.000002
Margin of Exposure	2,836	2,726

Percent of Person-Days that are User-Days = 96.12%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	361,372	90.00	0.000279	1,076
20.00	0.000010	29,463	95.00	0.000394	762
30.00	0.000022	13,428	97.50	0.000520	576
40.00	0.000039	7,636	99.00	0.000704	426
50.00	0.000059	5,124	99.50	0.000965	310
60.00	0.000082	3,665	99.75	0.001188	252
70.00	0.000118	2,546	99.90	0.001795	167
80.00	0.000173	1,738			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	567,226	90.00	0.000273	1,099
20.00	0.000005	58,255	95.00	0.000385	778
30.00	0.000019	15,883	97.50	0.000509	589
40.00	0.000034	8,782	99.00	0.000699	429
50.00	0.000055	5,439	99.50	0.000958	313
60.00	0.000078	3,844	99.75	0.001168	256

70.00	0.000113	2,656	99.90	0.001786	167
80.00	0.000168	1,786			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Non-hispanic whites — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000082	0.000084
Standard Deviation	0.000123	0.000124
Standard Error of mean	0.000001	0.000001
Margin of Exposure	3,640	3,559

Percent of Person-Days that are User-Days = 97.77%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	547,563	90.00	0.000219	1,371
20.00	0.000005	64,931	95.00	0.000314	955
30.00	0.000015	20,599	97.50	0.000418	717
40.00	0.000026	11,477	99.00	0.000582	515
50.00	0.000041	7,259	99.50	0.000699	429
60.00	0.000062	4,868	99.75	0.000863	347
70.00	0.000091	3,310	99.90	0.001101	272
80.00	0.000133	2,251			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	688,876	90.00	0.000216	1,390
20.00	0.000003	112,412	95.00	0.000311	964
30.00	0.000013	23,013	97.50	0.000416	721
40.00	0.000024	12,264	99.00	0.000577	520
50.00	0.000040	7,558	99.50	0.000694	432
60.00	0.000060	5,036	99.75	0.000852	351
70.00	0.000088	3,400	99.90	0.001083	276
80.00	0.000131	2,290			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Non-hispanic blacks — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000075	0.000077
Standard Deviation	0.000144	0.000146
Standard Error of mean	0.000002	0.000002
Margin of Exposure	4,022	3,880

Percent of Person-Days that are User-Days = 96.46%

Estimated percentile of user-days falling below calculated exposure

in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	875,814	90.00	0.000211	1,419
20.00	0.000001	437,907	95.00	0.000321	934
30.00	0.000005	54,945	97.50	0.000418	716
40.00	0.000014	20,999	99.00	0.000635	472
50.00	0.000027	11,008	99.50	0.000846	354
60.00	0.000045	6,626	99.75	0.001120	267
70.00	0.000073	4,101	99.90	0.001341	223
80.00	0.000115	2,605			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000208	1,441
20.00	0.000001	513,232	95.00	0.000316	948
30.00	0.000003	86,543	97.50	0.000414	724
40.00	0.000012	24,593	99.00	0.000626	478
50.00	0.000023	12,780	99.50	0.000839	357
60.00	0.000042	7,121	99.75	0.001112	269
70.00	0.000070	4,270	99.90	0.001303	230
80.00	0.000109	2,753			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Non-hisp/non-white/non-black

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000086	0.000093
Standard Deviation	0.000154	0.000158
Standard Error of mean	0.000003	0.000004
Margin of Exposure	3,483	3,230

Percent of Person-Days that are User-Days = 92.73%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	689,514	90.00	0.000235	1,278
20.00	0.000001	344,757	95.00	0.000353	850
30.00	0.000008	36,501	97.50	0.000468	640
40.00	0.000022	13,502	99.00	0.000752	398
50.00	0.000041	7,249	99.50	0.000874	343
60.00	0.000067	4,446	99.75	0.000885	339
70.00	0.000099	3,015	99.90	0.001118	268
80.00	0.000151	1,986			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000229	1,312
20.00	0.000001	502,224	95.00	0.000342	876
30.00	0.000003	106,432	97.50	0.000458	655
40.00	0.000015	19,706	99.00	0.000690	434
50.00	0.000032	9,246	99.50	0.000872	344
60.00	0.000059	5,061	99.75	0.000884	339
70.00	0.000089	3,379	99.90	0.001056	284
80.00	0.000141	2,133			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

All infants — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000039	0.000107
Standard Deviation	0.000138	0.000212
Standard Error of mean	0.000003	0.000007
Margin of Exposure	7,682	2,797

Percent of Person-Days that are User-Days = 36.41%
Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	486,588	90.00	0.000296	1,014
20.00	0.000002	176,595	95.00	0.000574	522
30.00	0.000008	35,483	97.50	0.000682	439
40.00	0.000021	14,477	99.00	0.000979	306
50.00	0.000031	9,695	99.50	0.001126	266
60.00	0.000049	6,067	99.75	0.001295	231
70.00	0.000075	4,001	99.90	0.002472	121
80.00	0.000139	2,165			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000086	3,468
20.00	0.000000	>1,000,000	95.00	0.000209	1,434
30.00	0.000000	>1,000,000	97.50	0.000428	701
40.00	0.000000	>1,000,000	99.00	0.000680	441
50.00	0.000000	>1,000,000	99.50	0.000875	342
60.00	0.000000	>1,000,000	99.75	0.001116	268
70.00	0.000001	266,881	99.90	0.001292	232
80.00	0.000026	11,764			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Nursing infants (<1 yr old)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000015	0.000076
Standard Deviation	0.000069	0.000140
Standard Error of mean	0.000002	0.000011
Margin of Exposure	20,195	3,955

Percent of Person-Days that are User-Days = 19.59%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	833,401	90.00	0.000227	1,322
20.00	0.000001	416,700	95.00	0.000366	818
30.00	0.000003	88,468	97.50	0.000458	655
40.00	0.000013	22,968	99.00	0.000717	418
50.00	0.000021	14,043	99.50	0.000731	410
60.00	0.000030	9,869	99.75	0.000960	312
70.00	0.000053	5,611	99.90	0.000961	312
80.00	0.000120	2,500			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000020	15,215
20.00	0.000000	>1,000,000	95.00	0.000075	4,014
30.00	0.000000	>1,000,000	97.50	0.000169	1,775
40.00	0.000000	>1,000,000	99.00	0.000366	820
50.00	0.000000	>1,000,000	99.50	0.000457	655
60.00	0.000000	>1,000,000	99.75	0.000704	425
70.00	0.000000	>1,000,000	99.90	0.000731	410
80.00	0.000000	>1,000,000			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Non-nursing infants (<1 yr old) Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000048	0.000113
Standard Deviation	0.000156	0.000222
Standard Error of mean	0.000003	0.000007
Margin of Exposure	6,219	2,662

Percent of Person-Days that are User-Days = 42.80%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	442,130	90.00	0.000315	953
20.00	0.000002	157,340	95.00	0.000604	496
30.00	0.000009	31,702	97.50	0.000718	417
40.00	0.000023	13,170	99.00	0.001048	286
50.00	0.000034	8,947	99.50	0.001132	265
60.00	0.000051	5,869	99.75	0.001300	230
70.00	0.000080	3,746	99.90	0.002480	120
80.00	0.000140	2,138			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000114	2,636
20.00	0.000000	>1,000,000	95.00	0.000263	1,139
30.00	0.000000	>1,000,000	97.50	0.000567	528
40.00	0.000000	>1,000,000	99.00	0.000723	414
50.00	0.000000	>1,000,000	99.50	0.000979	306
60.00	0.000000	676,040	99.75	0.001126	266
70.00	0.000009	32,099	99.90	0.001302	230
80.00	0.000040	7,589			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Children 1-6 yrs — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000166	0.000169
Standard Deviation	0.000244	0.000245
Standard Error of mean	0.000002	0.000002
Margin of Exposure	1,809	1,774

Percent of Person-Days that are User-Days = 98.09%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	301,911	90.00	0.000461	650
20.00	0.000005	56,355	95.00	0.000646	464
30.00	0.000024	12,315	97.50	0.000817	367
40.00	0.000047	6,384	99.00	0.001122	267
50.00	0.000076	3,930	99.50	0.001348	222
60.00	0.000115	2,606	99.75	0.001603	187
70.00	0.000180	1,664	99.90	0.002064	145
80.00	0.000286	1,049			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	366,052	90.00	0.000457	655
20.00	0.000003	91,913	95.00	0.000640	468
30.00	0.000022	13,880	97.50	0.000812	369
40.00	0.000044	6,775	99.00	0.001117	268
50.00	0.000072	4,153	99.50	0.001342	223
60.00	0.000111	2,690	99.75	0.001558	192
70.00	0.000176	1,708	99.90	0.002054	146
80.00	0.000281	1,067			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

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Children 7-12 yrs

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000112	0.000113
Standard Deviation	0.000156	0.000156
Standard Error of mean	0.000003	0.000003
Margin of Exposure	2,680	2,660

Percent of Person-Days that are User-Days = 99.27%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	385,039	90.00	0.000294	1,018
20.00	0.000007	44,966	95.00	0.000409	734
30.00	0.000021	14,443	97.50	0.000551	544
40.00	0.000038	7,993	99.00	0.000743	403
50.00	0.000059	5,114	99.50	0.000864	347
60.00	0.000084	3,580	99.75	0.001009	297
70.00	0.000121	2,484	99.90	0.001220	245
80.00	0.000183	1,642			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	412,398	90.00	0.000293	1,024
20.00	0.000006	50,103	95.00	0.000407	736

30.00	0.000020	15,029	97.50	0.000548	547
40.00	0.000037	8,109	99.00	0.000739	405
50.00	0.000058	5,216	99.50	0.000864	347
60.00	0.000083	3,623	99.75	0.001009	297
70.00	0.000120	2,500	99.90	0.001220	245
80.00	0.000182	1,647			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Females 13+ (preg/not nursing)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000077	0.000079
Standard Deviation	0.000097	0.000098
Standard Error of mean	0.000008	0.000008
Margin of Exposure	3,881	3,783

Percent of Person-Days that are User-Days = 97.47%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	539,654	90.00	0.000242	1,238
20.00	0.000006	53,273	95.00	0.000292	1,028
30.00	0.000015	19,760	97.50	0.000333	901
40.00	0.000028	10,902	99.00	0.000414	724
50.00	0.000037	8,049	99.50	0.000418	718
60.00	0.000057	5,257	99.75	0.000492	609
70.00	0.000087	3,441	99.90	0.000493	607
80.00	0.000139	2,156			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	704,321	90.00	0.000239	1,255
20.00	0.000004	72,455	95.00	0.000291	1,030
30.00	0.000014	20,794	97.50	0.000333	901
40.00	0.000022	13,535	99.00	0.000414	724
50.00	0.000036	8,315	99.50	0.000418	718
60.00	0.000055	5,414	99.75	0.000492	609
70.00	0.000086	3,495	99.90	0.000493	607
80.00	0.000137	2,195			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Females 13+ (nursing)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000075	0.000075
Standard Deviation	0.000095	0.000095
Standard Error of mean	0.000010	0.000010
Margin of Exposure	4,023	4,023

