

Modifications and Additions to the Candidate Toxic Air Contaminant List

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INTRODUCTION

Assembly Bills 1807/3219 require the California Department of Food and Agriculture (CDFA) to declare and regulate as toxic air contaminants (TAC) air pollutants which "...may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health" (Sec. 14021, Food and Agricultural Code). In order to accomplish this goal, CDFA proposes a candidate list of pesticides to be evaluated under this program. On a given timetable, CDFA requests ARB to monitor for specific pesticides. By an agreement between the two agencies, ARB has fifteen months from the date of the request to conduct and report this monitoring. During this time, CDFA sends a comprehensive health effects and environmental fate bibliography with a request for additional information to other governmental agencies, registrants, and interested parties. After the monitoring data have been received from the ARB, an environmental fate, health effects, and risk characterization report is prepared. This report is peer reviewed within CDFA and ARB and by the Department of Health Services and it is then released for public comment. After all comments have been addressed, the report is submitted to the Scientific Review Panel (SRP) for determination of scientific accuracy. Once the panel has found the report to not be scientifically deficient, the Director of CDFA makes a determination as to whether or not the pesticide should be listed as a toxic air contaminant.

This document describes the initial step in the process in which pesticides are selected for evaluation as toxic air contaminants and prioritized for the candidate list under the mandates of AB 1807/3219. This document includes twelve additions to the initial list of pesticides as well as pesticide use information and health effects summaries for all the candidate toxic air contaminants. This information is summarized in Table 1.

AB 1807/3219 lists five types of information to be used in prioritizing pesticides that enter the process. According to Article 1.5, Section 14022 of the Food and Agricultural Code, CDFA is instructed to "...give priority to the evaluation and regulation of substances based on:

- factors related to the risk of harm to the public
- amount or potential amount of emissions
- manner of usage of the pesticide in California
- persistence in the atmosphere
- and ambient concentrations in the community".

These factors have been addressed as follows:

A. Factors Related to the Risk of Harm to the Public

The principal factor used to select and rank pesticides in the AB 1807/3219 process is the potential of the pesticide to produce adverse health effects. CDFA has given priority to pesticides that may represent a hazard to the public based upon toxicology studies which indicate that these pesticides may produce developmental or reproductive effects, oncogenicity, chronic toxicity, be highly acutely toxic, or otherwise be potentially injurious. CDFA regulates pesticides through its authority to register, reevaluate, review, or cancel the registration of pesticides. In exercising this authority, CDFA investigates reports of possible adverse health effects resulting from pesticide use and assesses the potential for adverse health effects based on information submitted by the registrants of pesticides. Additionally, CDFA reviews toxicology studies submitted by registrants in response to the requirements of SB 950, the Birth Defects Prevention Act. These ongoing departmental activities, as well as information obtained from EPA and the open literature, provided the toxicology data for the selection and prioritization of candidate toxic air contaminants.

B. Potential Amount of Emissions

Two sources of data, the pesticide use report system and reports on the amount of active ingredient sold, were used to assess potential emissions of candidate toxic air contaminants. Since actual emission data were not available for these pesticides (see Section D, p.v), the pesticide use and sales data were the primary sources of exposure data used in the selection of the candidate pesticides.

Pesticide Use Report Data

One of the best sources of information for pesticide use is the pesticide use reporting system. Pesticide Use Reports (PUR) are filed with the county agricultural commissioner in the county where application occurs. The commissioners submit these reports to CDFA where they are compiled on computer tapes and summarized in the annual Pesticide Use Report. These reports contain information about the location of product use, what commodities or sites were treated, the amount of product applied, and the method of application (i.e. aircraft or ground equipment). All applications by licensed pest control operators and all applications of restricted materials must be

reported; however, when private applicators apply non-restricted materials, these applications are not required to be reported.

Sales Records

The Food and Agricultural Code requires pesticide manufacturers to pay an assessment fee based on the amount of active ingredient sold. These sales data are compiled into a summary report which lists the amount of active ingredient sold annually. In instances where an active ingredient is not a restricted use material, sales data may provide a more realistic assessment of potential emissions than pesticide use report information. For a pesticide for which there are three or fewer companies involved, sales data are considered to be confidential trade secrets and are not reported in this document.

C. Manner of Usage of the Pesticide in California

The manner of usage was considered in the initial selection of the candidate pesticides, but not in the prioritization. Several types of information concerning manner of use were considered in the selection of pesticides. Consideration was given to the type of application equipment that typically is used to apply a pesticide. Application methods such as air-blast sprayers and aircraft, which disperse spray mixtures into a large air volume, may contribute to the presence of the pesticide in air away from the site of application. When conventional hydraulic application equipment is used, the spray mixture is directed downwards toward the crop and is less likely to move from the field during application. Pesticides which are injected or worked into the soil are generally not subject to transport in air from the site of application and were not considered for the candidate list unless they are relatively volatile. Pesticide use report data were utilized to identify instances where application of a pesticide by aircraft accounted for a significant percent (>10%) of its reported use. Almost all of the candidate pesticides met this criterion. Crop use patterns were used to determine if appreciable amounts of a pesticide were applied to a large number of acres over a short or long period of time, or near significant population centers.

D. Persistence in the Atmosphere and Ambient Concentrations in the Community

Actual data on the persistence of pesticides in the atmosphere were not available for use in the selection and prioritization of the candidate toxic air contaminants;

however, factors which could influence the mobility and persistence in the atmosphere, such as vapor pressure and solubility were considered. These factors were not weighed as heavily in the selection process as reported use, sales data and the health effects data, because of the uncertainty of their complex environmental interactions. The issue of persistence in the atmosphere will be further pursued under AB 1807/3219.

CDFA has attempted to identify data which document community ambient air concentrations that could serve as a guide in the AB 1807/3219 process. These data were generally nonexistent and, hence, not available for use in the selection and prioritization of candidate pesticides.

SELECTION AND RANKING OF THE CURRENT CANDIDATE LIST

In selecting the pesticides to be evaluated under this program, an initial list was compiled based on potential adverse health effects. The pesticides on this list were then evaluated for their potential to be present in ambient air based on use information (Pesticide Use Reports and Sales Records), manner of usage, and physical-chemical properties. Additional factors, such as high public concern, were considered in a few cases, which are discussed in the health summaries. Pesticides which did not have significant use or which were applied in such a manner that little ambient air exposure would be expected were not placed on the list. The initial list of candidate pesticides consisted of suspected carcinogens, teratogens or highly acutely toxic chemicals. In the selection of the additional twelve pesticides, emphasis was placed on the inclusion of potential carcinogens and pesticides with chronic toxicity.

The entire candidate list was reprioritized when these new pesticides were added. The re-ranking of the original candidate pesticides was based on whether monitoring had been requested or completed (as well as the potential health effects). Because of the potential fifteen month time period between the request to ARB for monitoring and the receipt by CDFA of the monitoring report, it was decided to evaluate first the pesticides which had completed monitoring studies so that the monitoring data would not be outdated by the time the report was prepared. Thus the pesticides at the top of the list (i.e. methyl parathion, paraquat, azinphos-methyl, bromoxynil and benomyl) had some or all of the monitoring data collected in descending order of completeness. Of the original candidate pesticides, diquat dibromide and 2,4-D had not

entered the monitoring process. Upon reevaluation, it was determined that their health effects were of less concern than those of the new additions and they were placed at the bottom of the list. Where possible, potential carcinogens on the initial list such as chlorothalonil and captan, were moved up in priority. The ranking of the new additions to the list were based on potential carcinogenicity of the pesticide and then on other health effects, which included both chronic and acute effects (i.e. developmental, cholinesterase inhibition).

Finally, many of the pesticides are being reviewed under other programs both at CDFA and at EPA and there have been instances where a registration has been cancelled or not renewed. These actions have resulted in the removal of pesticides from the candidate list.

TABLE 1

SUMMARY OF DATA AND PRIORITY RANKING FOR CANDIDATE TOXIC AIR CONTAMINANTS								
Active Ingredient	Potential Adverse Health Effects	EPA Carcin. Classif.	Rat Oral LD50 (mg/kg)(4)	Pounds Sold (6)	Air App. (9)	Solubility (mg/l)	V.P. (mm Hg)	Pounds Used (14)
Ethyl parathion	cholinesterase inhibition, neuropathy, retinopathy	C	3.5 to 13	826,882	Y	2.40E+01 (10,11)	9.65E-6 (4,11)	814,091
Methyl parathion	cholinesterase inhibition, neuropathy, retinopathy	-	12	683,477	Y	6.00E+01 (4,11)	1.80E-05 (4,11)	172,778
Paraquat	lung lesions, mutagenicity	C	110 to 160	687,864	Y	7.00E+05 (10,12)	negligible (10,11)	568,440
Azinphos-methyl	cholinesterase inhibition, mutagenicity	D	4.6	519,854	Y	2.80E+01 (4,12)	1.60E-06 (4,12)	509,143
Bromoxynil (1)	teratogenicity, mutagenicity	C	260 to 690	252,699 (7)	Y	8.00E-06 (4,11)	4.80E-06 (4,11)	104,519 (7)
Benomyl	teratogenicity, oncogenicity, testicular lesions	C	>10,000	302,444	Y	2.00E+00 (10,11)	negligible (10,11)	107,786
Chlorothalonil	oncogenicity	B2	>10,000	734,771	Y	1.20E+00 (4,11)	2.00E-06 (4,11)	283,718
Captan	oncogenicity, mutagenicity	B2	10,000	1,039,086	Y	5.10E+00 (4,11)	8.00E-08 (4,11)	483,371
Chloropicrin	severe irritation of eyes, skin, respiratory tract	-	250	4,362,400	N	1.62E+03 (10,11)	2.40E+01 (10,11)	2,009,726
Methomyl	cholinesterase inhibition, oncogenicity	-	17	834,726	Y	5.79E+04 (10,11)	4.99E-02 (10,11)	854,553
Monocrotophos	cholinesterase inhibition, developmental effects, decreased fertility, oncogenicity, mutagenicity	-	18 to 23	see (8)	Y	miscible (4,11)	6.75E-05 (10,12)	57,680
Methyl bromide	neurotoxicity, mutagenicity	-	2,800 ppm (5)	12,913,952	N	1.35E+03 (10,11)	1.70E+03 (10,11)	10,031,345
S,S,S-Tributylphosphorotrithioate	neurotoxicity	-	175 to 200	see (8)	Y	2.30E+00 (4,12)	1.70E-06 (4,12)	756,047 (7)
Mancozeb (2)	oncogenicity, teratogenicity, thyroid effects	B2	>4,500	789,669	Y	insoluble (10,11)	negligible (10,11)	269,294
Maneb (2)	oncogenicity, teratogenicity, thyroid effects	B2	6,750	1,045,586	Y	insoluble (10,11)	negligible (10,11)	732,416
1,3-Dichloropropene (2)	oncogenicity	B2	713	14,491,483	N	2.32E+03 (10,12)	2.78E+01 (10,12)	14,057,100
Ziram (2)	oncogenicity	-	1,400	1,891,680	Y	6.50E+01 (10,11)	negligible (10,11)	982,520
Naled (2)	cholinesterase inhibition, fetal toxicity, testicular effects	-	250	309,326	Y	2.0E+03 (4,11)	5.0E-04 (4,11)	176,256
Carbofuran (2)	cholinesterase inhibition, mutagenicity, testicular effects, fetal toxicity	-	13.3	205,491	Y	3.51E+02 (4,11)	1.28E-06 (4,11)	237,728
Oxydemeton-methyl (2)	epididymal lesions, cholinesterase inhibition	-	60	142,255	Y	2.00E+05 (4,12)	2.85E-05 (4,12)	148,547
Bentazon (2)	fetal toxicity, hematological effects, pancreatic and testicular effects	-	1,100	see (8)	Y	5.30E+03 (4,11)	negligible (10,11)	214,913
Triadimefon (2)	teratogenicity, liver effects	-	568	215,149	Y	6.50E+01 (4,12)	4.5E-08 (4,12)	49,628
Methidathion (2)	cholinesterase inhibition, liver effects, oncogenicity	C	20	239,984	Y	2.20E+02 (10,12)	9.75E-07 (10,12)	306,972
Acephate (2)	cholinesterase inhibition, oncogenicity, mutagenicity	C	945	467,807	Y	7.90E+05 (10,12)	1.70E-06 (10,13)	449,616
Permethrin (2)	neonatal toxicity (eye, liver, kidney effects), liver effects	C	333 to 4,000	143,376	Y	7.00E-02 (4,11)	3.40E-07 (4,12)	122,857
Diquat dibromide	cataracts, nephrotoxicity	-	400 to 440	154,999	N	6.77E+05 (4,12)	negligible (10,11)	48,495
2,4-D (3)	oncogenicity, fetal toxicity	D	375 to 800	888,420 (7)	Y	7.29E+05 (4,11)	1.4E-07 (4,11)	875,697 (7)

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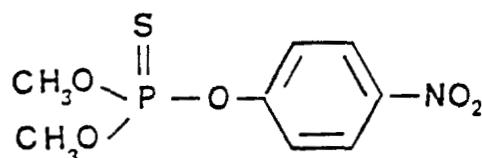
Footnotes on following page

TABLE 1 CONTINUED

Footnotes

- (1) Reported vapor pressure and solubility values are for bromoxynil octanoate.
- (2) Additions to the Candidate Toxic Air Contaminants List.
- (3) Reported value for solubility is for 2,4-D dimethyl amine and vapor pressure value is for 2,4-D free acid.
- (4) CDFA Registration Data.
- (5) LC50.
- (6) 1986 Sales for California.
- (7) Value is sum of reported pesticides which contain this active ingredient.
- (8) Confidential, Considered Trade Secret.
- (9) 1984 Pesticide Use Report for California ("Y" indicates that the ratio of amount air applied to total amount exceeds 10%).
- (10) Royal Chemistry Society Agrichemicals Handbook.
- (11) 25 Degrees Centigrade.
- (12) 20 Degrees Centigrade.
- (13) 24 Degrees Centigrade.
- (14) 1986 Pesticide Use Report for California.