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)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	712,783	90.00	0.000213	1,410
20.00	0.000001	248,604	95.00	0.000307	976
30.00	0.000016	18,998	97.50	0.000315	951
40.00	0.000030	10,018	99.00	0.000397	756
50.00	0.000035	8,451	99.50	0.000482	623
60.00	0.000066	4,551	99.75	0.000483	621
70.00	0.000079	3,789	99.90	0.000483	620
80.00	0.000123	2,435			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	712,783	90.00	0.000213	1,410
20.00	0.000001	248,604	95.00	0.000307	976
30.00	0.000016	18,998	97.50	0.000315	951
40.00	0.000030	10,018	99.00	0.000397	756
50.00	0.000035	8,451	99.50	0.000482	623
60.00	0.000066	4,551	99.75	0.000483	621
70.00	0.000079	3,789	99.90	0.000483	620
80.00	0.000123	2,435			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Females 13-19 (not preg or nursing)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000082	0.000083
Standard Deviation	0.000133	0.000134
Standard Error of mean	0.000004	0.000004
Margin of Exposure	3,680	3,614

Percent of Person-Days that are User-Days = 98.21%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	543,412	90.00	0.000212	1,414
20.00	0.000006	52,823	95.00	0.000299	1,002
30.00	0.000016	18,436	97.50	0.000360	834
40.00	0.000028	10,847	99.00	0.000484	619
50.00	0.000044	6,843	99.50	0.000556	539
60.00	0.000065	4,608	99.75	0.000702	427
70.00	0.000096	3,124	99.90	0.001412	212
80.00	0.000132	2,272			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	649,899	90.00	0.000210	1,425
20.00	0.000004	82,423	95.00	0.000299	1,003
30.00	0.000014	20,883	97.50	0.000359	836
40.00	0.000026	11,425	99.00	0.000484	619
50.00	0.000042	7,122	99.50	0.000556	539
60.00	0.000063	4,766	99.75	0.000701	427
70.00	0.000094	3,203	99.90	0.001412	212
80.00	0.000130	2,300			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Females 20+ (not preg or nursing)

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000065	0.000067
Standard Deviation	0.000091	0.000092
Standard Error of mean	0.000001	0.000001
Margin of Exposure	4,603	4,501

Percent of Person-Days that are User-Days = 97.79%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	833,900	90.00	0.000179	1,679
20.00	0.000002	176,470	95.00	0.000248	1,209
30.00	0.000010	29,065	97.50	0.000320	937
40.00	0.000020	15,308	99.00	0.000420	713
50.00	0.000032	9,374	99.50	0.000501	599
60.00	0.000050	5,982	99.75	0.000582	515
70.00	0.000074	4,077	99.90	0.000671	447
80.00	0.000113	2,661			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000176	1,703
20.00	0.000001	458,357	95.00	0.000246	1,217
30.00	0.000009	33,290	97.50	0.000317	946
40.00	0.000018	16,338	99.00	0.000418	717
50.00	0.000030	9,901	99.50	0.000493	608
60.00	0.000048	6,242	99.75	0.000580	517
70.00	0.000072	4,178	99.90	0.000663	452
80.00	0.000111	2,713			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Females 13-50 yrs — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000070	0.000072
Standard Deviation	0.000102	0.000102
Standard Error of mean	0.000001	0.000001
Margin of Exposure	4,266	4,163

Percent of Person-Days that are User-Days = 97.60%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	713,158	90.00	0.000187	1,604
20.00	0.000003	112,379	95.00	0.000261	1,150
30.00	0.000012	24,415	97.50	0.000334	897
40.00	0.000023	12,859	99.00	0.000426	704
50.00	0.000037	8,066	99.50	0.000528	568
60.00	0.000056	5,367	99.75	0.000597	502
70.00	0.000081	3,717	99.90	0.000682	439
80.00	0.000121	2,480			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	915,853	90.00	0.000185	1,621
20.00	0.000001	236,772	95.00	0.000257	1,169
30.00	0.000010	28,943	97.50	0.000333	902
40.00	0.000022	13,815	99.00	0.000424	708
50.00	0.000035	8,518	99.50	0.000503	596
60.00	0.000054	5,554	99.75	0.000595	504
70.00	0.000078	3,855	99.90	0.000681	440
80.00	0.000118	2,534			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Males 13-19 yrs — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User

	per Capita	per User
Mean	0.000095	0.000097
Standard Deviation	0.000127	0.000127
Standard Error of mean	0.000004	0.000004
Margin of Exposure	3,165	3,093

Percent of Person-Days that are User-Days = 97.73%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	437,891	90.00	0.000250	1,198
20.00	0.000009	34,244	95.00	0.000344	871
30.00	0.000022	13,674	97.50	0.000427	703
40.00	0.000038	7,837	99.00	0.000623	481
50.00	0.000060	5,039	99.50	0.000681	440
60.00	0.000079	3,787	99.75	0.000747	401
70.00	0.000106	2,830	99.90	0.000914	328
80.00	0.000147	2,040			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000001	553,452	90.00	0.000246	1,217
20.00	0.000006	50,671	95.00	0.000339	885
30.00	0.000020	15,272	97.50	0.000426	704
40.00	0.000035	8,492	99.00	0.000616	487
50.00	0.000057	5,277	99.50	0.000681	440
60.00	0.000077	3,882	99.75	0.000747	401
70.00	0.000105	2,861	99.90	0.000914	328
80.00	0.000145	2,072			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Males 20+ yrs — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000075	0.000076
Standard Deviation	0.000104	0.000105
Standard Error of mean	0.000001	0.000001
Margin of Exposure	4,006	3,934

Percent of Person-Days that are User-Days = 98.18%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	601,634	90.00	0.000196	1,528
20.00	0.000004	68,984	95.00	0.000279	1,074
30.00	0.000014	21,720	97.50	0.000360	832
40.00	0.000025	12,028	99.00	0.000467	642
50.00	0.000040	7,578	99.50	0.000567	528
60.00	0.000059	5,126	99.75	0.000685	438
70.00	0.000085	3,519	99.90	0.000885	339
80.00	0.000125	2,401			

Estimated percentile of per-capita days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	721,883	90.00	0.000195	1,537
20.00	0.000003	102,453	95.00	0.000277	1,081
30.00	0.000013	23,486	97.50	0.000359	835
40.00	0.000024	12,726	99.00	0.000464	647
50.00	0.000038	7,828	99.50	0.000567	529
60.00	0.000057	5,306	99.75	0.000684	438
70.00	0.000083	3,601	99.90	0.000884	339
80.00	0.000123	2,447			

DEEM ACUTE Analysis for METHAMIDOPHOS (1994-98 data)
Residue file: monitoracute.R96 Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001 Residue file dated: 01-31-2000
NOEL (Acute) = 0.300000 mg/kg body-wt/day

Seniors 55+

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000062	0.000063
Standard Deviation	0.000090	0.000091
Standard Error of mean	0.000001	0.000001
Margin of Exposure	4,877	4,799

Percent of Person-Days that are User-Days = 98.40%

Estimated percentile of user-days falling below calculated exposure
in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	932,447	90.00	0.000172	1,742
20.00	0.000001	321,121	95.00	0.000238	1,258
30.00	0.000009	31,745	97.50	0.000312	962
40.00	0.000016	18,642	99.00	0.000405	740
50.00	0.000027	11,171	99.50	0.000490	612
60.00	0.000044	6,850	99.75	0.000614	488
70.00	0.000068	4,417	99.90	0.000734	408
80.00	0.000105	2,869			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000171	1,758
20.00	0.000001	498,698	95.00	0.000237	1,264
30.00	0.000008	36,426	97.50	0.000311	964
40.00	0.000015	19,669	99.00	0.000402	745
50.00	0.000025	11,766	99.50	0.000489	613
60.00	0.000043	7,042	99.75	0.000613	489
70.00	0.000067	4,493	99.90	0.000733	409
80.00	0.000103	2,912			

ATTACHMENT B

Chronic Dietary Exposure Assessment

California Department of Pesticide Regulation Ver. 7.72
DEEM **Chronic** analysis for METHAMIDOPHOS 1994-98 data
Residue file: D:\deem\Resi-files\monitorchronic.R96 Adjust. #2 used
Analysis Date 10-11-2001 Residue file dated: 01-31-2000
Reference dose (RfD) = 0.001 mg/kg bw/day. (NOEL) = 0.006 mg/kg bw/day
Comment: Dietary exposure analysis for 180.315 using REG & monitoring residue data.

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	Adj.Factors #1	#2 (%CT)
159	8	Tomatoes-whole	0.013000	1.000	0.850
160	8	Tomatoes-juice	0.013000	1.000	0.200
161	8	Tomatoes-puree	0.013000	1.000	0.200
162	8	Tomatoes-paste	0.013000	1.000	0.200
163	8	Tomatoes-catsup	0.013000	1.000	0.200
207	1C	Potatoes/white-whole	0.001900	1.000	0.300
208	1C	Potatoes/white-unspec.	0.001900	1.000	0.300
209	1C	Potatoes/white-peeled	0.001900	1.000	0.300
210	1C	Potatoes/white-dry	0.001900	6.500	0.300
211	1C	Potatoes/white-peel only	0.001900	1.000	0.300
290	O	Cottonseed-oil	0.005000	1.000	0.150
291	O	Cottonseed-meal	0.042000	1.000	0.150
423	8	Tomatoes-dried	0.013000	14.30	0.850

California Department of Pesticide Regulation Ver. 7.76 (1994-98 data)
DEEM **Chronic** analysis for METHAMIDOPHOS (Adjustment factor #2 used)
Analysis Date 03-04-2003. Residue file dated: 03-04-2003 File Name: monitorchronic.RS7
Chronic RfD (U.S. EPA) = .0003 mg/kg bw/day. DPR NOEL (Chronic) = .02 mg/kg bw/day
COMMENT 1: Dietary exposure analysis for 180.315 using REG & monitoring residue data.

Total exposure by population subgroup

Population Subgroup	mg/kg body wt/day	Margin of Exposure 1/	Percent of RfD
U.S. Population (total)	0.000007	2,927	2.3%
U.S. Population (spring season)	0.000007	3,068	2.2%
U.S. Population (summer season)	0.000007	2,675	2.5%
U.S. Population (autumn season)	0.000007	2,899	2.3%
U.S. Population (winter season)	0.000006	3,129	2.1%
Northeast region	0.000007	2,952	2.3%
Midwest region	0.000007	2,859	2.3%
Southern region	0.000006	3,137	2.1%
Western region	0.000007	2,691	2.5%
Hispanics	0.000009	2,160	3.1%
Non-hispanic whites	0.000007	3,009	2.2%
Non-hispanic blacks	0.000006	3,538	1.9%
Non-hisp/non-white/non-black	0.000007	2,694	2.5%
All infants (< 1 year)	0.000003	6,447	1.0%
Nursing infants	0.000001	16,718	0.4%
Non-nursing infants	0.000004	5,228	1.3%
Children 1-6 yrs	0.000013	1,552	4.3%
Children 7-12 yrs	0.000008	2,421	2.8%
Females 13-19 (not preg or nursing)	0.000006	3,358	2.0%
Females 20+ (not preg or nursing)	0.000006	3,492	1.9%
Females 13-50 yrs	0.000006	3,441	1.9%
Females 13+ (preg/not nursing)	0.000006	3,204	2.1%
Females 13+ (nursing)	0.000007	2,890	2.3%
Males 13-19 yrs	0.000007	2,735	2.4%
Males 20+ yrs	0.000006	3,246	2.1%
Seniors 55+	0.000006	3,573	1.9%

1. MOE = NOEL ÷ Exposure

California Department of Pesticide Regulation Ver. 7.76 (1994-98 data)
DEEM **Chronic** analysis for METHAMIDOPHOS (**Adjustment factor #2 NOT USED**)
Analysis Date 03-04-2003. Residue file dated: 03-04-2003 File Name: monitorchronic.RS7
Chronic RfD (U.S. EPA) = .0003 mg/kg bw/day. DPR NOEL (Chronic) = .02 mg/kg bw/day
COMMENT 1: Dietary exposure analysis for 180.315 using REG & monitoring residue data.

Total exposure by population subgroup

Population Subgroup	mg/kg body wt/day	Margin of Exposure 1/	Percent of RfD
U.S. Population (total)	0.000014	1,443	4.6%
U.S. Population (spring season)	0.000013	1,501	4.4%
U.S. Population (summer season)	0.000014	1,388	4.8%
U.S. Population (autumn season)	0.000014	1,426	4.7%
U.S. Population (winter season)	0.000014	1,467	4.5%
Northeast region	0.000014	1,433	4.7%
Midwest region	0.000014	1,410	4.7%
Southern region	0.000013	1,529	4.4%
Western region	0.000015	1,366	4.9%
Hispanics	0.000017	1,153	5.8%
Non-hispanic whites	0.000014	1,472	4.5%
Non-hispanic blacks	0.000012	1,621	4.1%
Non-hisp/non-white/non-black	0.000014	1,409	4.7%
All infants (< 1 year)	0.000007	3,005	2.2%
Nursing infants	0.000003	7,949	0.8%
Non-nursing infants	0.000008	2,431	2.7%
Children 1-6 yrs	0.000027	729	9.1%
Children 7-12 yrs	0.000018	1,082	6.2%
Females 13-19 (not preg or nursing)	0.000013	1,491	4.5%
Females 20+ (not preg or nursing)	0.000011	1,867	3.6%
Females 13-50 yrs	0.000012	1,731	3.9%
Females 13+ (preg/not nursing)	0.000013	1,583	4.2%
Females 13+ (nursing)	0.000012	1,620	4.1%
Males 13-19 yrs	0.000016	1,278	5.2%
Males 20+ yrs	0.000012	1,622	4.1%
Seniors 55+	0.000010	1,969	3.4%

1. MOE = NOEL ÷ Exposure

APPENDIX C.

M E M O R A N D U M

TO: Gary Patterson, Ph.D., Chief
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FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section
1515 Clay Street, 16th Floor
Oakland, California 946122

DATE: January 16, 2004

SUBJECT: COMMENTS ON THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE INGREDIENT METHAMIDOPHOS PREPARED BY THE DEPARTMENT OF PESTICIDE REGULATION

Thank you for the opportunity to review the draft risk characterization document (RCD) for methamidophos prepared by the Department of Pesticide Regulation (DPR). The Office of Environmental Health Hazard Assessment (OEHHA) reviews risk assessments prepared by DPR under the general authority of the Health and Safety Code, Section 59004, and also under the Food and Agricultural Code (FAC), Section 13129, in which OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticide active ingredients.

Methamidophos is an organophosphate insecticide/acaricide used for the control of various pests on cotton, potatoes and tomatoes. Approximately 47,000 pounds of methamidophos was applied in California in 2001. DPR initiated this risk assessment based upon methamidophos' high acute toxicity and because of documented illnesses following occupational exposure. This RCD evaluates occupational, dietary and combined occupational and dietary exposures for acute, subchronic and chronic durations.

OEHHA comments on the RCD for methamidophos are as follows:

1. OEHHA agrees with DPR's choices of critical studies, toxicological endpoints and NOAELs used in the RCD for methamidophos. We find the section of the RCD comparing DPR's selection of critical values to those used by the United States Environmental Protection Agency (U.S. EPA) particularly informative and useful in our evaluation.
   DPR Response: The NOELs used for assessing risk from occupational exposure have been changed, following the use of dermal studies to better categorize such risk. Table 32 has been modified, accordingly.

2. The U.S. EPA applied an additional uncertainty factor of 3x due to concerns of organophosphate-induced delayed neuropathy (OPIDN). OPIDN-like symptoms were observed in hens and there are reports in the literature of the syndrome occurring in humans after extremely high-dose exposures (Johnson and Lotti, 1989). Based on our evaluation of the RCD and the completion of the developmental neurotoxicity study, OEHHA agrees with DPR's assessment that occupational and dietary exposures occur at levels considerably less than those associated with OPIDN, therefore, no additional uncertainty factor is necessary for the purposes of this RCD.
   DPR Response: agreed

3. Of particular concern, OEHHA notes that DPR's calculations found that for all occupational tasks evaluated for all exposure durations, margins of exposure (MOEs) were less than 100. Indeed, for mixers, loaders, applicators and flaggers, the majority of MOEs were less than 10, indicating a substantial potential risk for these workers. OEHHA urges DPR to expedite mitigation measures to reduce occupational exposures to methamidophos.
   DPR Response: The WH&S Branch of DPR will be dealing with this mitigation issue.

4. All dietary exposure scenarios evaluated resulted in MOEs greater than 100. OEHHA notes that this result is consistent with a similar recent evaluation by U.S. EPA (U.S. EPA, 2000), however, we recognize this evaluation is limited to dietary methamidophos exposure as result of methamidophos applications and does not consider cumulative exposure to other sources of the chemical. See item number 7 below for additional discussion.
   DPR Response: see 7, below.

5. DPR's tolerance assessment for the commodity tomatoes resulted in MOEs ranging from 26 to 76 depending upon the particular subpopulation under consideration. In discussing these values, it is stated in the RCD: "…USEPA should review the current tolerance of 1 ppm since the MOEs for all population subgroups are below 100." We also note (as mentioned in the RCD) that the U.S. EPA has recently increased the methamidophos tolerance for tomatoes. Considering the results of the tolerance assessment and the recent increase in the tomato tolerance by U.S. EPA, OEHHA urges DPR to engage U.S. EPA in discussions directed at reviewing the current federal tolerance for methamidophos on this commodity.
   DPR Response: Repeated efforts have been made to engage USEPA in a dialog on the tomato tolerance issue, but to no avail. It is anticipated that discussions can resolve this at the Assistant Director level.

6. Per the RCD, methamidophos has not been found in groundwater in California. The chemical possesses physio/chemical characteristics (high water solubility, weak soil adsorption) that suggests a high potential for leaching, however. Indeed, methamidophos has been detected in groundwater in other areas of the country (U.S. EPA, 2000). OEHHA recommends that DPR continue to monitor groundwater for methamidophos in high-use areas for possible contamination.
   DPR Response: Environmental Monitoring & Enforcement Branches are continuing to measure the residues of methamidophos in air and water in California.

7. The methamidophos RCD does not include exposure to methamidophos residues as a result of acephate applications (methamidophos is a major degradate of acephate). OEHHA notes that in the recent U.S. EPA risk assessment for methamidophos (U.S. EPA, 2000) dietary exposures with and without acephate contributions were evaluated. When acephate was considered, U.S. EPA concluded that at the 99.9th percentile exposure, dietary risks were of toxicological concern to the subpopulation of children 1-6 years old and that tomato consumption was the most significant contributor to the overall risk. OEHHA recommends that DPR conduct and/or complete an exposure assessment for acephate in order to assess cumulative risks from exposure to methamidophos.
   DPR Response: The draft, final version of the RCD for acephate is currently in review (within DPR). When completed, this will enable cumulative exposure to acephate and methamidophos to be estimated (Section V.D).

Again, thank you for the opportunity to review this document and we hope that you find our comments useful. Should you have any questions regarding OEHHA's review of this RCD, please contact Dr. David Rice at (916) 324-1277 (primary reviewer), Mr. Robert Schlag at (916) 323-2624, or me at (510) 622-3165.

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Office of Environmental Health Hazard Assessment

References

Johnson MK and M Lotti. 1989. Can methamidophos cause delayed polyneuropathy in man or test animals? Laboratory Report Number 100277. DPR Volume # 315-115.

U.S. EPA, 2000. Overview of the Revised Methamidophos Risk Assessment. Office of Pesticide Programs, U.S. Environmental Protection Agency. January 13, 2000. http://www.epa.gov/pesticides/op/methamidophos.htm

To: Ms. Ann Prichard
Department of Pesticide Regulation
California Environmental Protection Agency
1001 >I= Street
Sacramento, California 95812-4015

February 28, 2004
Bayer CropScience
RTP
P. O. Box 12014
RTP, NC 27709
Tel. 919 549-2000

Subject: **Methamidaphos**
Draft Risk Characterization Document
Bayer CropScience Comments and Additional Data Submissions.

Dear Ann,

Bayer CropScience (BCS) appreciates the opportunity to comment and refine CDPR's draft Risk Assessment Document for Methamidophos (Final Draft, dated November 4, 2003) and Human Exposure Assessment For Methamidophos (HS-1825 **(**Final Draft, dated August 4, 2003). Our comments are addressed in four attachments covering Toxicology and endpoint selection (Attachment 1), the dietary exposure assessment (Attachment
2), and the occupational exposure assessment for mixer/loader/applicators (Attachment 3) and re-entry (Attachment 4). Detailed issues are described in each of these attachments. Bayer CropScience are concerned that there are significant generic and product specific issues raised by the assessments and would appreciate the opportunity to discuss them fully in a meeting with CDPR experts. Notably the following issues need to be addressed:

1) BCS disagrees with CDPR selection of the subchronic NOEL of 0.5 ppm, equivalent to 0.03 mg/kg/day from the 8-week dietary study, for the use to determine MOEs for seasonal occupational exposure. The 21-day dermal
study has a NOEL of 0.745 mg/kg/day. CDPR did not use this study because it lacked hematology and clinical chemistry. However, the database clearly shows the most sensitive clinical finding is cholinesterase inhibition, leaving the rationale for rejection without scientific merit.

Response to <u>Bayer comment 1</u>: We agree that dermal toxicity studies are probably the most appropriate ones for conducting occupational exposure risk assessments. DPR has therefore used an acute rat dermal NOEL for acute occupational risk assessment and the 21-day rat dermal study NOEL was used to estimate risks for seasonal and chronic occupational exposure. DPR does not possess a valid rat dermal absorption study. The study submitted was considered unacceptable because of low recovery of ^{14}C, 64 – 88% (see Volume 2, IV.1.1). Therefore, human dermal absorption (measured *in vivo*) of 29% (Vol. 2, Section IV.1) was used to estimate absorbed dosages from the rat studies. These changes are reflected in the changes in Tables 25 (exposure) and 28 (MOE).

2) BCS feel that CPDR did not include in its review the subchronic human study with methamidophos. This study demonstrates that rats and human are similar in their response to this material and that the uncertainty factor used to
extrapolate from animals to humans can be reduced from 10x to 1x.

Response to <u>Bayer comment 2</u>: The human sub-chronic study has now been received and reviewed. For the reasons given, DPR considers this study to be supplementary and inadequate for the purpose of quantitative risk assessment of methamidophos.