METHYL PARATHION



Methyl parathion (O,O-dimethyl-O-4-nitrophenol phosphorothioate) is an insecticide-acaricide which is an active ingredient in 106 currently registered products. Methyl parathion containing products are formulated as dusts, granules, wettable powders, and emulsifiable concentrates. In 1986, reported methyl parathion use totaled 172,778 pounds of active ingredient. Methyl parathion is registered for use on many crops, however the majority of reported use occurred on rice (48,621 pounds of active ingredient), and alfalfa (46,393).

Methyl parathion is an organophosphate compound which produces its toxicity by cholinesterase inhibition. Metabolic conversion or environmental degradation to the oxygen analog, methyl paraoxon, is necessary for the anticholinesterase activity. Methyl parathion is highly toxic on an acute basis by all routes of exposure, and it has been classified as a Toxicity Category I compound by EPA. Methyl parathion is a restricted use pesticide in the State of California. The oral LD₅₀ in the rat is approximately 12 mg/kg, the dermal LD₅₀ for the rat is 67 mg/kg, and the inhalation LC₅₀ (4 hours) in the rat is 0.12 mg/l.

In addition to cholinesterase inhibition which is observed following acute, subchronic, and chronic exposures, retinal degeneration and sciatic nerve damage were identified in rats which were exposed to methyl parathion chronically in the diet at concentrations of 0, 0.5, 5 or 50 ppm (Daly, 1983). A NOEL of 5 ppm (0.18 mg/kg-day) was established, although further studies have been required by EPA to determine if functional impairment of the eye occurs at lower doses.

A possible increase in thyroid adenomas was observed in male Wistar rats at the highest concentration (50 ppm) in a two year dietary study (Bomhard et al., 1981); however, no oncogenic effects have been identified in either Fischer F344 rat or B6C3F1 mouse bioassays (NCI, 1979). Additional studies have been requested in both species due to design flaws in the

original studies. Methyl parathion was determined to be mutagenic in Salmonella typhimurium (Herbold, 1982) and E. coli assays (Fahrig, 1974) with and without metabolic activation. Furthermore, increases in sister chromatid exchanges (SCE's) were observed in mammalian cells in vitro (Singh et al., 1984).

EPA has set a provisional acceptable daily intake (PADI) at 0.0015 mg/kg/day based on a NOEL for cholinesterase inhibition of 0.3 mg/kg/day in a subchronic study in the dog. ACGIH³ has recommended a TLV-TWA for methyl parathion of 0.2 mg/m³ based on cholinesterase inhibition (ACGIH).

Methyl parathion was placed in Formal Reevaluation at California Department of Food and Agriculture for potential adverse effects identified in the chronic rat study, which include retinopathies and sciatic nerve damage. A risk assessment will be conducted on methyl parathion.

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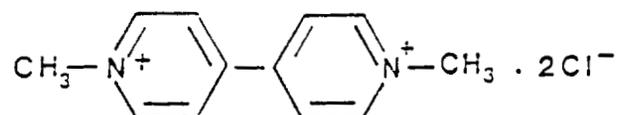
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PARAQUAT



Paraquat (1,1'-dimethyl-4,4'-bipyridinium ion; as dichloride or as dimethylsulfate) is an herbicide, defoliant, and plant growth regulator which is an active ingredient in four currently registered products formulated as liquids and emulsifiable concentrates. In 1986, reported paraquat use totaled 568,440 pounds of active ingredient. Paraquat is registered for use on many crops, however the majority of reported use occurred on cotton (235,180 pounds of active ingredient), grapes (78,936), almonds (67,112), and alfalfa (43,601).

EPA classified paraquat as a Category I chemical, and in California, it is a restricted use pesticide. Paraquat is poorly absorbed in the gastrointestinal tract and is primarily excreted as the unmetabolized parent compound. The toxicity associated with paraquat is dependent on the cationic moiety. The acute oral LD₅₀ in the rat ranges from 110-160 mg/kg bw; guinea pig, dog and cow range from 25-60 mg/kg, while the LD₅₀ for man is approximately 30 mg/kg bw. The inhalation LC₅₀ (4 hr) for the rabbit is 6.4 mg/m³, while in rats, the LC₅₀ is between 0.6-1.4 mg/m³. Acute inhalation exposure is extremely toxic due to local irritant action. Acute effects include pulmonary edema, epithelial swelling, and intraalveolar hemorrhaging.

The lung is the primary target organ in the dog, rat, rabbit, and man, due to the affinity of paraquat for lung tissue independent of route of exposure (Hayes, 1982). In a chronic study, Fischer F344 rats fed 25, 75, or 150 ppm paraquat cation exhibited fibrosis, hyperplasia, and non-neoplastic lesions, primarily at the 75 and 150 ppm levels, as well as varying degrees of pneumonitis (Woolsgrove, 1983). The onset of respiratory symptoms was frequently delayed. Rats chronically fed paraquat exhibited lenticular cataracts (NOEL <25 ppm), nerve degeneration, lung lesions, fibrosis, and/or tumors (NOEL 25 ppm or approx. 1.25 mg/kg/day) (Woolsgrove, 1983). Dog

feeding studies showed lung fibrosis, inflammation, and alveolar cell hyperplasia at 30 and 50 ppm, with a NOEL of 15 ppm (approx. 0.38 mg/kg/day) (Kalinowski et al, 1983).

Oncogenicity studies in the mouse are negative for both males and females. For albino mice fed 12.5, 37.5, and 100/125 ppm paraquat cation in a 99 week study, no oncogenic effects were noted (Litchfield, 1981). In a combined chronic toxicity and carcinogenicity study, Fischer F344 rats (70/sex/dose) were treated with 0, 25, 75, or 150 ppm paraquat cation, which resulted in equivocal lung lesion data. Observed increases in tumor incidence, primarily in high dose males, were not statistically significant (Woolsgrove, 1983). Squamous cell tumors in the head region were notably increased over controls in high-dose males, but group housing conditions prevented exclusion of other causal factors. Chromosomal aberration studies using human lymphocytes showed increased abnormal cells, while an increase in sister chromatid exchanges (SCE's) was reported for Chinese hamster cells (CHO) (Richardson, 1985). Paraquat is considered to be weakly mutagenic by EPA. EPA has classified paraquat as a Class C carcinogen (possible human carcinogen) due to the limited evidence of carcinogenicity from the available study dealing with one species, one strain, and with positive findings in the high-dose males only.

An ADI of 0.0045 mg/kg based on chronic lung effects has been set by EPA, while FAO/WHO has established an ADI of 0.002 mg/kg/day for paraquat dichloride and 0.0014 mg/kg/day for paraquat ion. The ACGIH TLY-TWA value is 0.1 mg/m³ for particles <5um, and 5 mg/m³ for those >5um based on paraquat's pulmonary toxicity.

Paraquat will be entering the risk assessment process at California Department of Food and Agriculture under SB950 (Birth Defect Prevention Act of 1984), based on potential adverse effects identified in the chronic toxicity/carcinogenicity, chronic toxicity, oncogenicity, and mutagenicity studies. In addition to these health effects, the considerable public concern about this pesticide was factored into the decision to include paraquat on the candidate 1807 list.

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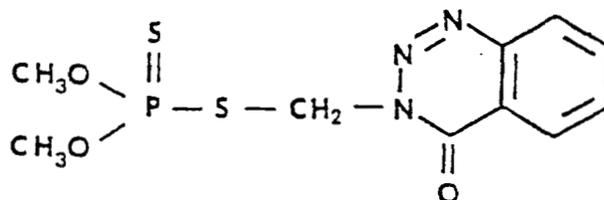
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AZINPHOS-METHYL



Azinphos-methyl (O,O-dimethyl S-[(4-oxo-1,2,3-benzotriazin-3(4H)-yl) methyl]phosphorodithioate), an organophosphate insecticide-acaricide, is an active ingredient in seven currently registered products. Azinphos-methyl containing products are formulated as emulsifiable concentrates (2 products), wettable powders (2), dusts (2), and granules (1). In 1986, reported azinphos-methyl use totaled 509,143 pounds of active ingredient. Azinphos-methyl is registered for use on many crops, however the majority of reported use occurred on almonds (244,051 pounds of active ingredient), peaches (68,749), pears (49,595), and apples (33,395).

The main mode of azinphos-methyl toxicity is cholinesterase inhibition. The oxygen analog of azinphos-methyl, produced by the microsomal oxidative desulfuration, is the active anticholinesterase agent. Azinphos-methyl is highly toxic on an acute basis (oral LD₅₀ rat: 4.6 mg/kg b.w.) and it has been classified by EPA as a Toxicity Category I chemical. Dermal LD₅₀'s for the rat range from 155 to 250 mg/kg. Because of the high acute toxicity, azinphos-methyl is a restricted use pesticide in the State of California.

Cholinesterase inhibition was the most significant effect noted in dietary chronic toxicity studies in the rat and the dog, and the NOEL for this inhibition is 5 ppm (Lorke 1966a, 1966b). Oncogenicity studies have reported conflicting results. In an NCI (1978) mouse feeding study, no increases in tumors were observed in either sex at concentrations of 31.3 and 62.5 ppm (males) or 62.5 and 125 ppm (females). Neoplasms of the thyroid gland and pancreas were observed in male rats which were fed 78 or 156 ppm for 80 weeks (NCI 1978). No tumors were seen in female rats in the same study (62.5 or 125 ppm). This study was judged to be unacceptable by EPA and CDFA and an additional rat oncogenicity study has been requested. Azinphos-methyl is currently classified by EPA as a Group D carcinogen (not classifiable as to human carcinogenicity).

The potential of azinphosmethyl to induce adverse mutagenic effects was examined in a cytogenetic study with human lymphocyte cultures. Azinphosmethyl (91.9%) was tested with human lymphocytes from one male and one female subject at 0, 1, 10, or 100 ug/ml for 24 hours without activation, and at 0, 5, 50 or 500 ug/ml for 2.5 hours with rat liver S9 activation, followed by 21.5 hours further incubation with two cultures per concentration per subject (Herbold, 1987). A several fold increase in aberrations (excluding gaps), metaphases with exchanges, and in metaphases with polyploidy at 500 ug/ml with activation was reported in the presence of a mitotic index approximately 43% of control. No increase was observed without activation at any concentration.

An ADI of 0.025 mg/kg b.w. has been set by EPA based on a NOEL of 5 ppm (0.25 mg/kg) for cholinesterase inhibition in rats with a ten-fold safety factor (EPA 1986b). FAO/WHO has set an ADI of 0.0025 mg/kg b.w. The American Conference of Governmental Industrial Hygienists (ACGIH) established a TLV-TWA of 0.2 mg/m³ which was extrapolated from oral exposures producing cholinesterase depression.

Azinphos-methyl has entered Formal Reevaluation at the California Department of Food and Agriculture based on cholinesterase inhibition, as well as under SB950 (Birth Defect Prevention Act of 1984) for potential adverse effects identified in mutagenicity studies.