It is included in the RCD (Vol. 1, Section III.I, p.48), as follows:

"<u>Subchronic: Human</u>

A subchronic toxicity study was conducted with human volunteers, subjected to mixtures of methamidophos and acephate (1:4 or 1:9) for periods of 10 (1:4) or 21 (1:9) days (Garofalo, 1973). The insecticides were dissolved in corn oil and were administered orally in gelatin capsules three times per day, at doses of 0, 0.1 (M+F), 0.2 (M+F), 0.3 (M+F) or 0.4 (F) mg/kg/day. A total of 7 males and 7 females took part in the investigation. Blood samples were taken at 1, 3, 7, 14 or 16 and 21

days and ChE activity in RBC and plasma enzyme was recorded. The enzyme activity at each time point was compared with the pre-testing activity for each subject and the criterion for inhibition was satisfied if the activity fell more than 2 SDs below the pre-dosing level. No inhibition of RBC ChE was recorded during the study. For plasma ChE, however, all volunteers (2M+2F) dosed at 0.2 mg/kg/day of 1:4 showed inhibition after 16 days' dosing. Likewise, at 0.3 mg/kg/day of the 1:9 mixture, 3/3M and 0/3F showed inhibited plasma ChE and at 0.4 mg/kg/day of 1:9, at 10 days, 2/3F exhibited lowered ChE. None of the subjects had any clinical signs or symptoms during or after the study. Overall, the study indicates that humans may be no more susceptible than rodents to the toxic effects of methamidophos but several factors compromise the validity of the study for quantitative risk assessment: the study was conducted by IBT, an organization with a dubious reputation; mixtures of methamidophos and acephate were used for dosing; GLP standards were not in force, making it uncertain whether or not the subjects dosed themselves over the weekend periods during the study; inadequate number of replicates to show statistical significance. It was concluded that the study was supplemental."

3) In recent dietary assessments with several compounds, BCS have noted many inconsistencies and differences between the assessments as to appropriate residue data to use, use of percent crop treated data, which percentile of
exposure to regulate at, and when to do further refinements in the assessment. BCS could find no document which outlines current accepted California DPR

Rules and Policies for exposure assessment. The assessment presented for methamidophos are conservative assessments because:
i) No dissipation or breakdown of residue is accounted for.
ii) No washing or further processing factors are used (except when inherent
in monitoring data).
iii) No reduction using measured processing factors is incorporated.
iv) All foods contain the highest reported residue or tolerance (except for
Monte Carlo analysis).
v) Full LODs are assumed for non-detect values in acute assessment.
vi) No percent of crop treated is included in acute analyses.
vii) Of use of older PDP data which may not reflect current usage.
viii) Of use of the distribution of user's only and not the per capita distribution
for calculating risk.

Response to <u>Bayer comment 3:</u> For dietary risk assessment, DPR is in the process of changing over from TAS* to DEEM* programs. Over the last few years, several RCDs have been finalized without necessarily conforming to identical guidelines. This is simply because the best protocol(s) for evaluating dietary exposure are continually evolving, as refinements are made to the dietary exposure software. Moreover, specific pesticides may require different criteria to be used depending on a range of factors. The registrants may be interested in a comparison of TAS* and DEEM* for the evaluation of methamidophos dietary exposure presented at the 3rd. PPCPS conference in 2003. It was found that the "old" TAS* system consistently gave higher exposure estimates than did DEEM,* but this has not been included in the RCD. The tolerance for tomato (1 ppm) is clearly too high. A tolerance assessment resulted in MOE values below 100 for each population sub-group, whether DEEM* or TAS* was used.

The rules and policies listed by Bayer have been addressed in Section IV.B.2, in Section V. and also in the ACS Symposium Volume chapter describing the aforementioned presentation: Gammon, D.W.; Carr, W.C.; Pfeifer, K.F. Dietary risk assessment of the organophosphate insecticide/ acaricide methamidophos, Chapter 13 in ***Environmental Fate & Safety Management of Agrochemicals*** Eds. J.M. Clark & H. Ohkawa, ACS Symposium Series 899 Oxford University Press (in press).

4) With the mixer/loader/applicator assessment BCS has the following concerns:
i) DPR simultaneously subsets the Pesticide Handler Exposure Database for dermal, hand, and inhalation grade data. This practice unnecessarily eliminates acceptable grade data records that would be captured by
subsetting for the dermal, hand, and inhalation grade data independently.
ii) DPR based its open cab groundboom applicator exposure estimate on the use of long pants, a long-sleeve shirt, chemical-resistant gloves, protective headgear, and a respirator. This is not consistent with the

label-required
coveralls over shorts and a short-sleeved shirt, chemical-resistant gloves, and a respirator. The protective headgear is required only with overhead exposure that would not occur with methamidophos application to cotton,
potatoes, tomatoes, or alfalfa.
iii) The exposure assessment has adopted significant policy changes that are inconsistent with the published HS-1612 guidance and relies on evolving policy changes that significantly increase the estimated exposure estimate
and are inconsistent with NAFTA harmonization policies. The estimate exposure appears to increase approximately 10-fold compared to estimates consistent with both HS-1612 and current EPA and PMRA methodology.

Response to Bayer comment 4: Mixer/Loader concerns: see Zhao memo of June 9, 2004.

5) With the postapplication exposure and risk assessment BCS has the following comments:

i) The use patterns of methamidophos do not result in long-term exposure or risk.
ii) Because methamidophos is applied late season to tomatoes in California, pruning, staking, tying, and activities associated with immature plants are not a re-entry issue. Scouting activities by crop advisors are adequately
covered under the Worker Protection Standard.

Response to Bayer comment 5: Post-application exposure: see Zhao memo of June 9, 2004.

To provide the most current and appropriate risk assessment on this chemical, we request CDPR address the above issues. We would appreciate meeting with CDPR to discuss them further. If you have any questions, please contact me at 919-549-2628 or karen.cain@bayercropscience.com.
Yours sincerely,
State Regulatory Affairs Team Lead
Bayer CropScience
Enclosures: 4 Attachments
04 Methamidophos Draft RCD 022804.doc

To: Ms. Ann Prichard
Department of Pesticide Regulation
California Environmental Protection Agency
1001 >I= Street
Sacramento, California 95812-4015
February 28, 2004
Bayer CropScience
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P. O. Box 12014
RTP, NC 27709
Tel. 919 549-2000

Subject: **Methamidaphos**
Draft Risk Characterization Document
Dear Ann,
Bayer CropScience is providing additional comments to CDPR, as directed by Valent U.S.A. Corporation. In explanation, Valent also is a registrant of the active ingredient, methamidophos, and is a member of the methamidophos task force. They (Valent) have asked that we share their comments with CDPR. Accordingly,
attached are specific comments developed by Valent.
If you have any questions, please contact me at 919-549-2628 or
karen.cain@bayercropscience.com.
Yours sincerely,
State Regulatory Affairs Team Lead
Bayer CropScience
Enclosure: Valent correspondence dated January 14, 2004
from J. Powell to K. Cain

January 14, 2004
Methamidophos (Monitor)
CDPR Risk Characterization Document
Registrant's Risk Assessment Comments
Dr. Karen Cain
State Regulatory Affairs Team Lead
Bayer CropScience
Crop Protection Division
2 T.W. Alexander Drive
RTP, North Carolina 27709.

Dear Dr. Cain:
As a U.S.A. co-registrant like Bayer CropScience of the active ingredient, methamidophos, Valent U.S.A. Corporation would like to share comments we have developed in response to CDPR's December, 2003 Risk Characterization Assessment on methamidophos. Valent would like to ask that you include our comments will those that Bayer CropScience plans on submitting to CDPR by the end of January 2004 and advise CDPR that all comments submitted to address their Risk Characterization Assessment on methamidophos were jointly developed between Valent U.S.A. Corporation and Bayer CropScience.
Our comments are listed below:
General Comments
In regards to CDPR's choice or selection of endpoints for the acute and seasonal worker risk assessment, CDPR chose to use two dietary studies for these endpoints. For the acute worker assessment, a NOEL of 0.3 mg/kg/day was
taken from the rat acute dietary neurotoxicity study. For the seasonal worker assessment, a NOEL of 0.03 mg/kg/day was taken from an 8-week rat dietary toxicity study. Valent disagrees with the use of these studies for the risk
assessment when a more appropriate dermal study is available for citation. In this instance, Valent agrees with the USEPA that the 21-day dermal study with a NOEL of 0.75 mg/kg/day is the most appropriate study in both cases. CDPR has found this study to be unacceptable due to a lack of clinical chemistry data. Valent finds this criticism invalid because the NOEL/LOEL determination is based on cholinesterase inhibition, a biomarker of exposure greatly more sensitive than clinical chemistry effects.

Response to Valent General comment: see response to Bayer in 1/, above

Specific Page Comments
Page 4, (bottom) Acephate is not a "pro-insecticide". While it is easy to think that acephate is converted to methamidophos and is then toxic, there is virtually no evidence that this is true.

Response to Valent comment on page 4: Page 4: it is generally agreed among insecticide toxicologists that acephate has negligible activity as an inhibitor of ChE and that it owes its toxicity, to both insects and mammals, to its enzymatic conversion to methamidophos (e.g. McGee, 1982 in RCD Vol. 1).

Page 7, The two references O'Malley, 1994 and O'Malley, 1995 are not in the reference list.
Response to Valent comment on page 7: I have added on page 7:
O'Malley, M., 1995. Illnesses associated with exposure to methamidophos in California. WH&S Branch Report #HS-1683
O'Malley, M, Verder-Carlos, M-L, Mehler, L. and Richmond, D., 1994. Risk factors for cholinesterase and non-cholinesterase effects of exposure to organophosphate insecticides in California agricultural workers: 1982-1990. WH&S Branch Report #HS-1688.

Page 8, The short paragraph on the top of page 8 is misplaced.
Response to Valent comment on page 8: fixed

Page 11, End of Pharmacokinetics Summary -- What is meant by " . . . the (parent) hydroxylamine."
Response to Valent comment on page 11: this refers to N-hydroxymethamidophos, as described by Mahajna & Casida, 1998. This has been added on page 12.

Page 47, In the discussion of the optical isomers of methamidophos, the designations L(-) and D(+) are incorrect. Capital D and L refer to stereochemical identity to the absolute configuration at carbon-2 in the aldotriose glyceraldehyde. The steric disposition of the three substituents and the phosphoryl oxygen about the chiral phosphorus atom in methamidophos is unrelated to glyceraldehyde. Instead, if the absolute configuration at phosphorus is known, the S and R designations can be used, or if only the direction of optical rotation is known
(small) d and l, or (+) and (-) should be used.
Response to Valent comment on page 47: L(-) and D(+) have been replaced with (-) and (+).

Page 65, The conversion of acephate to methamidophos in mammals is barely detectable. Methamidophos is formed from acephate as part of the acephate residue on plants. Thus, it is a correct statement that the dietary exposure to
methamidophos is probably underestimated by considering only methamidophos treated crops. However, acephate is not inactive against AChE, and assuming that acephate activity is attributable to conversion to methamidophos is not correct.
Response to Valent comment on page 65: the reduced toxicity of acephate vs. methamidophos in mammals is probably related to the fact that the primary metabolic route is O-demethylation (inactivation), whereas in insects, it is deacetylation (activation) to methamidophos (Eto, 2002). A lower level of conversion to methamidophos occurs in mammals.

Eto, M, 2002. Organophosphoros insecticides, pp. 1150-1177 in Encyclopedia of Agrochemicals. Ed. J.R. Plimmer, D.W. Gammon, N.N. Ragsdale. John Wiley & Sons, NJ.

If you have any questions regarding Valent's comments please call me at (925) 256-2719.

Sincerely,
Joseph L. Powell
State Project Manager
Registration & Regulatory Affairs
cc: Ms. Danielle Larochelle, Bayer CropSciences Corporation
bcc: John Aleck
Moire Creek
Dan Fay, Eric Tamichi, Dave Wustner, Valent Files

Attachment 1

Bayer Crop Science's Toxicology Comments on CDPR
Risk Characterization Document for
Methamidophos (Monitor)
General Comments

On Page 2 of the Summary, CDPR states the following "A NOEL of 0.3 mg/kg/day from a rat acute oral neurotoxicity study was used as the critical NOEL value to determine the MOEs for potential occupation and dietary exposure. A subchronic NOEL of 0.5 ppm, equivalent to 0.03 mg/kg/day from an 8-week dietary study, was used to determine MOEs for seasonal occupational exposure. A chronic, estimated NOEL of 0.02 mg/kg/day, based on (18%, $p<0.001$) inhibition of brain cholinesterase (CHE) at the LOEL of 2 ppm (0.06 mg/kg/day) in a 1-year dog study in males was used as the critical NOEL value to determine MOE values for potential occupational and dietary exposure." Bayer CropScience (BCS) disagrees with CDPR selection of the subchronic NOEL of 0.5 ppm, equivalent to 0.03 from the 8-week dietary study, for the use to determine MOEs for seasonal occupational exposure. BCS firmly believes that the selection of this study is inappropriate because another study exist which can better estimate the MOEs for the potential dermal occupational exposure. BSC feels that that the 21-day dermal study is more appropriate study for this endpoint and would better characterize the occupational risk which is predominantly the dermal route of exposure. This is the study which EPA is currently using in its risk assessment to characterize the occupational exposure route. This EPA acceptable dermal study has a NOEL of 0.745 mg/kg/day. As stated, this is the value that EPA is currently using in its risk assessment. EPA did not consider the study unacceptable because it lacked hematology and clinical chemistry. Additionally, the goal of the dermal study is to confirm that a similar toxicology spectrum is observed as was shown in the extensive number of studies performed via the oral route of exposure. On page 52 of the CDPR risk characterization document, CDPR reviewed the 21-day dermal study and stated the following "Methamidophos (purity, 76.9%-80.5%) was applied as an aqueous solution (1 ml/kg) to the shaved back of groups of 9 or 10 SD rats/sex/dose for 6 h/day for a total of 18/22 days (male) or 17/21 days (female) at (nominal) doses of 0, 1, 15 or 50 mg/kg/day, equivalent to 0, 1, 15 or 47 mg/kg/day measured. No effects were observed on a variety of parameters, including clinical observations, changes in body weight or food intake, and the only effects found were inhibition of ChE. The activity of plasma, RBC and brain ChE was suppressed dose-dependently at 15 and 47 mg/kg/day, but not at 1 mg/kg/day. Thus the LOEL and NOEL values for the subchronic, dermal toxicity of Methamidophos were 15 and 1 mg/kg/day, respectively. There were no apparent differences between males and females. The study was unacceptable to DPR due to a lack of clinical chemistry data." CDPR rejected this study solely on the bases that a complete clinical chemistry package was not performed for this study. BCS feels that this rejection is totally without scientific merit and can state clearly that the most sensitive clinical finding which was cholinesterase inhibition was measured in the study. CDPR can not disagree with the fact that cholinesterase inhibition is the most sensitive finding in the entire toxicological data base for this product. Measuring other clinical chemical, urological or hematological parameters would not have affected the outcome of the study and would not have changed the NOEL observed in this study. BCS would like to point out to CDPR that we examined the parameters mentioned above in several other studies such as the 8-week chronic rat study, 13-week dietary oral rat study, the several hen studies, chronic rat and mouse studies, 1-year chronic dog study and oncogenicity or carcinogenicity studies. In all of these studies, the most sensitive endpoint for clinical chemistry was cholinesterase inhibition. CDPR in their extensive review spent significant time and effort in their document outlining cholinesterase inhibition for Methamidophos as the major finding and served as the bases for setting the various reference doses (see table 32 below which was taken from the CDPR risk characterization document). CDPR itself has reviewed all the other studies and determined them to be acceptable and met the criteria set forth in SB950 (see Data Gap Status in risk assessment document).

Table 32: Comparison of NOELs used by DPR and USEPA for conducting risk assessments for Methamidophos.

Exposure type	DPR	USEPA	Study type
Acute, dietary	0.3 mg/kg/day[a/]	0.3 mg/kg/day[a/]	Rat gavage[a/]

Acute, worker	0.3 mg/kg/day[a/]	0.745 mg/kg/day[b/]	Rat, dermal, 21-d[b/]
Seasonal, worker	0.03 mg/kg/day[c/]	0.745 mg/kg/day[b/]	Rat, diet, 8-wk[c/]
Chronic, dietary Chronic, worker	0.02 mg/kg./day[d/] 0.02 mg/kg./day[d/]	0.03 mg/kg./day[c/] not applicable	Dog, diet, 1-yr[d/]

a/ Sheets, 1994.
b/ Sheets & Gastner, 1997: unacceptable to DPR due to a lack of clinical chemistry data. 21-day dermal rat study
c/ Mobay, 1991.
d/ Hayes, 1984c.

Therefore, BCS believes that CDPR should reverse it decision on this study and consider it to be acceptable for regulatory purposes and use the NOEL of 0.745 mg/kg/day which was obtained in this study to characterize the occupational risk assessment.

For your reference, below is the review of the 21-day dermal rat by EPA:
In a 21-day dermal toxicity study, Methamidophos technical(76.9 to 80.5% a.i.)] was administered to 9 to 10 male and female Sprague-Dawley rats dermally in pH 7.3 phosphate buffer solution(dose volume of 1 ml/kg of body weight) at dose levels of 0, 1, 15,and 50 mg/kg/day. Since the technical material has a relatively low concentration of active ingredient, dose levels corrected in terms of active ingredient are significantly lower. The corrected dose levels would then be 0.749, 11.2, and 36.5 mg/kg/day (using the actual analytically confirmed values of 0.974, 14.5 and 47.4 mg/kg/day, respectively and 76.9% a.i). These dose levels should be utilized for risk assessment purposes. No compound related effects on mortality, clinical signs, body weight, food consumption, or gross and histopathology were apparent at any dose level. Dose related plasma, RBC and brain cholinesterase inhibition were noted at 15 and 50 mg/kg/day of technical. A statistically significant increase in relative lung weights was observed at the high dose males, but this was not supported by histopathologic findings. Therefore, the **LOEL is 11.2 mg/kg/day technical (based on correction of the nominal, 15 mg/kg/day, for the analytical concentration of the active ingredient) and is based on brain, RBC and plasma cholinesterase inhibition. The NOEL is 0.749 mg/kg/day technical (based on correction of the nominal, 1 mg/kg/day, for the analytical concentration of the active ingredient).** This dermal toxicity study was originally classified as unacceptable due to the lack of analytical and stability data. Based upon the addendum report submitted on September 29, 1998,this study is upgraded to acceptable and now satisfies the guideline requirement for a 21-day dermal study (82-2) in the rat MRID No. 44525301 and Addendum to MRID No. 44525301). Additionally, BCS feel that CPDR did not include in its review of the subchronic human study with Methamidophos and this study clearly demonstrated that rats and human are similar in their response to this material and that the uncertainty factor used to extrapolate from animals to humans can be reduced from 10x to 1x. This adjustment would significantly impact the risk characterization of this product. We extracted the EPA review of this study for your reference. Subchronic oral human study In a subchronic study in humans, seven male and seven female Volunteers were given mixtures of *Methamidophos (Monitor; purity not stated)* and Acephate (Orthene) in two ratios, 1:4 or 1:9 (Monitor:Acephate) in gelatin capsules containing corn oil. The group receiving the 1:9 ratio (3 males and 3 females) were given0.1, 0.2, 0.3 or 0.4 mg/kg/day of the mixture (equivalent to 0.01, 0.02, 0.03 or 0.04 mg/kg/day Methamidophos). The group receiving the 1:4 ratios (2 males and 2 females) was given only 0.1 or 0.2 mg/kg/day (equivalent to 0.02 or 0.04 mg/kg/day Methamidophos). Each group received increasing levels of the test materials until a significant inhibition of ChE activity occurred (i.e., ChE inhibition "was greater than two standard deviations below mean pretest activity for two consecutive bleedings"). Dosing human subjects with graded levels of Monitor: Orthene mixtures for a total of 37-73 days had no effects on RBC ChE activity, hematology, blood chemistry, blood pressure, pulse rate, pupil size, light reflex, eye accommodation, chest sound, muscle tone, knee jerk, tongue tremor or finger tremor. The only systemic effect was the significant inhibition of plasma ChE activities in the 1:4 and 1:9 (Monitor: Orthene) groups. In the 1:4 groups, significant inhibition was first noted at 0.2 mg/kg/day; it occurred after 16 days and in all subjects. Significant plasma Chef

inhibition was first detected in the 1:9 groups at 0.3 mg/kg/day level after 21 days of dosing but only in the male subjects. The first significant response observed in the 1:9 group females occurred at 0.4 mg/kg/day level after 10 days of dosing (2 of the 3 females exhibited significant ChE depression). All suppressed ChE activity returned to the pretest values during the 7-day recovery period.

Based on the findings, NOELs and LOELs were as follows:

1:4 mixture: NOEL (both sexes) = 0.1 mg/kg/day (0.02 mg/kg Methamidophos); LOEL = 0.2 mg/kg/day (0.04 mg/kg Methamidophos)

1:9 mixture: NOEL (%) = 0.2 mg/kg/day (0.02 mg/kg Methamidophos); LOEL = 0.3 mg/kg/day (0.03 mg/kg Methamidophos)

1:9 mixture: NOEL (&) = 0.3 mg/kg/day (0.03 mg/kg Methamidophos); LOEL = 0.4 mg/kg/day (0.04 mg/kg Methamidophos)

This subchronic toxicity study in humans was classified acceptable as supplementary data. (see HED Document No. 012477; (MRID No. 00015160)).