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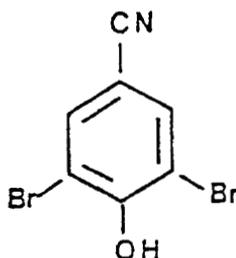
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BROMOXYNIL



Bromoxynil (3,5-dibromo-4-hydroxybenzonitrile) butyric acid ester and bromoxynil octanoate are selective herbicides which are active ingredients in three and eleven currently registered products, respectively. The free phenol form of bromoxynil is rarely used, however, and most formulations are comprised of either the octanoic acid ester or the butyric acid ester. The kinetics of these three compounds appear to be similar and it has been reported that the free phenol is the terminal residue following application. Products containing the butyric acid ester are formulated as emulsifiable concentrates and granules; those containing the octanoate are formulated as liquids and emulsifiable concentrates. In 1986, reported bromoxynil use totaled 8,304 pounds of active ingredient for the butyric acid ester and 96,214 pounds for the octanoate. The majority of reported use for the butyric acid ester occurred on rights of way (2,560 pounds of active ingredient), wheat (2,207), and garlic (67,112). The majority of reported use for the octanoate occurred on wheat (50,043 pounds of active ingredient), oats (12,194), rights of way (9,658), and barley (9,314).

Most toxicological studies have used either the phenol or the octanoic acid ester, and very little information is available on the butyric acid ester. The assessment, therefore, will be a compilation of all three forms of bromoxynil.

Bromoxynil has a relatively low acute toxicity. The oral LD₅₀ for the rat ranges between 260 and 690 mg/kg (depending on the formulation), the dermal LD₅₀ in rabbits is approximately 2 g/kg, and the LC₅₀ (4 hour) for the rat is 12 mg/l.

Major malformations (including hydrocephaly and micro- and anophthalmia) were observed in two oral rabbit studies (Copping 1983; Holson 1984). These effects were seen at 15, 30 and 60 mg/kg/day in one study and at 45 and 60 mg/kg/day in the second

study. Maternal toxicity was observed only at 60 mg/kg/day in both studies. Developmental effects have also been reported in the rat. Bromoxynil was administered by gavage to Sprague Dawley rats (28/group) on days 5-17 of gestation in dosages of 0, 5, 15, or 35 mg/kg/day (Copping, 1981). Skeletal anomalies, late uterine deaths, microphthalmia, and hydrocephaly were reported primarily in the higher doses, however a developmental NOEL was not established (developmental NOEL <5 mg/kg). Maternal toxicity was seen at dosages of 15 and 35 mg/kg/day, but not at 5 mg/kg/day. In a more recent study, pregnant Sprague Dawley rats were treated with bromoxynil in dosages of 0, 4, 12.5, or 40 mg/kg/day (p.o., 22/group) on days 6-15 of gestation (Rubin, 1987). While the NOEL for maternal toxicity and developmental toxicity were both 12.5 mg/kg, the fetal effects observed (skeletal anomalies and micro- and anophthalmia) confirmed the results reported in the previous study. In two studies utilizing percutaneous administration, possible adverse effects were also seen. In one study pregnant Sprague-Dawley rats, 8 per group, received Bromoxynil octanoate (33.8% purity) applied topically to the back, at levels of 0, 1, 2, 5, 10, 20, 40, and 100 mg AI/kg on days 6-15 of gestation (Hoberman, 1988a). An increased incidence of thoracic ribs and the occurrence of cervical ribs appeared to be compound related. Maternal and developmental NOELs were calculated to be 5 mg AI/kg/day based on erythema (maternal effect) and extra thoracic ribs (developmental effect). A second percutaneous study employed the sodium salt of unesterified bromoxynil (different from Bromoxynil octanoate which is being registered as a pesticide) (Hoberman, 1988b). Mated Sprague-Dawley rats, 23/group, were treated with bromoxynil, (sodium salt, purity unstated) at nominal levels of 0, 5, 10, 50, and 100 mg/kg/day, 6 hours/day, on days 6-15 of gestation. Maternal effects of slight decreases in body weight gains were seen at 100 mg/kg/day (NOEL = 50 mg/kg/day). Fetal effects observed were increased incidences of extra thoracic ribs at 50 and 100 mg/kg/day (NOEL = 10 mg/kg/day).

In a Swiss albino mouse oncogenicity study, a dose-related increase in proliferative liver lesions (hyperplastic nodules and tumors) was observed in male mice, but not female mice, at dietary concentrations of bromoxynil between 10 and 100 ppm (Johnson 1981). No oncogenic effects were reported in a feeding study conducted in Fischer 344 rats at concentrations of 0, 10, 30 and 100 ppm (Becci 1982). Bromoxynil induced gene mutations in mouse lymphoma cells *in vitro* (Cifone 1982) and increased chromosome breaks in CHO cells (Galloway 1982). Other studies for gene mutation, chromosomal aberrations, and DNA repair were negative (Gallo 1977; Holstrom and McGregor 1982; Rundell 1982). EPA has designated bromoxynil as a class C carcinogen (possible human carcinogen).

Bromoxynil entered the risk assessment process at California Department of Food and Agriculture under SB950 (Birth Defects Prevention Act of 1984) because of the identification of potential teratogenic, oncogenic and mutagenic effects. A draft of the risk assessment document is currently being reviewed within the California Department of Food and Agriculture.

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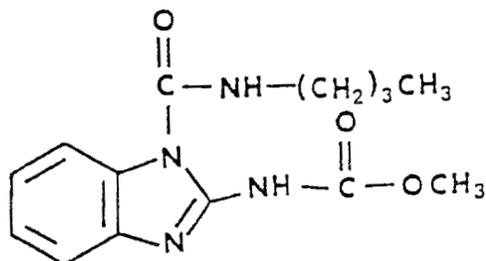
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BENOMYL



Benomyl (methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate), a systemic fungicide, is an active ingredient in nineteen currently registered products formulated as wettable powders, liquids, dusts, and soluble powders. In 1986, reported benomyl use totaled 107,786 pounds of active ingredient. Benomyl is registered for use on many crops, however the majority of reported use occurred on almonds (40,051 pounds of active ingredient), strawberries (11,771), and grapes (11,086).

The primary metabolite of benomyl is methyl-2-benzimidazole (MBC) which is further metabolized to several conjugated species and excreted in the urine. Both benomyl and MBC are reported to be direct acting toxicants. Benomyl has a low acute toxicity with an oral LD₅₀ in the rat >10,000 mg/kg and a 4 hour LC₅₀ >2 mg/l.

Benomyl and MBC have produced tumors in mice in separate feeding studies. Female CD-1 mice, which were fed benomyl at concentrations ranging from 500 to 5000 ppm, had an increased occurrence of hepatocellular adenomas and carcinomas in the mid and high dose groups (Wiechman 1980). There were no treatment-related tumor increases in the males. MBC induced an increase in hepatic adenomas and carcinomas in female CD-1 mice, but not males, at dietary concentrations from 500 to 7500 ppm (Beems et al. 1976). MBC in feed concentrations of 100 to 5000 ppm produced hepatocellular adenomas in female Swiss strain mice and hepatoblastomas in male mice (Wood 1980a). Neither benomyl nor MBC were oncogenic in CD rats (EPA 1986a). Benomyl and MBC are weak mutagens whose activities are consistent with spindle poisons (EPA 1986a). EPA has designated benomyl as a Class C carcinogen (possible human carcinogen).

Benomyl and MBC produced hepatotoxicity in chronic feeding studies in the dog, rat and mouse (Lee 1977; Sherman 1972; Wiechman 1980; Wood 1980a). Additionally, testicular lesions and spermatogenic effects were identified in the dog studies with a NOEL <100 ppm.

Developmental effects (principally microphthalmia) have been observed in rats in two teratology studies at doses which did not produce maternal toxicity (Feussner 1985; Barba 1982). A developmental NOEL between 3 and 30 mg/kg/day was established from these data.

EPA has set an ADI at 0.125 mg/kg/day and the TLV-TWA (ACGIH) is 10 mg/m³.

Benomyl has been placed in Formal Reevaluation at California Department of Food and Agriculture because of the oncogenic, teratogenic and testicular effects. A risk assessment document is under preparation.

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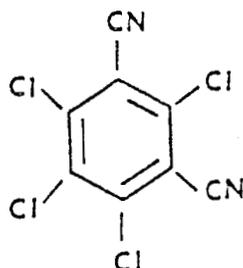
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CHLOROTHALONIL



Chlorothalonil (2,4,5,6-tetrachloro-1,3-benzenedicarbonitrile; 2,4,5,6-tetrachloroisophthalonitrile) is a fungicide which is an active ingredient in twenty-six currently registered products. Chlorothalonil containing products are formulated as flowables, granules, and wettable powders. In 1986, reported chlorothalonil use totaled 283,718 pounds of active ingredient. The three crops with the highest reported use were tomatoes (110,858 pounds of active ingredient), celery (53,987), and broccoli (25,915). Chlorothalonil also has noncrop application use.

Chlorothalonil has a low acute toxicity with the oral and dermal LD_{50} for the rat being greater than 10,000 mg/kg, and the inhalation $LC_{50} = 0.35$ mg/l. EPA has classified chlorothalonil as a Toxicity Category I chemical based on eye irritation.

Chlorothalonil is a potential oncogen and has produced tumors in both rats and mice. Male and female Fischer rats ingested chlorothalonil in the diet at 0, 40, 80, and 175 mg/kg/day (Wilson, 1985). Dose-related increases in renal tubular adenomas and carcinomas were observed in both males and females, as well as nonneoplastic renal changes (glomerulonephritis, tubular cysts, and cortical and medullary hyperplasia). Additionally, a two year feeding study in CD-1 mice at concentrations of 0, 750, 1500, and 3000 ppm produced an increased incidence in kidney tumors in the males (Wilson, 1983). Gene mutation assays for chlorothalonil were negative (Banzer, 1977a; 1977b; Jones, 1985) and most tests for chromosomal aberrations and DNA damage and repair were negative (Killeen et al., 1983a; 1983b). EPA has classified chlorothalonil as a Class B-2 carcinogen (probable human carcinogen).

EPA has set an acceptable daily intake (ADI) at 1.5 mg/kg/day, based on renal tubular lesions in a chronic dog study (EPA, 1984). The ADI (temporary) set by FAO/WHO is 0.03 mg/kg/day.

Chlorothalonil entered the risk assessment process at California Department of Food and Agriculture under Formal Reevaluation because of the potential for oncogenic effects. A draft risk assessment document has been prepared and is currently undergoing Departmental review.

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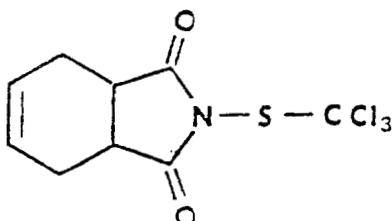
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CAPTAN



Captan (N-trichloromethylthio-4-cyclohexene-1,2-dicarboximide), a broad spectrum fungicide, is an active ingredient in 101 currently registered products. Captan containing products are formulated as dusts, flowables, and wettable powders. In 1986, reported captan use totaled 483,371 pounds of active ingredient. Captan is registered for use on many crops, however the majority of reported use occurred on grapes (200,050 pounds of active ingredient), almonds (83,329), prunes (65,003), and strawberries (55,469).

Tests using the technical grade captan report an oral rat LD₅₀ of 10 g/kg and an inhalation LC₅₀ of 17.56 mg/L (1 hr). The dermal rabbit LD₅₀ is 7.5 g/kg. Captan falls in Category IV for oral toxicity and in Category III for inhalation toxicity. In animals, captan is metabolized rapidly and excreted as phthalimide related compounds, mainly in the urine, and it does not accumulate in the body.