Attachment 2

Comments on California DPR Risk Characterization Document for Methamidophos Dietary Exposure Assessment

General Comments

Although there are many compound specific dietary exposure assessments on the California DPR web site, there are no general documents which outline the policies and SOPs used by DPR to evaluate dietary exposure and risk. BCS is reviewing three Risk Characterization Documents (RCD) from DPR at this time: methamidophos, azinphosmethyl and DEF (tribufos). Even within these three documents there are many inconsistencies between the assessments as to appropriate residue data to use, use of percent crop treated data, which percentile of exposure to regulate at, and when to do further refinements in the assessment. Therefore it is difficult to make comments when different compounds use different data and procedures and there is no document which outlines accepted California DPR Rules and Policies for exposure assessment. Although there are no policy documents as mentioned above, many statements made in the various assessments lead one to believe that the policies internally accepted (but not documented) at DPR are in some ways very different from accepted US EPA Policies and SOPs on dietary exposure and risk assessment. The US EPA went through a public and transparent process for outlining it's policies, and comments from the public and industry were reviewed and considered before policies were finalized. This has resulted in a scientifically defensible set of rules for dietary exposure assessment, although there is still much disagreement about some policy areas, such as the percentile of regulation for acute assessment. Differences in the Cal DPR assessments occur in the incorporation of percent crop treated data in acute and chronic assessment, percentiles of regulation for various assessments and use of LODs and 1/2LODs in acute and chronic assessments, to name a few. BCS suggests that it would be helpful if Cal DPR would institute a similar process of policy making for the dietary exposure assessment area so that the scientific arguments could be presented and discussed in a public venue. This would give DPR a chance to present its views and why different choices have been made for dietary exposure assessment than those at US EPA. Finally, DPR conducts an Acute Tolerance Assessment. The three RCD documents state that "A tolerance is the legal maximum residue concentration of a pesticide which is allowed on a raw agricultural commodity or processed food. The tolerances are established at the levels necessary for the maximum application rate and frequency and not expected to produce deleterious health effects in humans from chronic dietary exposure." Also all three documents go on to state that in California, Assembly Bill 2161, generally referred to as 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. Presumably the Act specifies that a safety assessment must be conducted with tolerance level residues. The RCDs also state that "less than 1% of all sampled commodities have residue levels at or above the established tolerances". In fact numerous monitoring studies of a wide variety of commodities including FDA, USDA/PDP, California Monitoring Programs, Market Basket Surveys, and others, have shown that the majority of residues on available commodities are orders of magnitude below the tolerance levels, if they are detected at all. These monitoring studies, in some cases, do not account for reductions that might occur after consumer purchases such as further washing, storage, cooking, canning, etc. Despite this evidence of the low probabilities of tolerance level residues occurring in the real world, DPR uses the tolerance level for the commodity with no adjustment for percent crop treated in the acute DEEM™ assessment. They then look at the 95th or 97.5th percentile (depending on which RCD you are reading) of the resulting exposure distribution for the population. This assumes that all of the commodity (i.e. all apples) every person in that population consumed in the last 24 hours had the tolerance level of residue present. The 95th (or 97.5th) percentile represents the more extreme eaters of the commodity or high end consumers. The probability of these events occurring (tolerance level residue on all product consumed in 24 hours and high consumption) is extremely low and not appropriate for decisions on correct tolerances

Methamidophos Specific Comments

DPR apparently can use two processes for determining acute risk. The first uses a "deterministic" approach, which uses a high end point estimate for the residue level which does not incorporate percent crop treated, and the entire consumption distribution. The second approach uses a Monte Carlo approach, which uses an entire distribution of residue values from field trials or monitoring which still does not incorporate percent crop treated, and the entire consumption distribution. Both of these methods result in distributions of exposure. If the "deterministic" residue is used the 95th percentile is chosen for MOEs. If the Monte Carlo method is used both the 95th and 99.9th percentiles are chosen. In fact both of these methods are highly conservative and overestimate exposure. For methamidophos very acceptable MOEs were obtained with the deterministic residue (460 or better for all populations) so it is not clear why the Monte Carlo method was invoked which has lower MOEs at the 99.9th percentile (210 or better) but are highly unrealistic since percent of crop treated is not incorporated in this assessment. If one is going to move to a probabilistic approach, the point is to use data that is as realistic as

possible. Percent crop treated should be incorporated into a probabilistic approach, as the reality is that not all of a given commodity is treated with the pesticide. When percent crop treated is not used the method assumes that every time a person eats that commodity it has been treated with the pesticide.1 When the PDP data is used in the acute probabilistic assessment, non-detects are assumed to have pesticide present at the full LOD. This is again very conservative and highly unlikely. US EPA policy allows the use of ½ LOD for non-detects that are assumed treated based on scientific arguments.2 California chooses to look at user-days only for regulation of the dietary assessment. This is not a true population based assessment as there are many people in the populations that might not eat a particular commodity. These people with zero exposure to the pesticide must be included in the exposure distribution to give a true picture of the population distribution of exposure. This is especially important since the upper tails of the distribution (which contain the extreme situations) are chosen by DPR for regulation. The assessment for methamidophos appears to be several years old. The PDP data used is from 1994-1997. PDP data for the years 1998-2001 are currently available and include fresh tomatoes (1998-1999), canned tomatoes (1999-2000), tomato paste (2001) and potatoes (2000-2001).3 The addition of this data would be likely to reduce the overall risk, especially for the processed tomato items for methamidophos since conservative processing factors were used. Although data exist to show actual reduction in residues when tomato processing occurs, DPR chooses to set the processing factors for tomatoes to 1.0, another conservatism in the analysis.4 In the Acute Tolerance Assessment section for methamidophos, the recommendation is made that US EPA review the tomato tolerance because the MOEs for most populations are below 100 (Children 1-6 at 26). These assessments are highly conservative and unrealistic (see section above) and do not reflect any real risk to populations. An MOE of 26 means that the postulated exposure (extremely conservative) is still 26 times higher than the level at which no adverse effects were seen in the animal study. In the methamidophos Acute Tolerance Assessment the 97.5th percentile of exposure is chosen for MOEs. However for azinphos-methyl and tribufos the 95th percentile is chosen. No reasons are given for either of these choices. In all cases these percentiles are not reasonable for regulation given the extreme conservatism contained in the analyses. Percent crop treated data for the methamidophos chronic assessment is based on 1995-1997 data. More recent percent crop treated data would be more appropriate for this assessment since DPR itself stated that methamidophos use has been steadily declining since 1995. This is especially true for cotton which must exit the market by 2007. In summary, these are conservative assessments because:

1.) No dissipation or breakdown of residue is accounted for.
2.) No washing or further processing factors are used (except when inherent in monitoring data).
3.) All processing results in concentration of residue, or a residue level the same as in the RAC, no reduction is used.
4.) All foods contain the highest reported residue or tolerance (except for Monte Carlo analysis).
5.) Full LODs are assumed for non-detect values in acute assessment.
6.) No percent of crop treated is included in acute analyses.
7.) Use of older PDP data which may not reflect current usage.
8.) Use of the distribution of user's only and not the per capita distribution for calculating risk.

Despite these multiple conservatisms on the exposure side, and conservatisms which are also likely on the toxicology side, DPR chooses to calculate risk from exposures taken from the upper percentiles of the acute exposure distributions. The end result is a very unrealistic and potentially misleading evaluation of risk for methamidophos from dietary sources.

1. US EPA. 2000. "Available Information On Assessing Exposure From Pesticides In Food. A User's Guide."
2. US EPA. 2000. "Assigning Values to Non-detected/Non-quantified Pesticide Residues In Human Health Food Exposure Assessments."
3. http://www.ams.usda.gov/science/pdp/
4. US EPA. 2000. "Guidance for Refining Anticipated Residue Estimates For Use in Acute Dietary Probabilistic Risk Assessment.

Attachment 3

Occupation Exposure Assessment for Mixer/Loader/Applicators

SUMMARY

Bayer has reviewed the occupational exposure assessment prepared by DPR for methamidophos. Based on this review Bayer has the following comments and concerns.

1. DPR simultaneously subsets the Pesticide Handler Exposure Database for dermal, hand, and inhalation grade data. This practice unnecessarily eliminates acceptable grade data records that would be captured by subsetting for the dermal, hand, and inhalation grade data independently.
2. DPR based its open cab groundboom applicator exposure estimate on the use of long pants, a long-sleeve shirt, chemical-resistant gloves, protective headgear, and a respirator. This is not consistent with the label-required coveralls over shorts and a short-sleeved shirt, chemical-resistant gloves, and a respirator. The protective headgear is required only with overhead exposure that would not occur with methamidophos application to cotton, potatoes, tomatoes, or alfalfa.
3. The exposure assessment has adopted significant policy changes that are inconsistent with the published HS-1612 guidance and relies on evolving policy changes that significantly increase the estimated exposure estimate and are
inconsistent with NAFTA harmonization policies. The estimate exposure appears to increase approximately 10-fold compared to estimates consistent with both HS-1612 and current EPA and PMRA methodology.

INTRODUCTION

Bayer CropScience has evaluated HS-1825, Human Exposure Assessment For Methamidophos (Zhao, W. and Formoli, T. 4 August 2003) as part of the comment period for the risk characterization evaluation of methamidophos. Bayer's comments are specific to the use of the Pesticide Handlers Exposure Database (PHED) to estimate mixer/loader and applicator exposures and the methodology used to estimate the daily and seasonal exposures based on the PHED estimates.

DPR USE OF PHED

Section VI of HS-1825 provides a detailed description of the exposure assessment used for methamidophos with appendices 1 through 4 providing the specific PHED subsets created by DPR to estimate exposure. Methamidophos is currently registered for use on cotton, alfalfa, potatoes, and tomatoes. The U.S. EPA has proposed cancellation of all cotton uses and a requirement for the applicators to be in enclosed cab vehicles as a result of the reregistration process. Methamidophos use in California requires a closed loading system for mixing/loading. The use of the closed loading system permits the mixer/loader to wear long pants, a longsleeved shirt, chemical-resistant gloves, and a chemical-resistant apron. Application by either groundboom equipment or aerial equipment requires the applicator to wear coveralls over a short-sleeve shirt and short pants, chemical-resistant gloves, chemical-resistant footwear, and respiratory protection. When the applicator is in an enclosed cab or cockpit the double layer of clothing can be reduced to a long-sleeved shirt and long pants. DPR estimated the PHED exposures based on long-sleeved shirts, long pants, and chemical-resistant gloves for the mixer/loaders with adjustments for a chemical-resistant apron. Open-cab groundboom applicator exposure was estimated for aerial applicators based on a long-sleeved shirt and long pants. Bayer believes this is consistent with enclosed cockpit aircraft. The groundboom applicator PHED estimates (Appendix 3, HS-1825) are based on an open cab groundboom tractor with the use of long pants and long-sleeved shirts. Head exposure is adjusted for the use of chemical-resistant headgear that is required only for overhead applications. Because the product is applied to cotton, alfalfa, tomatoes, and potatoes, Bayer is uncertain as to why an adjustment was made for protective headgear. Hand exposure is adjusted for the required chemical-resistant gloves. Application by open-cab requires an adjustment for the chest, back, upper arms, and thighs to account for the label required coveralls over a short-sleeved short and shorts. The mixer/loader and groundboom applicator PHED assessments prepared by DPR are addressed in greater detail in the following sections.

Mixer/Loader Exposure

DPR estimated the dermal and inhalation exposures for a mixer/loader as 19.68 µg/lb a.i. and 0.163 µg/lb a.i., respectively. The specific subset specifications for the PHED mixer/loader subset are provided in Appendix 1 of HS-1825. Bayer believes that the DPR specifications for a closed loading system, the liquid formulations available in
PHED, and the use of long pants, long-sleeved shirt, and gloves are reasonable although not necessarily the exact specifications that Bayer would have selected. Bayer has reproduced the selection criteria used by DPR and presents the PHED outputs below. The subset is presented prior to making selections for the dermal, hand, and inhalation data quality because Bayer does not agree with the methodology used by DPR for subset definitions based on data quality. Bayer does concur with the selection of only grade A and B data as the highest quality data. Specifically, DPR appears to have subset for hand grade, dermal grade, and inhalation grade data equal to grades A and B
simultaneously. Such practice restricts the number of grade A and B data actually available as detailed