Captan's potential as an oncogen is indicated in mouse and rat studies. A Charles River CD rat study reported a marginal increase in treatment-related tumors (pancreatic, renal tubular adenomas and adenocarcinomas) mainly at the high dose in males fed 0, 25, 100 or 250 mg/kg (Rajasekaran, 1982). Renal tubular tumors occurred at 1%, 1%, 4% and 6% (control to high dose group). Given the low historical incidence of renal tubular adenomas and carcinomas in this strain of rat in this laboratory, these occurrences, with the apparent dose-response, were considered to be indicative of a significant oncogenic effect. A study of dietary captan with Osborne Mendel rats (50/sex/dose) reported a positive treatment-related trend (P=0.047) in adrenal cortex tumor incidence in high dose females, as well as thyroid C-cells (P=0.035) in both low and high dose females (NCI Bioassay, 1977). The low dose level was given at 4000 ppm for 21 weeks, then 2000 ppm for 59 weeks, while the high dose was administered at 8000 ppm for 21 weeks, then reduced to 4000 ppm for 39 weeks. Due to the variable incidence of spontaneous tumors in this strain and the low

overall occurrence, treatment-related response was not clearly established for the rat. CD-1 mice (80/sex/dose) were fed levels of 2000, 6000 or 10,000 ppm captan technical (90.7% purity) for 4 weeks, then increased to 6000, 10,000 and 16,000 ppm respectively for the remaining 109 weeks. (Wong, 1981). An increased dose-related incidence of benign and malignant duodenal tumors was observed in males and females. In a second CD-1 mouse study (100/dose/sex) dietary captan was fed at concentrations of 100, 400, 800 and 6000 ppm for 22 months (Daly, 1983). Post mortem inspection revealed increased intestinal masses, nodules and raised areas in female mice at 800 and 6000 ppm doses. Microscopic examinations indicated a compound related increased incidence in benign and malignant tumors in the small intestine for both sexes. A CD-1 male mouse study (190/dose) were fed 0 or 6000 ppm captan technical (89.1% purity) (Pavkov, 1985). Animals were sacrificed at 3, 6, 9, 12, 18, and 20 months for detailed examination. Significant pathologic changes were seen in the stomach at 3 months (hyperplasia), adenomas at 9 months and adenocarcinomas at 18 months, mainly in the small intestine.

Mutagenicity tests were positive in bacterial systems (Simmons et al, 1977; Bridges et al, 1973) and in mammalian in vitro systems (Ficsor et al, 1976), under some conditions. Human embryo lung cells, rat kangaroo cells, and Chinese hamster cell cultures were positive for sister chromatid exchanges and chromosomal aberrations (Tezuka et al, 1980). DNA damage/repair studies with several bacteria and a recombinant assay with S. cerevisiae (Tezuka et al, 1980) were positive. Dominant lethal tests were also positive (Tezuka et al, 1980). Based on the available evidence, EPA has classified captan as a Class B2 carcinogen (probable human carcinogen).

EPA and FAO/WHO have established an ADI of 0.125 mg/kg based on the potential oncogenic risk. The ACGIH TLV-TWA is 5 mg/m³ on the basis of available toxicity data including skin irritation and oncogenicity observed in animal studies.

Captan entered the risk assessment process at California Department of Food and Agriculture under SB-950 (Birth Defect Prevention Act of 1984), because of the oncogenicity and mutagenic potential of this pesticide. A draft document is currently undergoing intradepartmental review.

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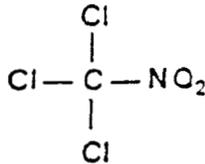
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CHLOROPICRIN



Chloropicrin (trichloronitromethane), a liquid fumigant, is an active ingredient in sixty-one currently registered products. Chloropicrin is a colorless, slightly oily liquid with an intense odor and lacrimatory effect, used as a soil, commodity, and structural fumigant. Because of severe irritating properties, it also serves as a warning agent when mixed with other gases. In 1986, reported chloropicrin use totaled 2,009,726 pounds of active ingredient. Chloropicrin is registered for use on many crops and sites, however the majority of reported use occurred on strawberries (1,406,593 pounds of active ingredient), roses (144,370), and fallow farm land (73,023).

Acute studies indicate chloropicrin is highly toxic and meets criteria for classification by EPA in Toxicity Category I. The acute oral LD₅₀ in rats is 250 mg/kg, and an acute dermal toxicity study in rabbits indicates an LD₅₀ of 100mg/kg (Harton and Rawl 1976). Inhalation LC₅₀ values in rats have been measured at 11.9 ppm for 4 hours, 25.5 ppm (0.178 mg/m³) for 1 hour, and 21.7 to 45.5 ppm for 30 minute exposure (Yoshida 1987). Chloropicrin has restricted use status within the State of California.

Chloropicrin vapor is a severe irritant of the eyes, skin and respiratory tract. Eye irritation and tearing may be induced from exposures as low as 2 mg/m³ (0.5 ppm), a value lower than the limit of detectability by odor, 7 mg/m³ (1.8 ppm). It also causes cough, nausea, vomiting and severe irritation of the skin. A respiratory study conducted on mice revealed an RD (concentration of an airborne irritant producing a 50% reduction in respiration rate) of 8 ppm for 6h/day for 5 days.

Relatively low concentrations of chloropicrin vapor in rats may produce acute symptoms such as dyspnea, cyanosis, large increases in lung weight, and diffuse pulmonary edema. Lethal exposure for humans is stated to be 119 ppm for 30

minutes, with death usually resulting from pulmonary edema (Buckley 1984).

Osborne-Mendel rats were treated by gavage to 20-26 mg/kg/day of chloropicrin, but due to excessive mortality early in the study an adequate evaluation of carcinogenicity was not made. No statistically significant increases over control values in tumor incidence were reported in B6C3F1 mice which were exposed by gavage to 33 or 66 mg/kg chloropicrin (NCI 1978). The mutagenic potential of chloropicrin is unknown.

The American Conference of Governmental Industrial Hygienists has established the threshold limit value (TLV) at 0.1 ppm, based on eye irritation reported at 0.3 to 0.37 ppm within 3 to 30 seconds exposure, which is below levels detectable by odor or irritation to man (ACGIH 1986). The OSHA permissible exposure level (PEL) is currently 0.1 ppm or 0.7 mg/m³.

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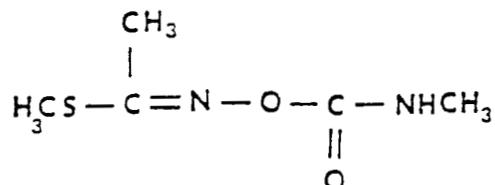
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METHOMYL



Methomyl (S-methyl N((methycarbamoyl)oxy)-thioacetimidate) is an insecticide which is an active ingredient in fifteen currently registered products formulated as liquids and soluble powders. In 1986, reported methomyl use totaled 854,553 pounds of active ingredient. Methomyl is registered for use on many crops, however the majority of reported use occurred on lettuce (head) (192,448 pounds of active ingredient), alfalfa (147,514), and grapes (143,867).

Methomyl is a carbamate compound whose mode of action is cholinesterase inhibition. Methomyl is highly toxic on an acute basis (oral LD₅₀ rat-male 17 mg/kg, female 24 mg/kg, LC₅₀ 300 mg/m³ - 4 hr. exposure, dermal rabbit LD₅₀ 5880 mg/kg) and it has been classified by EPA as a Toxicity Category I chemical. Because of its high acute toxicity, methomyl is a restricted use pesticide in the State of California. Cholinesterase inhibition was the most significant effect noted in rat, guinea pig, dog and monkey oral acute toxicity studies. Methomyl is readily absorbed through inhalation or dermal exposure, not requiring metabolism for its anticholinesterase effect. However, the cholinesterase inhibition is quickly reversed due to rapid metabolism of the compound.

A Charles River CD rat (35/sex/dose) two-year chronic dietary study at 0, 50, 100, 200, and 400 ppm showed a dose-related trend of reduced hemoglobin values in females. Kidney lesions were observed in males and females at 400 ppm, and spleen hematopoiesis in females fed 200 and 400 ppm. The NOEL for these effects was 100 ppm (4.9 mg/kg/day) (Kaplan and Sherman, 1977). In a chronic dietary study dogs treated with 0, 50, 100, 400 or 1000 ppm methomyl exhibited dose-related histopathological kidney as well as hematopoietic effects at the 400 and 1000 ppm levels (Kaplan and Sherman, 1977). There was no depression of plasma cholinesterase nor red blood cell acetylcholinesterase observed in either of these studies.

Oncogenicity studies, in which Charles River CD rats (80/sex/dose) were fed 0, 50, 100 or 400 ppm, and CD-1 albino mice (80/sex/dose) were fed 50, 100, 400, and 1000 ppm methomyl (99% purity), were negative (Kaplan 1981). These studies, however, were not conclusive and additional studies have been requested by the California Department of Food and Agriculture. A possible adverse DNA effect was indicated in a mitotic recombinant assay with Saccharomyces cerevisiae (Simmon et al, 1977).

An ADI of 0.025 mg/kg bw has been set by EPA based on methomyl's acute toxicity as an anticholinesterase agent, although no ADI has been established by FAO/WHO. No federal level has been set but the ACGIH TLV-TWA value is 2.5 mg/m³ based on cholinesterase inhibition.

Methomyl has entered the risk assessment process at California Department of Food and Agriculture under SB950 (Birth Defect Prevention Act of 1984) based on adverse effects identified in oncogenicity studies.

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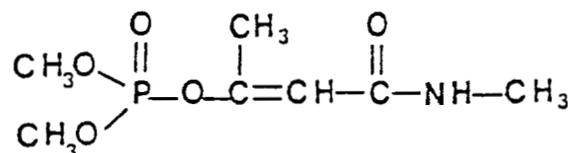
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MONOCROTOPHOS



Monocrotophos (O,O-dimethyl-O-(1-methyl-3-methylamino-3-oxo-propenyl) phosphate) is a contact and systemic liquid insecticide-acaricide which is an active ingredient in one currently registered product. In 1986, reported monocrotophos use totaled 57,680 pounds of active ingredient. The majority of reported use occurred on cotton (49,759 pounds of active ingredient), turf (3,751), and roses (2,655).

Monocrotophos is a potent cholinesterase inhibitor which does not need to be metabolized in order to produce this effect. The oral LD₅₀ for the rat is between 18 and 23 mg/kg, the dermal LD₅₀ is 354 mg/kg, and the inhalation LC₅₀ is 63 mg/m³ (4 hrs). Because of the high acute toxicity associated with monocrotophos, EPA has placed monocrotophos in Toxicity Category I, and the California Department of Food and Agriculture has classified monocrotophos as a restricted use material.

In a two year dietary study using Wistar rats at concentrations of 0, 0.01, 0.03, 0.1, 1.0, or 10 ppm, cholinesterase inhibition was the most significant effect observed (Brown, 1983). The NOEL for cholinesterase inhibition was determined to be 0.03 ppm (0.0015 mg/kg/day). Additionally in this study, a high incidence of pituitary tumors was observed in the females in the 10 ppm group; however, a corresponding high incidence in the control females prevented a definitive conclusion. Furthermore, no oncogenic effects were seen in a two year CD mouse study where the animals were fed diets containing 0, 1, 2, 5, or 10 ppm of monocrotophos (Brown, 1983).

Monocrotophos-induced gene mutations were observed in several *Salmonella typhimurium* assays, although the majority of these were negative (Simmon et al., 1984). No dominant lethality was seen in mice and tests for micronuclei formation were negative (Simmon et al., 1984). An increase in sister chromatid exchange (SCE) frequencies was reported in CHO

(Chinese hamster ovary) cells; an increase in mitotic recombinations was seen in Saccharomyces cerevisiae; and, an increase in unscheduled DNA synthesis (UDS) was observed in WI38 cells (Simmon et al., 1984).

Adverse reproductive effects have been reported in two 3-generation dietary studies in the rat. Monocrotophos concentrations used in these studies were 0, 0.1, 1.0, 3.0, and 10 ppm and 0, 2, 5, 12, and 30 ppm. The adverse effects include decreased pup viability, fertility and litter sizes, as well as a change in lactation indices (Felkner, 1985; Thorpe, 1982). The NOEL for reproductive effects from these studies was 1 ppm, while the systemic NOEL was 3 ppm (lowered body weights). No teratogenic effects have been reported (Dearlove, 1987; Dix and Wilson, 1972; Lu, 1983).

The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a TWA-TLV (time weighted average, threshold limit value) of 0.25 ppm for monocrotophos based on cholinesterase inhibition (ACGIH, 1986). EPA has set an ADI for monocrotophos at 0.00015 mg/kg/day based on cholinesterase inhibition in the chronic rat study reviewed above (EPA, 1982).

Monocrotophos will be entering the risk assessment process at California Department of Food and Agriculture under SB950 (Birth Defect Prevention Act of 1984), because of the adverse effects identified in reproductive, mutagenicity and oncogenicity studies.

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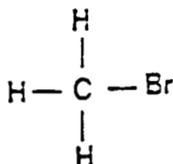
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METHYL BROMIDE



Methyl bromide (bromomethane) is a gaseous fumigant which is an active ingredient in ninety currently registered products. Methyl bromide is used as a soil, commodity, and structural fumigant. In 1986, reported methyl bromide use totaled 10,031,345 pounds of active ingredient. Methyl bromide is registered for use on many crops and sites, however the majority of reported use occurred on strawberries (3,081,162 pounds of active ingredient), structural pest control (2,220,337), and grapes (1,050,527).

Methyl bromide is a highly reactive gas which tends to break up and form bromide ions and methyl radicals. These products react readily with nucleophilic groups such as proteins and DNA. EPA has classified methyl bromide in Toxicity Category I, and the compound has restricted use status within the State of California. Fatal inhalation exposures in humans have been found ranging from 8,600 ppm to 60,000 ppm, while non-fatal poisoning has resulted from concentrations as low as 100-500 ppm. Neurological symptoms, including CNS damage, have been observed in humans with prolonged non-fatal exposure (Greenberg 1971). Pulmonary edema is the most evident symptom of acute poisoning from methyl bromide gas. The inhalation LC₅₀ in rats has been reported to be 2800 ppm for 30 minute exposure (Alexeeff 1985).

Mutagenicity has been demonstrated in various assay systems. Methyl bromide was found to be mutagenic in Salmonella typhimurium, Escherichia coli, and Klebsiella pneumoniae in the absence of metabolic activation (Moriya 1983). A dose-response increase in sister chromatid exchanges (SCEs) was observed in Chinese Hamster Ovary (CHO) cells (Tucker 1985, Rounds 1980). An increase in mitotic recombinations in S. cerevisiae was observed both in the presence and in the absence of metabolic activation (Mortelmans and Shepherd 1980).

A 90-day study conducted on Wistar rats at dose levels of 0, 0.4, 2, 10 or 50 mg/kg given by gavage 5 times a week, reported an increase in forestomach squamous cell carcinomas in the high dose group and a dose-related increase in hyperplasia

of the forestomach epithelium (Danse et al. 1984). Preliminary results from a two-year inhalation oncogenicity bioassay (completed 9/86 by the National Toxicology Program), indicated no increases in tumor formation in B6C3F₁ mice treated at 0, 10, 33 or 100 ppm, 6 hours/day/5 days/week (Haber et al. 1986).

A TLV-TWA of 5 ppm (20 mg/m³), as a time-weighted average, has been recommended by the American Conference of Governmental Industrial Hygienists (ACGIH 1986) to prevent serious neurological and pulmonary effects.

Methyl bromide will be entering the risk assessment process at the California Department of Food and Agriculture under SB950 (Birth Defects Prevention Act of 1984) based on potential adverse effects identified in mutagenicity studies.

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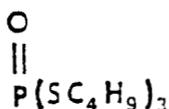
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S,S,S-TRIBUTYLPHOSPHOROTRITHIOATE



S,S,S-tributylphosphorotrithioate (DEF), an organophosphate herbicide, is an active ingredient in two products (formulated as emulsifiable concentrates) currently registered for use on cotton only. In 1986, reported S,S,S-tributylphosphorotrithioate use totaled 558,045 pounds of active ingredient.

DEF is a moderately toxic cholinesterase inhibitor (acute oral rat LD₅₀ 175-200 mg/kg, dermal rat LD₅₀ 168 mg/kg) and is a restricted use pesticide in the State of California. Studies indicate DEF may induce toxic effects by all routes of exposure.

In neurotoxicity inhalation experiments, hens receiving a single 4-hr exposure to DEF displayed ataxia, weakness, and histopathologic changes at 1585 mg/m³ (NOEL 878 mg/m³) (Thyssen and Schilde, 1976a). Hens treated with five 4-hr exposures to DEF had a NOEL for these same effects of 62 mg/m³ (Thyssen and Schilde, 1976a). Another inhalation study in which hens were exposed to fifteen 6-hr doses at concentrations of 0, 8, 21, and 84 mg/m³ reported a NOEL of 21 mg/m³ for effects including paresis, minimal sciatic degeneration, axonal degeneration and myelin sheath vacuolation (Thyssen and Schilde, 1978). Oral doses of DEF between 50 to 1000 mg/kg resulted in no histopathological effects in hens, but clinical symptoms were observed including loss of weight, leg weakness, unsteadiness, diarrhea, and oral drainage at all dose levels in that test group (Abou-Donia, 1979b). In the same study, hens were exposed dermally to 400 and 1000 mg/kg. Both doses produced ataxia, and histopathological changes, including degeneration of the central and peripheral neural tissue, were seen at the 1000 mg/kg level. While available studies support the existence of a DEF induced delayed neurotoxic effect, additional information is needed to clarify clinical and histopathological NOEL values related to oral, inhalation and dermal administration.

Chronic dietary rat studies have found cholinesterase inhibition (NOEL <5 ppm) and cytoplasmic vacuoles in liver cells (systemic NOEL 25 ppm) (Root, et al, 1967). A mouse

feeding study at concentrations of 0, 10, 30, 90 and 270 ppm, reported brain cholinesterase inhibition above 90 ppm, erythrocyte dose-related inhibition above 10 ppm, and reduced plasma cholinesterase activity at all doses (Hayes, 1985). A 2-year dog feeding study at doses of 5 to 50 ppm reported cholinesterase inhibition at all levels with no other adverse effects noted (FDA, 1983). Neurotoxicity was not evaluated in these studies.

Oncogenicity studies in the mouse (Hayes, 1985), rat (Root et al, 1967), and dog (FDA, 1983) were negative under study conditions.

No ADI has been established by EPA or FAO/WHO, and no TLV-TWA has been set by ACGIH.

At the present, DEF has not been identified under Formal Reevaluation nor SB950 (Birth Defect Prevention Act of 1984) for risk assessment at California Department of Food and Agriculture. The considerable public concern about this pesticide was factored into the decision to include DEF on the candidate 1807 list.

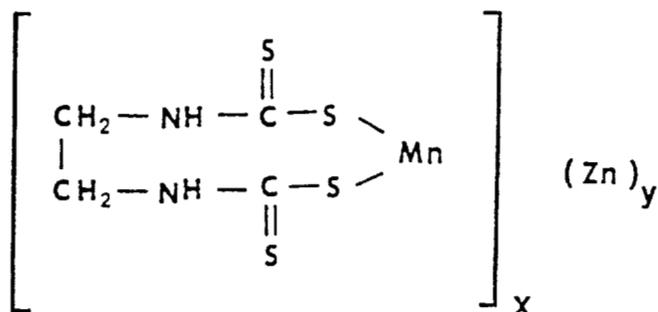
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MANCOZEB



Mancozeb (manganese zinc ethylenebisdithiocarbamate) is a fungicide which is an active ingredient in 23 currently registered products. Mancozeb containing products are formulated as wettable powders (11 products), liquids (4), dusts (6), soluble powders (1), and granules (1). In 1986, reported mancozeb use totaled 269,294 pounds of active ingredient. While mancozeb is registered for use on a wide range of crops, in 1986 the majority of reported use occurred on just three crops: potatoes (75,158 pounds of active ingredient), tomatoes (52,624), and onions (41,989).

Mancozeb is one of five currently registered pesticides that belong to the ethylene bisdithiocarbamate (EBDC) chemical group. Mancozeb inhibits enzyme activity by complexing with metal-containing enzymes, including those involved with adenosine triphosphate (ATP) production. The acute toxicity of mancozeb is relatively low. The oral and dermal LD₅₀ for the rat is greater than 4500 and 5000 mg/kg, respectively, and the inhalation LC₅₀ (4 hours) for the rat is 5.14 mg/L. EPA has classified mancozeb in Toxicity Category III. The principle concern with use of mancozeb, as with use of other EBDC's, is from exposure to ethylenethiourea (ETU), which is a contaminant, degradation product, and/or metabolite of EBDC products, and has been shown to produce significant thyroid, oncogenic and teratogenic effects (EPA, 1987b).

Mancozeb, when fed to Wistar rats (25/sex/group) at concentrations of 0, 25, 50, 100 or 1000 ppm in a 90 week chronic/oncogenicity study, produced significant dose-related increases in thyroid hyperplasia, and thyroid/body weight ratios in both sexes at 1000 ppm (Larson, 1965). Data did not indicate clearly whether other possible effects occurred.

The EBDC metabolite, ETU, increased incidences of thyroid adenomas and adenocarcinomas in two separate studies in rats,

and increased incidences of hepatomas in two strains of mice (EPA, 1987b). Administration of 175 or 350 ppm ETU in the diet of Charles River rats, 26/sex/group, for 18 months led to dose-related thyroid carcinomas, thyroid solid cell adenomas, and hyperplastic and simple goiter compared with no lesions observed in the control rats (Ulland et al., 1972). Thyroid carcinomas were found in 17 males and 8 females in the high dose group, and in 3 males and 3 females in the low dose group. One female at the high dose level and two at the low dose level had solid-cell adenoma. In a two-year study, Charles River rats, 68/sex/dose level, were placed on diets containing 0, 5, 25, 125, 250, or 500 ppm ETU (Graham et al., 1975). An increase in the number of rats with thyroid follicular adenocarcinoma/carcinoma and cataracts/keratitis was observed in the 250 and 500 ppm groups. In a study using two hybrid mouse strains (18/sex/group), animals were fed 646 ppm (equivalent to 215 mg/kg/day) ETU for 83 weeks (Innes, 1969). The incidence of liver tumors, classified as hepatomas, was significantly higher in treated groups (Strain X males, 14/16 treated vs. 3/14 control; strain X females, 18/18 treated vs. 0/18 control; strain Y males, 18/18 treated vs. 1/18 control; and strain Y females, 9/16 treated vs. 0/18 control).

The developmental toxicity of mancozeb was reported in a study in which mancozeb (83%, lot 4268), was given by gavage on days 6-15 of gestation to Sprague-Dawley rats (26/group) at dosages of 0, 2, 8, 32, 128 and 512 mg/kg/day (Kam et al., 1980). These exposures produced increased resorptions, dose-related forelimb flexure and other possible teratogenic effects (dilated ventricles, spinal cord hemorrhage and delayed/incomplete ossification of skull and ribs). These effects were observed at 512 mg/kg/day with a developmental NOEL of 128 mg/kg/day. Maternal toxicity (decreased body weight gain and decreased food intake) was reported at dosages of 128 and 512 mg/kg/day, and the maternal NOEL was set at 32 mg/kg/day. Since the developmental NOEL was considerably greater than the NOEL for maternal effects in this study, mancozeb was not considered to have developmental effects.

Teratogenic effects have been observed in animals exposed to ETU at doses that produced no maternal toxicity. In one ETU study, single daily oral doses of 100% ETU at 0, 5, 10, 20, 40 or 80 mg/kg were given to Wistar rats in one of three dosing regimes (Khera, 1973). The females were exposed 21-42 days before conception to gestation day 15 in Experiment I. In Experiment II, treatment was on days 6-15 of gestation, and in Experiment III, animals were dosed on days 7-20 of gestation. ETU induced central nervous system anomalies, i.e., meningo-encephalocele, exencephaly, hypoplastic cerebellum, and hydrocephalus, at doses of 20 mg/kg/day or more in Experiment

I, and at 10 mg/kg/day or more in Experiments II and III. Although fetal survival was unaffected, fetal growth was retarded at 40 and 80 mg/kg. In the same study, rabbits were treated on days 7-20 of gestation with oral doses of ETU at 0, 10, 20, 40, or 80 mg/kg/day. Malformations were not observed, although the number of resorption sites were increased and fetal brain weights were decreased at 80 mg/kg. In another ETU study, pregnant Wistar rats, which were given a single oral dose at 0, 15, 30 or 45 mg/kg on day 15 of gestation, produced hydrocephaly and microphthalmia in 90% of offspring at 30 mg/kg and above (Khera and Tryphonas, 1977). All live pups from the 45 mg/kg group died within 4 weeks of birth. In yet another trial, Wistar rats were given a single oral dose of 0, 1, 3, 5, 10, 20, 30 or 50 mg/kg ETU on day 17, 18, 19 or 20 of gestation (Lewerenz and Bleyl, 1980). Stillborn pups occurred in 0.8% of the 0 mg/kg dose group, compared with 15.6% of 30 mg/kg, and 45.9% of 50 mg/kg dose groups exposed day 20. All live pups in the 50 mg/kg group (exposure day 20) died within 4 days after birth. Twenty-eight of 127 surviving offspring from dams treated with 20 mg/kg and 19/119 treated with 10 mg/kg on days 18, 19 and 20 of pregnancy showed signs of hydrocephalus upon gross examination at 6 months of age. Hung (1985) reported that a single intragastric administration of either 120 or 240 mg/kg to pregnant SD rats gestation days 11 to 18 induced various types of CNS malformations, including spinal dysraphism, exencephaly, microencephaly, hydraencephaly and hydrocephalus. These malformations appeared to be dose-dependent and related to timing of administration. Swiss-Webster mice administered a single oral dose of 1600, 2000 or 2400 mg/kg ETU gestation day 12 produced significant hindpaw defects (Khera, 1984). Incidence ranges from the three dose levels were: hindpaw ectrodactyly, 2-6% at 1600 mg/kg, 4-20% at 2000 mg/kg, and 20-29% at the 2400 mg/kg; and hindpaw syndactyly, 3% at 1600, 6-14% at 2000 and 2-12% at 2400 mg/kg. In an experiment designed to investigate species differences in teratogenic response to ETU, 250 mg/kg of ETU was administered by gavage to Wistar rats (6/group) on day 12 or 14 of gestation, and 2000 mg/kg to ICR mice (12/group) on day 10 of gestation (Teramoto et al., 1983). All treated rat progeny had externally visible malformations e.g., mandibular micrognathia, cleft palate, short or kinky tail, and hypoplasia of genital tubercle. No significant malformations were observed in the mouse experiment.