below.
Figure 1. PHED subset prior to selecting for data grades (created by Bayer)
<< Specifications >> Page 1 of 1
Subset Specifications for DPR.MLCLOSED.MLOD
With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal t With Mixing Procedures Equal to 2 or Equal to 3
Subset originated from MLOD.FILE
The initial subset above was evaluated for the number of records that were graded A or B for airborne, dermal uncovered, dermal covered, or hand grade. The results are presented in the three screens below.
Figure 2. Data Grades For Closed System Mixer/loader Subset. It is very important to note that a record may be graded A or B for a category such as dermal grade uncovered but not for hand grade. Record 0422*D*02 is an example. Therefore subsetting by airborne grade, dermal grade, and hand grade equal to A or B
will produce only those records that meet the grade A or B criteria for all categories. This appears to be what was done in the DPR assessment. There are 17 records that are grade A for Airborne and Dermal Grade Uncovered and Hand Grade. This is consistent with the number of records presented by DPR in Appendix 1. This procedure is therefore eliminating nine grade A airborne records, five grade A dermal uncovered records, and 14 hand grade A records. In order to capture all the potential records the subsetting by grade must be conducted separately for dermal grade uncovered, hand, and airborne. The following screens present this procedure. Ignoring issues as to whether the median, geometric mean, or arithmetic mean is the most appropriate statistic of central tendency, the DPR use of the mean is used for direct comparison purposes. Whereas the DPR assessment had 17 records, subsetting for only dermal grade A or B provides 22 records. The number of observations increases to a 16 to 22 range compared to 16 or 17 in the DPR assessment. The total mean exposure for all body areas excluding the hands is 12.88 µg/lb a.i. Following DPR procedure for correcting for the use of a chemical-resistant apron requires adjusting the chest exposure by 0.05 and the thigh exposure by 0.05 for the front half of the thighs. The chest exposure is reduced from 1.8416 µg/lb a.i. to 0.09208 µg/lb a.i. The thigh exposure is split in half to 1.17 µg/lb a.i. and multiplied by the 0.05 correction factor to obtain a dermal exposure estimate of 0.058 µg/lb a.i. for the protected front of the thighs. This is
added to the back of the thigh estimate of 1.17 µg/lb a.i. to yield a protected thigh estimate of 1.23 µg/lb a.i. An estimated foot exposure is added by DPR by multiplying the lower leg exposure by 0.52. In this example the foot exposure is 1.292 µg/lb a.i. x 0.52 or 0.67 µg/lb a.i. The total dermal exposure excluding the hands for the grade A or B observations is 10.7 µg/lb a.i. Hand exposure is omitted from this subset because the subset was not restricted to only grade A or B hand observations. The grading procedure is repeated for the hands to provide the following subset as illustrated in the screens below.
There are 31 grade A or B hand observations with an arithmetic mean of 5.72 µg/lb a.i. compared to the 17 captured using DPR methods. The total dermal exposure for all grade A or B observations is the sum of the 5.72 µg/lb a.i. hand exposure and the 10.7 µg/lb a.i. dermal exposure excluding the hands or 16.4 µg/lb a.i. Inhalation exposure is handled in a similar fashion by subsetting the original 40 records by airborne grade A or B as illustrated below.
The PHED subset contains 27 grade A or B inhalation observations compared to the 17 captured by DPR. The arithmetic mean inhalation exposure is 0.221 µg/lb a.i. Based on capturing all grade A or B observations the total dermal exposure changes from the 19.68 µg/lb a.i. DPR estimate to 16.4 µg/lb a.i. and the inhalation exposure changes from the 0.163 µg/lb a.i. DPR estimate to 0.221 µg/lb a.i. It should be noted that although the 29 l/min respiration volume used by DPR is a default used by EPA, this breathing volume is not sustainable over and 8-hour work day and will overestimate the actual inhalation exposure. Although the magnitude of the difference in the dermal and inhalation exposure estimates between the DPR PHED estimates and the Bayer estimates are small; Bayer strongly believes that DPR must utilize subsetting procedures in PHED that captures all of the available grade A or B data. DPR itself comments in the methamidophos human exposure assessment that the number of PHED observations can become very small. Therefore it is incumbent on DPR to use methods that capture the greatest number of observations without diminishing the data grade quality.
Groundboom Applicator Exposure
Appendix 3 provides the details of the DPR assessment of open cab groundboom applicator exposure. As with the mixer/loader, the DPR subset methods unnecessarily eliminate many grade A or B observations. Bayer also believes that this assessment contains subset specifications that are inconsistent with the label requirements. The total dermal exposure presented in Appendix 3 is 58.86 µg/lb a.i. prior to adjusting for head gear, gloves, or foot exposure. Bayer also obtained a sum dermal exposure of 58.87 µg/lb a.i. prior to adjusting for the head gear, gloves, or foot exposure. It is noted that Appendix 3 contains a typographical error. Hand exposure is presented as 3.85 µg/lb a.i. rather than the actual 43.85 µg/lb a.i. Bayer's reproduction of the DPR subset is presented below. The issue with the subset instructions used by DPR again involves the concurrent subsetting by data grades. This practice significantly reduces the number of

grade A and B observations from the exposure assessment. Bayer redid the groundboom applicator assessment to illustrate the significant number of lost observations. The one minor difference was that Bayer excluded dust and granular formulations. DPR did not include subset specifications for formulation but captured only emulsifiable concentrates and wettable powders. The subset prior to selection of observations based on data grade contains 123 records. The browse function of PHED permits an evaluation of each record by data grade and the
outputs are present below.

Whereas the DPR subset contained 25 observations of grade A, B, or C inhalation data, there actually are 19 records of grade A and B inhalation data, which eliminates the need to rely on the lower quality C grade data. There are also 39 grade A or B dermal records compared to the 17 to 24 in the DPR subset and there are 34 grade A or B hand records compared to the 25 in the DPR subset. Bayer has reevaluated the groundboom subset by separating the data quality restrictions as follows.

Dermal Grade A, B evaluation

The dermal exposure for a single layer of clothing excluding hand exposure is 19.0 µg/lb a.i. Following DPR convention for foot exposure the lower leg exposure is extrapolated to the feet by the 0.52 surface area adjustment to obtain a foot exposure of 1.16 µg/lb a.i and a total dermal exposure estimate of 20.16 µg/lb a.i. excluding the hands. The number of observations per body area has increased from 17 to 24 in the DPR assessment to 20 to
37 in the above assessment. The current methamidophos label requires the applicator to wear coveralls over a shortsleeve shirt and shorts when applying in an open-cab tractor. Based on the label requirements the dermal exposure to the upper arms, chest, back, and thighs should be reduced by a factor of 0.1 based on the 90% protection factor provided in Table 4 of HS-1612. The dermal exposure for the coveralls over short-sleeved shirt and shorts scenario is 12.27 µg/lb a.i. compared to the DPR derived estimate of 13.13 µg/lb a.i. for long pants, a long-sleeved shirt, and protective headgear.

Hand Grade A, B evaluation

Although the number of grade A or B hand observations for no gloves has increased by one, there are now eight observations that involve the label required use of protective gloves as illustrated below. In this particular example the protected hand exposure based on adjusting the no glove hand exposure of 50.876 µg/lb a.i. by the 0.1 protection factor is 5.1 µg/lb a.i. compared to the actual hand exposure under gloves of 12.7 µg/lb a.i. The total dermal exposure for an open cab groundboom applicator with the label required protective clothing is the sum of the 12.7 µg/lb a.i gloved hand exposure and the 12.3 µg/lb a.i. dermal exposure or 25.0 µg/lb a.i.

Inhalation Grade A, B Evaluation

There are actually 19 grade A and B inhalation observations compared to 25 grade A, B, or C inhalation observations in the DPR assessment. The arithmetic mean inhalation exposure is 1.92 µg/lb a.i. compared to the DPR estimate of 0.813 µg/lb a.i. prior to adjusting for the use of respiratory protection. Adjusting the 1.92 µg/lb a.i. inhalation exposure for the 98% respirator protection factor provides an inhalation exposure estimate of 0.038 µg/lb a.i. A summary of the changes to the PHED based estimates for the mixer/loader and groundboom applicator is presented below. The changes are a result of capturing more grade A and B data for the mixer/loader and applicator and assuming the label required clothing for the applicator.

PHED Exposure Estimates For Mixer/Loaders and Ground Boom Applicators

DPR PHED Estimates (µg/lb a.i.) Bayer PHED Estimates (µg/lb a.i.) Job

Dermal Inhalation N Dermal Inhalation N M/L 19.68 0.163 17 16.4 0.221 22

Applicator 17.51 0.016 20 25.0 0.038 29

Bayer recognizes that the differences presented above do not significantly change the estimated dermal or inhalation exposure estimates. However, Bayer strongly believes that the more correct use of PHED is important in DPR's overall exposure assessment conduct and that the label required personal protective equipment must be reflected in the exposure assessments to the extent possible.

DPR CALCULATION OF ABSORBED DAILY AND SEASONAL DOSES

Bayer has significant and substantial concerns regarding policy changes that have been incorporated into the methamidophos exposure assessment. Current guidance for the preparation of pesticide exposure assessments is provided in HS-1612 (4 May 1993). This guidance document is referenced in the methamidophos HS-1825 exposure assessment, but appears to be superseded by an unpublished version that is currently under revision as referenced in HSM-02037 (Powell, 27 September 2002). The HS-1825 methamidophos assessment is actually referencing an earlier version of the Powell memo (HSM-01010, 23 August 2001 and rescinded on 27 September 2002). DPR needs to address why HS-1825 that was published on 4 August 2003 is citing the rescinded HSM-
01010 and not the current HSM-02037 document issued in 2002.

Current DPR policy as stated in HS-1612 states that *Exposure estimates to be used in the risk assessment*

process must represent the exposure of a worker after all protection provided by clothing, protective clothing and equipment or engineering controls specified on the product label are taken into consideration. Risk assessors may have to use a more conservative exposure estimate to determine the risk of acute exposure, e.g. reproductive effects. In order to satisfy this requirement, the mean (arithmetic or geometric depending on the normality of distribution) and the standard deviation of the mean will be used to report the worker exposure estimates. This will allow the risk assessor to apply the necessary degree of conservatism in using an exposure estimate for risk assessment. (Worker Exposure Section, General Information). This policy is consistent with the U.S. EPA policy and also that of the Health Canada, Pest Management Regulatory Agency and it is also consistent with harmonization policies under NAFTA. HSM-02037 and the apparent unpublished revisions to HS-1612 will significantly alter the exposure and risk assessment process in California to yield significantly higher exposure estimates without consideration for other variables in the exposure assessment that are typically conservative such as use of maximum acreages, maximum application rates, and low body weights. HSM-02037 is in itself a more radical revision of its rescinded predecessor HSM-01010 that is cited for in the HS-1825 methamidophos risk assessment. The specific shifts observed in DPR policy from those guidelines stated in HS-1612 have been, 1) the movement from the geometric mean for lognormal
distributions to the arithmetic mean for lognormal distributions followed by, 2) the shift from arithmetic means for lognormal distributions to the use of the 95th percentile for short-term assessments and the 90% upper confidence limit of the arithmetic mean for intermediate-term and long-term assessments as applied in HS-1825 based on rescinded HS-01010 to 3) the use of the 90% upper confidence limit of the 95th percentile when PHED is used for short-term assessments and continued use of the 90% upper confidence limit of the arithmetic mean for intermediate-term and long-term assessments as stated in HSM-02037. These shifts in policy present significant impacts on the risk assessment process and have not been presented for discussion with either registrants or the grower communities. This evolving shift observed through the succession of policy changes in memorandum and unpublished revisions to HS-1612 give the appearance of a Department attempting to develop the most extreme methodologies of exposure assessment without regard to the practical implications in the agricultural community.
Bayer's specific technical concerns with these changes are presented below.
Use Of The Arithmetic Mean
HS-1612 clearly has provided guidance that the geometric mean is the appropriate statistic for use with exposure distributions that have a lognormal distribution. The geometric mean is the measure of the central tendency or the 50th percentile of exposure. Simply put, the approximately half the workers are expected to have exposures less than the geometric mean and half will have exposures greater than the geometric mean. It is Bayer's understanding that DPR considers the arithmetic mean to be more appropriate because it measures the magnitude of the exposure distribution. A few, extremely high exposure estimates in the distribution significantly increase the arithmetic mean in a lognormal distribution. Typically the use of the arithmetic mean in a lognormal distribution means that approximately two-thirds of the workers have exposures that are less than the mean and only one-third have an exposure greater than the mean. The apparent philosophy behind the move to use the arithmetic mean for lognormal
distributions is to be more protective of all workers. Bayer believes strongly in providing adequate and realistic protection for all users of its products. However, unilateral shifts in one part of the exposure assessment equation without consideration for the overall assessment process will eventually produce unrealistically high estimates of exposure that have no reality to actual exposures occurring in agriculture. A comparison of the effect of the use of the arithmetic mean to the geometric mean is provided for the mixer/loader exposure assessment. DPR in Appendix 1 of HS-1825 estimated the arithmetic mean dermal and inhalation exposure estimates to be 19.68 µg/lb a.i. and 0.163 µg/lb a.i., respectively. Based on U.S. EPA guidance for the use of PHED, the best fit estimate[1] for dermal exposure excluding the hands is 7.37 µg/lb a.i.[2] and the hand exposure is 1.68 µg/lb a.i.[3] to provide

[1] The best fit estimate in PHED is based on the use of the arithmetic mean for a specific body area with a normal distribution, the geometric mean for a body area with a lognormal distribution, and the median for a body area with an "other" distribution. This is consistent with the current HS-1612 guidance.