Results of gene mutation and DNA repair assays with mancozeb were negative (CDFA, 1988). One in vitro sister chromatid exchange (SCE) assay in CHO cells, tested from 0 to 17.5 ug/ml of mancozeb, produced an increase in SCE's, without activation, in two trials, and, with mouse liver activation, an

increase in SCE's in one unrepeated trial (Ivett and Myhr, 1984).

EPA has classified mancozeb and ETU as Class B2 carcinogens, based on evidence of increased tumor incidence in two separate studies in two animal species. Because chronic studies on which to base an acceptable daily intake (ADI) for mancozeb are inadequate, EPA has set a provisional acceptable daily intake (PADI) of 0.003 mg/kg/day, based on a NOEL of 3.0 mg/kg/day from a subchronic dog feeding study (EPA, 1987a). EPA placed all products containing EBDC's into Special Review in July, 1987, because of concern with oncogenic risk to humans and potential thyroid and teratogenic effects (EPA, 1987c).

FAO/WHO has established a temporary acceptable daily intake (TADI) for dithiocarbamate fungicides of 0.02 mg/kg/day, with a full report due in 1988 (FAO/WHO, 1987).

Mancozeb entered the risk assessment process at the California Department of Food and Agriculture under Formal Reevaluation because of the identification of thyroid and possible teratogenic effects from mancozeb exposure, and possible thyroid, oncogenic, teratogenic and mutagenic effects from exposure to the principle metabolite, ETU.

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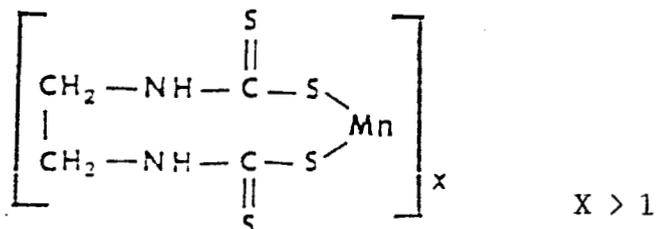
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MANEB



Maneb ([[1,2-ethanediy]bis[carbamo]dithioato]](2-) manganese) is a fungicide which is an active ingredient in seventeen currently registered products. Maneb containing products are formulated as wettable powders (6 products), liquids (1), dusts (8), emulsifiable concentrates (1), and granules (1). In 1986, reported maneb use totaled 732,416 pounds of active ingredient. While maneb is registered for use on a wide range of crops, in 1986 the majority of reported use occurred on just three crops: lettuce (475,063 pounds of active ingredient), almonds (36,655), and broccoli (30,826).

Maneb is one of five currently registered pesticides in the ethylenebisdithiocarbamate (EBDC) subgroup of the organosulfur dithiocarbamate compounds. These compounds are unstable tending to polymerize in the presence of certain ubiquitous metallic ions. Maneb inhibits enzyme activity by complexing with metal-containing enzymes, including those involved with adenosine triphosphate (ATP) production. The dominant environmental degradation products are ethylenebisdiisothiocyanato sulfide (EBIS) and ethylenethiourea (ETU). ETU is also an animal metabolite as well as a manufacturing contaminant. Significant amounts of EBDC residues have been shown to convert to ETU in mammals (Federal Register, 1987). EBDC residues also convert to ETU in commercial food processing, and home cooking (EPA PD#1, 1977). ETU is thought to be responsible for the antithyroid and teratogenic effects as well as the oncogenic potential of maneb. The acute rat oral LD₅₀ for maneb is 6750 mg/kg (Clayton, 1957), and for ETU it is 1832 mg/kg (Graham & Hansen, 1972). Adverse effects related to ETU are presented due to its inherent presence in maneb.

In an oncogenicity study, CD rats (26/sex/group) were given 175 or 350 ppm ETU (97%) in their diet for 18 months followed by a control diet for 6 months (Ulland et al., 1972). At the high dose, thyroid carcinomas were found in 17(65%)

males (2 with pulmonary metastases) and 8(31%) females, as well as hyperplastic goiter in 17(65%) males and 13(50%) females. At the low dose thyroid carcinomas occurred in 3(11.5%) males and 3(11.5%) females while hyperplastic goiter was seen in 9(35%) males and 6(23%) females. No thyroid carcinomas were seen in 32 male and 32 female control animals. In another ETU study, CD rats (68/sex/group) were fed diets containing concentrations of ETU of 0, 5, 25, 125, 250, or 500 ppm (Graham et al, 1975). These results showed ETU as a thyroid carcinogen when fed at levels of 250 and 500 ppm for 2 years. Thyroid tumors in rats fed the highest ETU concentration were generally follicular adenocarcinomas. In a bioassay study, which screened pesticides and industrial chemicals for tumorigenicity in mice, groups of Strain X and Strain Y mice (18/sex/dose) were given 215 mg/kg/day (646 ppm) ETU or 46.4 mg/kg (158 ppm) maneb from day 7 - 28 of age by gavage (Innes et al., 1969). Then, after weaning, subsequent daily doses of 215 mg/kg ETU or 46.4 mg/kg maneb were mixed in the diet until animals were approximately 83 weeks of age. Mice receiving ETU developed hepatomas (Strain X males, 14/16 treated vs. 3/14 controls; Strain X females, 18/18 treated vs. 0/18 controls; Strain Y males, 18/18 treated vs. 1/18 controls; and Strain Y females, 9/16 treated vs. 0/18 controls). Maneb was nontumorigenic under conditions of this study. In a subchronic toxicity study of maneb, groups of Strain A and C57BL mice were given 500 mg/kg, one dose/week for 6 weeks (IARC, 1976). A significant increase in benign lung tumors was observed in Strain A mice after 9 months (23/42 test animals, compared to 12/45 controls). EPA has classified maneb and ETU as B2 oncogens (probable human carcinogens).

Teratogenic effects have also been associated with ETU exposure in laboratory animals. A teratology study was conducted with maneb and ethylenethiourea in which pregnant CD rats and CD₁ mice were given water suspensions of 80% maneb or ETU (recrystallized) on days 6-20 gestation in the rat, and days 6-15 in the mouse (Chernoff, 1977). Rats received 120, 240 or 480 mg/kg/day 80% maneb, or 5, 10, 20, 40 or 80 mg/kg/day ETU. Maneb-treated rats exhibited a dose-related reduction in maternal weight gain ($p < 0.01$) with liver/body weight ratios slightly elevated. Significant decreases in fetal weight and caudal ossification centers were observed at the high dose. Varying degrees of hydrocephaly were seen in the ETU-treated rat high dose group. Mice received 300, 600, or 1200 mg/kg/day of maneb, or 100 or 200 mg/kg/day of ETU. The maneb-treated mice exhibited a significant ($p < 0.001$) dose-related increase in maternal liver/body weight ratios, and fetal dose-related decrease in caudal ossification centers ($p < 0.05$). ETU-treated mice showed elevated maternal liver/body weight ratios in both dose groups. Fetal effects seen were

exencephaly (not significant) and a statistically significant elevated incidence of supernumerary ribs. In a separate ETU study, single daily oral doses of 100% ETU at 0, 5, 10, 20, 40 or 80 mg/kg were given to Wistar rats in one of three dosing regimes (Khera, 1973). The females were exposed 21-42 days before conception to gestation day 15 in Experiment I. In Experiment II, treatment was on days 6-15 of gestation, and in Experiment III, animals were dosed on days 7-20 of gestation. ETU induced central nervous system anomalies, including meningoencephalocele, exencephaly, hypoplastic cerebellum, and hydrocephalus, at doses of 20 mg/kg/day or more in Experiment I, and at 10 mg/kg/day or more in Experiments II and III. While fetal survival was unaffected, fetal growth was retarded at 40 and 80 mg/kg. The incidence of most deformities was dose-dependent. ETU was teratogenic in rats at doses that produced no apparent maternal toxicity or fetal lethality. In the same study rabbits were treated on days 7-20 of gestation with oral doses of ETU of 0, 10, 20, 40, or 80 mg/kg/day. The rabbit results suggested increased incidence of resorption sites and decreased brain weight at 80 mg/kg, with no malformations observed. In a separate study pregnant Wistar rats, given a single oral dose of ETU at 0, 15, 30, or 45 mg/kg on day 15 of gestation, exhibited hydrocephaly and microphthalmia in 90% of the offspring receiving 30 mg/kg or above (Khera & Tryphonas, 1977). All live pups in the 45 mg/kg group died within 4 weeks of birth. Other research was conducted by Khera with Swiss Webster mice (11-17/group) treated with ETU (99%) by gavage with single doses of 0, 1600, 2000, or 2400 mg/kg, on day 12 of gestation (Khera, 1984). Maternal toxicity was observed at 2000 mg/kg and 2400 mg/kg (reduced weight gain, increased mortality). The percent incidence range for significant defects were: hindpaw ectrodactyly, 2-6% at 1600 mg/kg, 4-20% at 2000, and 20-29% at 2400 mg/kg; and hindpaw syndactyly, 3% at 1600 mg/kg, 6-14% at 2000, and 2-12% at 2400 mg/kg. Minor incidences of cleft palate and hindpaw polydactyly were also observed. Reduced fetal weight and increased incidence of resorptions were exhibited at all treatment levels. A rat study reported postnatal hydrocephalus at 10 mg/kg ETU and higher, with single oral doses of 1-50 mg/kg ETU on day 17, 18, 19, or 20 of gestation (Lewerenz & Bleyl, 1980). Progeny viability, measured by survival indices during the nursing period, was impaired in a dose-related manner after maternal treatment with doses of 10 mg/kg or more. Administration of 1, 3, or 5 mg/kg ETU on day 18 of gestation did not adversely affect postnatal development. The number of stillborns was significantly increased at dose levels of 30 and 50 mg/kg, with the highest incidence observed in litters from dams given ETU on day 20 of gestation. The percentages of stillborns were 16 and 46 at 30 and 50 mg/kg, respectively. All live pups in the 50 mg/kg group (gestation day 20) died

within 4 days after birth. Hung (1985) showed that a single intragastric administration of either 120 or 240 mg/kg ETU to pregnant SD rats from, gestation days 11 to 18, induced various types of CNS malformations, including spinal dysraphism, exencephaly, microencephaly, hydraencephaly, and hydrocephalus. These malformations appeared to be dose-dependent and related to timing of administration. In an experiment designed to investigate species differences in response to the teratogenic effects, ETU was administered to Wistar rats (6/group) and ICR mice (17 control, 10 test group) by gavage at concentrations of 0, or 250 mg/kg to rats on day 12 or 14 of gestation, and to mice at 0, or 2000 mg/kg on day 10 of gestation (Teramoto, 1982). ETU was teratogenic in rats with all fetuses exhibiting visible malformations, such as cranial meningocele, mandibular micrognathia, cleft palate, omphalocele, anal atresia, and oligodactyly. On the other hand, ETU was not teratogenic in mice at 2000 mg/kg.

Possible adverse effects have been reported in some mutagenicity studies conducted with maneb. One CHO/HGPRT mammalian cell mutation assay tested Chinese hamster ovary (CHO) cells with and without metabolic activation at concentrations of maneb (88.1% purity) ranging from 0.05 up to 50 ug/ml (Thomas, 1985a). No evidence of mutagenic response was seen. In another study, maneb (88% purity) was investigated for the potential to induce sister chromatid exchanges in CHO cells with and without metabolic activation (Thomas, 1986). Test concentrations ranged from 0.15 to 50 ug/ml. A positive effect was observed with >20% increase +S9(rat) at 15 and/or 30 ug/ml in two trials, and with +S9(mouse) at 5 ug/ml, but not at 10 ug/ml. A third study tested maneb (88.1% in DMSO) for induction of unscheduled DNA synthesis (UDS) in SD rat hepatocytes, at 0, 0.15, 0.5, 1.5, 5.0, and 15.0 ug/ml (Thomas, 1985b). No adverse effect was observed.

FAO/WHO has established a temporary acceptable daily intake (TADI) for dithiocarbamate fungicides of 0.002 mg/kg/day, with a full report due in 1988 (FAO/WHO, 1986). EPA placed all products containing EBDC's into Special Review July 17, 1987 due to concern regarding oncogenic risk to humans and potential thyroid and teratogenic effects.

Maneb has been placed in Formal Reevaluation at the California Department of Food and Agriculture based upon potential adverse effects from EBDC exposure and the EBDC metabolite, ETU, identified in oncogenicity studies, as well as the teratogenic potential of ETU.

**MANEB
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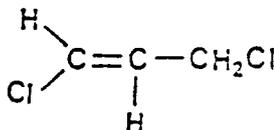
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1,3-DICHLOROPROPENE



1,3-Dichloropropene, a liquid, volatile fumigant, is an active ingredient in five currently registered products. It is injected into the soil prior to planting in order to control nematodes, fungi, insects, and weeds. In 1986 over 14 million pounds of 1,3-dichloropropene were used to fumigate soils for the production of a wide range of crops. The five crops or sites with the highest reported use were carrots (2,325,129 pounds of active ingredient), tomatoes (1,736,190), open land (1,231,094), broccoli (1,221,307), and sugarbeets (1,041,922).

1,3-dichloropropene is believed to act by chemical combination with a nucleophilic group, e.g., amine, sulfhydryl or hydroxyl, and an essential enzyme of the targeted pest. Telone, usually a half and half mixture of cis- and trans-isomers, has moderate acute toxicity. The oral LD₅₀ has been reported to be 713 mg/kg in male rats, and 470 mg/kg in female rats (Torkelson and Oyen, 1977). In rabbits, sexes combined, the dermal LD₅₀ was found to be 504 mg/kg. Liver and kidney are the sites primarily affected. The inhalation (4 hr) LC₅₀ for the rat has been measured at 729 ppm (~3280 mg/m³) (EPA, 1985). EPA has classified telone a restricted use pesticide, in Toxicity Category II for oral and eye exposure, and Toxicity Category III for dermal exposure.

Clear evidence of carcinogenicity has been demonstrated in both sexes of rats and mice by the results of a NTP two year chronic/carcinogenicity study (NTP, 1985). Technical grade 1,3-dichloropropene (88-90%) was given to Fisher 344/N rats by gavage in corn oil at dosages of 0, 25 or 50 mg/kg, 3 times per week, or to B6F3C1 mice at dose levels of 0, 50 or 100 mg/kg, 3 times/week. Dose-related increases of neoplastic lesions associated with administration of telone included squamous cell papillomas (male and female rats, female mice), squamous cell carcinomas of the forestomach (male rats, female mice), transitional cell carcinomas of the urinary bladder (female mice), alveolar/bronchiolar adenomas (female mice), and neoplastic nodules of the liver (male rats). Although the

study in male mice was considered inadequate due to deaths of 25/50 vehicle control animals during weeks 48-51, increases of alveolar/bronchiolar neoplasms, squamous cell papillomas, and transitional cell carcinomas in the high dose male mice suggest telone may have been causative in lesion production. The development of tumors at locations distant (e.g., liver, urinary bladder, lung) from the site of application may be related to the formation of reactive intermediates within the body.

Positive results in mutagenicity tests tend to support the oncogenicity findings, and suggest that telone is a direct acting base-pair substitution mutagen (IARC, 1986). Both cis- and trans- isomers of telone were found to be mutagenic when tested with Salmonella typhimurium tester strains TA1535, TA1978, and TA100, with and without microsomal activation (Neudecker et al., 1977 and De Lorenzo et al., 1977). Few other mutagenicity assays, however, have shown positive results (CDFA, 1988, and EPA, 1986).

EPA categorized 1,3-dichloropropene as a probable human carcinogen (B2), based largely on tumor data from the NTP study in rats and mice (EPA, 1986a). The California Department of Health Services Director has proposed a drinking water standard with a maximum contaminant level (MCL) of 0.5 ug/l for telone in California drinking water (CDHS, 1988).

1,3-dichloropropene has entered the risk assessment process at the California Department of Food and Agriculture under SB950 (Birth Defects Prevention Act of 1984) because of identified oncogenic and mutagenic effects.

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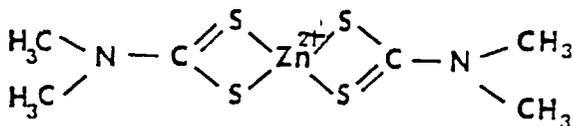
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ZIRAM



Ziram (zinc dimethyldithiocarbamate) is a fungicide which is an active ingredient in seventeen currently registered products. Ziram containing products are formulated as wettable powders (9 products), liquids (2), dusts (1), and granules (5). In 1986, reported ziram use totaled 982,520 pounds of active ingredient. While ziram is registered for use on several crops, in 1986 the majority of reported use occurred on almonds (879,831 pounds of active ingredient). The acute oral rat LD₅₀ for ziram is 1400 mg/kg.

The oncogenic potential of ziram was investigated in an NTP carcinogenicity bioassay conducted with F344/N rats and B6C3F1 mice (Goldman, 1983). Both species, 49 or 50 males/50 females/group, were fed ziram (89% purity with 6.5% thiram). Rats received 0, 300, or 600 ppm for 103 weeks. An increased dose-related trend for thyroid C-cell adenomas and carcinomas was found in male rats. The C-cell carcinomas occurred at 0/50 for control males, 2/49(4%) in low dose males, and 7/49(14%) in high dose males. The combined rat adenomas/carcinomas were 4/50(8%), 9/49(18%), and 12/49(24%), which was statistically significant at the high dose. There was no evidence for follicular cell changes. The systemic NOEL was >600 ppm, and apparent oncogenic NOEL <300 ppm. The mice received 0, 600, or 1200 ppm for 103 weeks. Alveolar/ bronchiolar adenomas were increased in female mice, with 2/50(4%) controls, 5/49(10%) at low dose, and 10/50(20%) at high dose. Combined alveolar/bronchiolar adenomas/carcinomas in the females were 4/50(8%), 6/49(12%), and 11/50(22%). Both tumor types were significant at the high dose. The systemic NOEL (body weight) was <600 ppm with a possible oncogenic NOEL of <600 ppm. The interpretation of lung tumor increase in mice was complicated by an intercurrent Sendai virus infection.

Reproductive effects were examined in a three generation reproduction study conducted with Sprague-Dawley rats (unknown#/sex/group) fed ziram (98%) at 0, 280, 1260, or 2800 ppm for 119 days; then, due to toxicity, levels were reduced to 140, 770, or 1400 ppm (Ravert, 1979). Adverse effects noted

were decreased fertility index, lactation index, litter size and pup survival in all generations, especially at high dose, with a NOEL = 140 ppm.

Toxic reactions to ziram include glycogenolysis, accumulation of acetaldehyde in the blood of animals fed ethanol, and testicular atrophy (Goldman 1983). Ziram metabolites include ferbam, thiram, tetramethylthiourea, and carbon disulfide. A chronic two-year study in which weanling Rochester strain rats (ex-Wistar, 1923), 25/sex/group, were fed diets of 0, 0.0025% (25 ppm), 0.025% (250 ppm), or 0.25% (2500 ppm) ferbam or ziram, reported retarded growth at the 0.25% (approximately 125 mg/kg/day) level with both compounds (Hodge et al., 1956). An abnormal neurological effect was seen after two months in males and females with both compounds at the 0.25% level (no numbers noted); when picked up by the tail they did not thrust their hind legs out like normal rats, but clasped the hind feet or crossed and stiffened the hind legs. Histological examination found atrophic testes in the 0.025% and 0.25% groups, apparently not dosage related. Under study conditions both compounds were not carcinogenic. In another study, a comparative toxicological assessment of some dithiocarbamates found ziram possessed greater cumulative teratogenic, gonadotoxic, and blastogenic effects on rats, mice, and rabbits than other pesticides tested, exhibiting high cytogenic activity as well (Antonovich, 1972).

Ziram has entered the risk assessment process at the California Department of Food and Agriculture under SB950 (Birth Defect Prevention Act of 1984) based on the identification of potential oncogenic effects.

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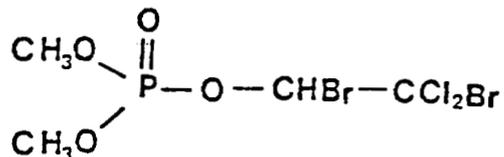
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NALED



Naled (1,2-dibromo-2,2-dichloroethyl dimethyl-phosphate), an organophosphate insecticide, is an active ingredient in 38 currently registered products. Naled containing products are formulated as liquids (7 products), dusts (16), emulsifiable concentrates (9), and 6 miscellaneous products such as baits. In 1986, reported naled use totaled 176,526 pounds of active ingredient. While naled is registered for use on a wide range of crops, in 1986 the majority of reported use occurred on just three crops: cotton (41,074 pounds of active ingredient), sugarbeets (40,664), and strawberries (19,555).

Naled readily converts to the more toxic dichlorvos (2,2-dichlorovinyl dimethyl phosphate) by debromination in plants and animals. Both compounds are cholinesterase inhibitors (ACGIH, 1986). The acute oral rat LD₅₀ for naled is 250 mg/kg, while the oral LD₅₀ value for dichlorvos in the female and male rat is 56 and 80 mg/kg, respectively (Gaines, 1960; Durham, 1957). Naled inhalation LC₅₀ values in Sprague-Dawley female and male rats were determined to be 190 and 200 mg/m³ (Rittenhouse, 1985), while the dichlorvos inhalation LC₅₀ value for the rat is >198 mg/m³, and is 218 mg/m³ in mice (Shell, 1970). The dermal naled rat LD₅₀ is 800 mg/kg, and for dichlorvos it is 75 mg/kg and 107 mg/kg for female and male rats, respectively. EPA has placed naled in Category II, based on available acute oral and dermal data, and in Category I because of primary eye irritation data (EPA Fact Sheet, 1983).

Naled oncogenicity was explored in several studies. In a chronic/oncogenicity experiment, Sprague Dawley rats, 65/sex/dose, were treated daily with 0, 0.2, 2.0, or 10 mg/kg of naled (91.0% purity) by gavage for 105 weeks. While there initially appeared to be an increased incidence of male mammary adenocarcinomas, upon re-analysis these values were determined to be within historical control values. The significant adverse effect detected was cholinesterase inhibition in brain, plasma and red blood cells, with a NOEL for these effects of 0.2 mg/kg/day (Batham, 1984; Cushman, 1987). In another oncogenicity study, CD₁ mice (60/sex/group) were given naled

(92.7% purity) at dosages of 0, 3, 15, or 75/50 mg/kg/day by gavage for 89 weeks. The high dose group received 75 mg/kg for 27 weeks, which was then reduced to 50 mg/kg/day for the remaining 62 weeks (Johnson, 1984). No oncogenic effects were found. There was a statistically significant trend for decreased body weight, especially in males. However, no changes in general appearance or behavior related to the test article were observed, and the hematology data did not indicate any treatment related effects. The systemic NOEL = 15 mg/kg based on increased mortality at the 75 mg/kg dose.

The oncogenic potential of the naled metabolite, dichlorvos, has also been examined in several studies. In a study commissioned by NTP, dichlorvos (99% purity) dissolved in corn oil was administered by gavage to F344/N rats (50/sex/group) for 103 weeks at dosages of 0, 4 or 8 mg/kg/day. Significant frequencies of potentially dose-related pancreatic adenomas and mononuclear leukemia were seen in males as well as mammary tumors in females (Chan, 1987). An inhalation study with dichlorvos was performed with CFE rats (50/sex/group) exposed to nominal concentrations of 0, 0.05, 0.5, or 5 ug dichlorvos/l, 23 hr/day for two years. Actuarial analysis showed no dose-related increase in age-adjusted tumor rates, although a significant trend for pituitary adenomas was seen in high dose females (Blair et al., 1976). In a mouse study commissioned by NTP, 99% pure dichlorvos, dissolved in corn oil, was administered by gavage to B6C3F1 mice (50/sex/group) for 103 weeks at dosages of 0, 10, or 20 mg/kg/day for males, and 0, 20, or 40 mg/kg/day for females (Chan, 1987). A NOEL was established at 10 mg/kg/day in males and 20 mg/kg/day in females, based on papillomas of the forestomach. These tumors in conjunction with gavage-dosing, and an extremely high-fat diet, cloud the interpretation of the significance of these results for humans. In addition, female controls had an unusually high incidence of stomach papillomas, indicating a possible vehicle effect.