[2] From PHED subset DPR.MLCLOSED.DERAB.MLOD in which the geometric mean hand exposure estimate of 2.30 µg/lb a.i. is subtracted from the 9.21 µg/lb a.i. best fit dermal exposure estimate and 0.52 x the geometric mean lower leg exposure of 0.8778 µg/lb a.i. is added to estimate foot exposure.

[3] From PHED subset DPR.MLCLOSEDHANDAB.MLOD

a total dermal exposure estimate of 9.05 µg/lb a.i. The inhalation exposure had a
lognormal distribution and the geometric mean inhalation exposure is 0.083 µg/lb a.i.[4]

DPR policy is apparently shifting again from the use of the arithmetic mean for lognormal distributions to the use of the 95th percentile of the exposure distribution based on rescinded HSM-01010 and its successor HSM-02037. The current HSM-02037
memorandum states on the first page that *The 95th percentile of absorbed daily dosage (ADD) is generally*

used to represent short-term (up to 7 days in duration) exposure. The recommended statistic is the estimate of the 95th percentile of a lognormal population. When ADD is estimated using the PHED, the 90% upper confidence limit on the 95th percentile should be used.

Bayer requests that DPR provide documentation to support the statement that the 95th percentile is generally used to represent short-term exposure. Considering that EPA and PMRA currently use means and operator exposure assessments under 91/414 in the European Union are based on the 75th percentile of the UK POEM model and the geometric mean of the German model, the statement of general use of the 95th percentile is curious. This assessment will not address the issue of whether the mathematics underlying HSM-02037 are correct and for the purposes of this assessment will accept them at face-value. Table 2. of HSM-02037 provides multipliers to estimate the 90% upper confidence limit for the 95th percentile as a multiple of the PHED arithmetic mean. The multipliers are based on the median number of replicates in the PHED subset and decrease with increasing numbers of replicates. This is a reason that inclusion of the maximum number of grade A and B observations is important in the DPR use of PHED. For the DPR mixer/loader subset the number of replicates was 17. Based on Table 2 of HSM-02037, the multiplier of the arithmetic mean is 5 for datasets with 12 to 19 replicates. The acute ADD presented in Table 4 of HS-1825 clearly is following the policy laid out in rescinded HSM-01010 based on footnote “d” of the table rather than the current HSM-02037. DPR calculated the ADD for a groundboom mixer/loader treating 80 acres/day as follows where the maximum application rate is 1 lb a.i./A, the dermal absorption is 29%, the inhalation absorption is 50%, and the body weight is 70 kg:

Dermal ADD = 19.68 µg/lb a.i. x 80 A/day x 1 lb a.i./A x 0.29 ÷ 70 kg = 6.52 µg/kg/day
Inhalation ADD = 0.163 µg/lb a.i. x 80 A/day x 1 lb a.i./A x 0.5 ÷ 70 kg = 0.093 µg/kg/day
Total ADD = 6.52 µg/kg/day + 0.093 µg/kg/day = 6.62 µg/kg/day

The Acute ADD based on the use of the 95th percentile of exposure was calculated in Table 4 of HS-1825 as follows:

Total Acute ADD = 6.62 µg/kg/day x 3.0 = 19.9 µg/kg/day

[4] From PHED subset DPR.MLCLOSEDINHAB.MLOD

The multiplier of 3 comes from HS-01010 that was rescinded prior to the completion of the methamidophos exposure assessment. The multiplier of 3 is intended to estimate the 95th percentile of a lognormal distribution.

If DPR used its current policy as stated in HSM-02037 that was finalized prior to the completion of the methamidophos assessment in HS-1825 the estimate of the Total Acute ADD would be based on the more extreme 90% upper confidence limit of the 95th percentile. The multiplier for the 90% upper confidence limit of the 95th percentile is 5 and the Total Acute ADD would be estimated as follows:

Total Acute ADD = 6.62 µg/kg/day x 5.0 = 33.1 µg/kg/day

The impact of the changes in DPR procedures results in an increase in the exposure estimate from 3.0 µg/kg/day based on PHED best fit estimates[5] to the estimate of 19.9 µg/kg/day based on rescinded HSM-01010 to an estimate of 33.1 µg/kg/day based on the current HSM-02037. Such changes in policy would yield MOEs that appear to be 10-fold lower than MOEs based on HS-1612 or existing EPA policy. Regardless of how DPR incorporates such changes into its risk decision-making process, the public will perceive a change in risk potential despite no changes in actual risk. Based on the acute NOEL of 0.3 mg/kg/day the MOEs would decrease from 100 using the best fit from PHED consistent with the current HS-1612 to a MOE of 15 based on the HS-1825 exposure estimate and to a MOE of 9 if the acute ADD was estimated based on the current HSM-02037.

DPR recognizes in the Risk Characterization Document that the use of the 95th percentile is overly conservative. The Occupational Exposure summary on page 65 states *However, it is possible that the 95th percentile of exposure, which was calculated for the M/L/A using PHED, is overly conservative with respect to normal use practices, where the mean exposure might be more appropriate.*

This DPR statement is consistent with Bayer’s concerns that the use of the HSM-02037 policy may not be the most appropriate. Therefore, Bayer’s position is that DPR must obtain public comment prior to adoption of any changes to HS-1612 and prior to the proper open review process that the current HS-1612 guidance must be used in the methamidophos exposure assessment.

[5] Dermal ADD = 9.05 µg/lb a.i. x 80 A/day x 1 lb a.i./A x 0.29 ÷ 70 kg = 3.00 µg/kg/day
Inhalation ADD = 0.083 µg/lb a.i. x 80 A/day x 1 lb a.i./A x 0.5 ÷ 70 kg = 0.047 µg/kg/day
Total ADD = 3.00 µg/kg/day + 0.047 µg/kg/day = 3.047 µg/kg/day

Attachment 4

Bayer CropScience's Comments on the Risk Assessment for Re-entry Activities

SUMMARY

Bayer CropScience does not agree with CDPRs postapplication exposure and risk assessment for methamidophos for the following reasons:

1. CDPR used oral NOELs and a 29% dermal absorption to assess postapplication risk. Bayer CropScience maintains that the dermal NOEL is a more appropriate toxicological endpoint for postapplication risk assessment.
2. CDPR used an oral chronic NOEL of 0.02 mg/kg/day for lifetime risk assessment. Bayer CropScience maintains that the use patterns of methamidophos do not result in long-term exposure or risk.
3. Because methamidophos is applied late season to tomatoes in California, pruning, staking, tying, and activities associated with immature plants are not a re-entry issue. Scouting activities by crop advisors are adequately covered under the Worker Protection Standard.

INTRODUCTION

Bayer CropScience has evaluated HS-1825, Human Exposure Assessment For Methamidophos (Zhao, W. and Formoli, T. 4 August 2003) as part of the comment period for the risk characterization evaluation of methamidophos. These comments are specific to the use patterns of methamidophos in cotton, tomatoes, and potatoes.

POSTAPPLICATION EXPOSURE AND RISK ASSESSMENT

Selection of appropriate toxicological endpoints is discussed in depth in the Toxicology section of the Bayer CropScience response. This section will address the methodology of exposure and risk assessment used by CDPR.

CDPR calculated daily exposures in terms of µg/person/day for various postapplication activities in cotton, tomatoes and potatoes. CDPR used the estimated DFR at the appropriate REI or PHI for the crop and the transfer coefficient derived from US EPA Policy 3.1 on agricultural transfer coefficients to calculate these daily exposures, assuming a 6 hour workday for scouting in cotton and an 8 hour work day for all other activities in the three crops. Bayer CropScience agrees with CDPRs calculated daily exposures in terms of µg/person/day for various postapplication activities in cotton, tomatoes and potatoes. CDPR calculated seasonal average daily dosages (SADD) in the same manner as the ADD, using the DFR values from 2 days after the REI expired or 3 days after the PHI, which CDPR termed average DFR. CDPR calculated annual average daily dosage (AADD) by multiplying the SADD by the number of months of exposure per year divided by 12 months. Further, CDPR calculated acute, seasonal, and annual MOEs from these absorbed doses using 0.3 mg/kg/day, 0.03 mg/kg/day, and 0.02 mg/kg/day for the acute, intermediate term, and chronic oral NOELs. The DPR estimates are presented in Table 1.

TABLE 1. CDPRs Acute, Seasonal, and Annual Risk Calculations.

Crop	Job Category	Acute ADD (µg/kg/day)	Acute MOE	SADD (µg/kg/day)	Seasonal MOE	AADD (µg/kg/day)	Annual MOE
Cotton	Scouting	3.50	86	1.68	18	0.42	48
Tomatoes	Scouting Irrigating	3.09	97	1.95	15	0.65	31
Tomatoes	Staking/Tying	4.41	68	2.78	11	0.46	43
Tomatoes	Transplanting Pruning	4.41	68	2.78	11	0.93	22
Tomatoes	Hand Harvesting	1.76	170	0.89	34	0.30	67
Potatoes	Hand Harvesting	0.83	361				

IMPACT OF METHAMIDOPHOS USE PATTERNS ON EXPOSURE AND RISK

Use of methamidophos, and therefore reentry exposure to methamidophos, is seasonal. Exposure occurs over a 2 to 4 month period. Because the most sensitive toxicological effect of methamidophos exposure is cholinesterase inhibition, which is slowly reversible, no enzyme inhibition is carried into subsequent growing seasons. Therefore,

chronic worker exposure to methamidophos is highly unlikely. Annual and lifetime exposure and risk calculations are not relevant for the use pattern and toxicology endpoint. As illustrated in Table 1, acute MOEs for hand harvesting tomatoes and potatoes are above the target MOE of 100, indicating no adverse risk from these worker activities. MOEs for the other activities in cotton and tomatoes are below 100. However, methamidophos is applied late season to tomatoes in California. Therefore, pruning, staking, tying and activities associated with immature plants are not a re-entry issue. Scouting is a handler activity under the WPS. Certified or licensed crop advisors, and

persons under their direct supervision, may enter treated areas during the REI provided they use the handler personal protective equipment (PPE) specified on the label.