While several mutagenicity studies have been reviewed, they provided inadequate information for complete assessment of the mutagenic potential of naled. Four studies reported adverse effects in S. typhimurium, with mutagenicity indicated in either or both Strains TA100 and TA1535 (CDFA, 1988). One study also found positive results with B.subtilis Strains TKJ5211 and TKJ6321.

Naled (91.4% purity) was administered at 0, 0.2, 2.0, or 20 mg/kg/day (6 dogs/sex/group) in a one-year chronic dog study. Effects reported were mild testicular degeneration, focal mineralization of the spinal cord, anemia, mild splenic siderosis, plasma, RBC and brain cholinesterase inhibition

(Johnson, 1986). The overall NOEL was 0.2 mg/kg/day for these effects.

Reproductive effects related to naled were investigated in a two-generation CD rat study (Schroeder, 1985). Rats (15 males, 30 females/dose) were treated with naled (91.0% purity) at levels of 0, 2, 6, or 18 mg/kg/day by gavage. A reproductive NOEL of 2 mg/kg was established, based on effects in the F_{2b} generation of decreased pup survival and body weights at 18 mg/kg, with reduced number of pups at birth at the 6 and 18 mg/kg doses.

The American Congress of Governmental Industrial Hygienists (ACGIH) has established a TLV-TWA of 3 mg/m³ (with a skin notation) for naled exposure based on data available and the analogy to DDVP. EPA has set the Theoretical Maximum Residue Contribution (TMRC) at 0.75 mg/day/1.5 kg diet, corresponding to an intake of 0.0125 mg/kg/day for a 60 kg person. No ADI has been established by EPA or FAO/WHO.

Naled entered the risk assessment process at the California Department of Food and Agriculture under SB950 (Birth Defect Prevention Act of 1984) based on potential adverse effects identified in reproductive, chronic, and combined oncogenicity/chronic toxicity studies.

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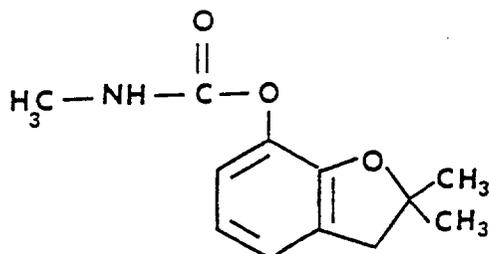
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CARBOFURAN



Carbofuran (2,3-dihydro-2,2-dimethyl-7-benzofuranyl methyl carbamate), an insecticide and nematicide, is an active ingredient in seven currently registered products. Carbofuran containing products are formulated as liquids (2 products) and granules (5). In 1986, reported carbofuran use totaled 237,728 pounds of active ingredient. While carbofuran is registered for use on several crops, in 1986 the majority of reported use occurred on just three crops: alfalfa (98,774 pounds of active ingredient), rice (56,685), and grapes (54,885).

A potent carbamate, carbofuran inhibits acetylcholinesterase (AChE) directly and produces signs and symptoms rapidly after absorption. Carbofuran is a reversible AChE inhibitor, i.e., the inhibition effect of the enzyme is reversed by hydrolysis of the carbamylated enzyme and, to a lesser extent, by formation of new AChE (Tobin 1970). Acute toxicity studies conducted in several test species show carbofuran to be highly toxic by oral ingestion and inhalation, and moderately toxic by dermal exposure. Acute oral LD₅₀'s of 13.3, 5.6 and 2.0 mg/kg have been reported in male rats, female rats, and mice, respectively (Norvell et al., 1983; Fahney et al., 1970). Acute inhalation (4 hr.) LC₅₀ values in the rat range from 0.017 to 0.047 mg/L (ACGIH, 1986). The dermal LD₅₀ in rabbits has been measured at 14.7 mg/kg (Kimmerle, 1966). Like other carbamates, carbofuran metabolizes rapidly in animals into less toxic and finally non-toxic metabolites (EPA 1985). Because of acute toxic effects, EPA has classified carbofuran in Toxicity Category I, and has required restricted use of the pesticide.

Although carbofuran is considered more toxic by oral or inhalation routes, its use has been reported in several cases of adverse effects to applicators from dermal exposure (Tobin, 1970). Hayes (1978) describes an incident in which, of 142 children who collected corn tassels in a field treated with

carbofuran the evening before, 74 were rapidly affected with dizziness, nausea and blurred vision.

In a one-year study in which carbofuran was presented to Beagle dogs (6/sex/dose) in the food at concentrations of 0, 10, 20 or 500 ppm, carbofuran produced weight loss from food emesis and loose stools, inflammatory lung changes, kidney weight increases and heart weight decreases, plasma and RBC AChE depression, seminiferous tubule degeneration, testicular aspermia and uterine hyperplasia and hydrometria at 500 ppm (Taylor et al., 1983). On the basis of cholinesterase depression and testicular degeneration in males, a NOEL of 20 ppm (0.5 mg/kg/day) was established (EPA, 1985). Neither of two rodent studies reported evidence of oncogenicity or other histopathologic lesions. In a two-year chronic toxicity/carcinogenicity study on Charles River rats (60/sex/group), carbofuran, given at 0, 10, 20 or 100 ppm in the diet, produced only plasma, RBC and brain ChE inhibition in both sexes at 100 ppm (Marshall et al., 1979). A similar study conducted in CD-1 mice (70/sex/group) with feed concentrations of 0, 20, 125 or 500 ppm, again produced reductions in brain cholinesterase levels at 125 and 500 ppm (Marshall et al., 1980). A NOEL on the basis of cholinesterase inhibition was established at 20 ppm for both studies (EPA, 1984a).

In a three-generation study in rats which were fed carbofuran at concentrations of 0, 20 or 100 ppm, reduced body weight gain of parents and reduced birth weight of offspring of the F1b generation were reported at 100 ppm (Schwartz et al., 1979).

At least eight Ames tests noted a marginal increase in number of revertants with Salmonella typhimurium, especially with strain TA1535, without activation (CDFA, 1987a). These and two slightly positive mouse lymphoma tests (Kirby et al., 1983), suggest carbofuran may be a weak mutagen, although no other short term assays have indicated positive results (NAS, 1983).

Based on the chronic dog study, EPA has calculated an acceptable daily intake (ADI) of 0.3 mg/kg/day (EPA, 1984a). Neither carbofuran nor its metabolites have been found oncogenic, teratogenic or mutagenic by EPA review (1984b). For carcinogenic risk, EPA classified carbofuran in Group E: (no evidence of carcinogenicity in humans).

Carbofuran entered the risk assessment process at the California Department of Food and Agriculture under SB950 (Birth Defects Prevention Act of 1984) because of the identification of potential chronic, reproductive and mutagenic

effects. Additionally, concern over its acute toxicity has been a primary consideration in its selection as a candidate toxic air contaminant for AB1807 review.

**CARBOFURAN
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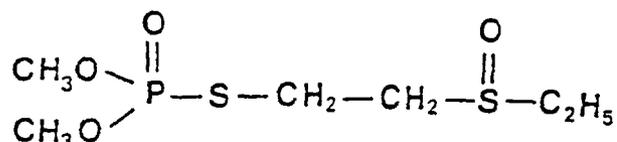
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OXYDEMETON-METHYL



Oxydemeton-methyl (S-[2-(ethylsulfinyl)ethyl] O,O-dimethyl phosphorothioate), a restricted use insecticide, is an active ingredient in three currently registered products used primarily for the systemic control of aphids, mites, and thrips. Oxydemeton-methyl containing products are formulated as liquids (1 product) and emulsifiable concentrates (2). In 1986, reported oxydemeton-methyl use totaled 148,547 pounds of active ingredient. While oxydemeton-methyl is registered for use on a wide range of crops, in 1986 the majority of reported use occurred on just three crops: broccoli (45,702 pounds of active ingredient), cauliflower (34,822), and sugarbeets (14,645).

Oxydemeton-methyl pesticidal activity is due to inhibition of acetylcholinesterase (AChE) with subsequent disruption of nervous system function in target organisms. The acute rat oral and dermal LD₅₀ values are 60 and 112 mg/kg, respectively (EPA, 1987). Female rat and mouse LC₅₀ inhalation values are 1.5 and 0.51 mg/L, respectively. The toxicity categories for technical oxydemeton-methyl are Category I for dermal exposure, and Category II for both oral and inhalation exposures.

Potential reproductive effects were investigated in a two litter, two-generation reproduction/fertility study. Oxydemeton-methyl (50%) was fed to Wistar rats (10/sex/group) at concentrations of 0, 1, 10, or 50 ppm (Kroetlinger & Kaliner, 1985). Due to reported degradation of oxydemeton-methyl in the diet, actual concentrations received were less. Epididymal vacuolation was observed in male rats receiving 10 and 50 ppm. Testicular atrophy and epididymal aspermia were also noted at 50 ppm. A NOEL of 1 ppm (approx. 0.025 mg/kg/day) was reported. In order to assess the time course and severity of epididymal alterations, a satellite reproductive study with Charles River male CD rats (40/group) was conducted. Oxydemeton-methyl (50%) was fed in the diet at

concentrations of 0, 3, 9, or 50 ppm with sacrifices of 9-10/group at 2, 4, 6, or 8 months (Eigenberg, 1987). Additional groups were added to assess the potential for recovery. These rats were fed a diet containing 50 ppm of oxydemeton-methyl for 3.5 or 4 months, then sacrificed after receiving basal feed for two weeks or two months, respectively. Epididymal vacuolation was reported in 9 and 50 ppm groups between 2-8 months, and partial recovery was observed in the recovery groups. In order to assess the effect of methylisobutyl ketone (MIBK), which constituted 50% of the oxydemeton-methyl concentrate, three groups of CD rats received either oxydemeton-methyl 50% concentrate, technical grade (95%) oxydemeton-methyl, or technical grade MIBK at feed concentrations of 50 ppm, with a control group receiving plain feed (Eigenberg, 1987). Epididymal lesions were similar to those reported in the two-generation study for the oxydemeton-methyl group. There were no differences in epididymal alterations caused by either the technical oxydemeton-methyl or the 50% concentrate. Animals receiving MIBK only were comparable to controls. Likewise, no difference in inhibition of ChE by technical oxydemeton-methyl versus the 50% concentrate was observed, and there was no effect on ChE with MIBK.

Due to its activity as a potent cholinesterase inhibitor, oxydemeton-methyl's effects on human cholinesterase activity were examined (EPA, 1987). Human volunteers were exposed to either a single oral dose or repeated oral doses for 60 days. The dosage levels for the single oral dose ranged from 0.0125 to 1.5 mg/kg/day (one volunteer per dose level), and the dosage levels for repeated exposure were from 0.05 to 0.4 mg/kg/day (one volunteer per dose level). Single oral doses of oxydemeton-methyl up to and including 0.5 mg/kg/day did not produce any change in either the plasma or red blood cell (RBC) cholinesterase activity. At 1.0 and 1.5 mg/kg/day, plasma and RBC cholinesterase activities were decreased. Oral administration of 0.05 mg/kg/day for up to 60 days was without noticeable effects on human blood cholinesterase activities. Inhibition of plasma and RBC cholinesterase activities were found in individuals administered any dose higher than 0.05 mg/kg/day. In humans, the cholinesterase NOELS after single and repeated oral administration were established at 0.5 mg/kg/day and 0.05 mg/kg/day, respectively.

EPA has established an Acceptable Daily Intake (ADI) of 0.005 mg/kg body weight/day based on cholinesterase inhibition (FDA, 1982).

Oxydemeton-methyl has entered the risk assessment process at California Department of Food and Agriculture under SB950

(Birth Defects Prevention Act of 1984) because of the identification of potential reproductive effects. In addition, concern over the potential adverse effects of oxydemeton-methyl on cholinesterase inhibition was a consideration for its selection as a candidate toxic air contaminant for AB 1807 review.

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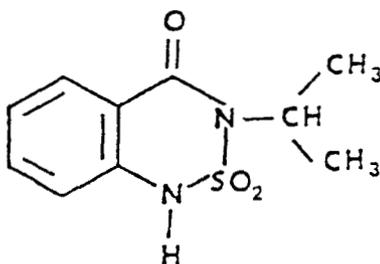
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BENTAZON



Bentazon (1H-2,1,3-benzothiadiazin-4(3H)-one-2,2-dioxide, 3-isopropyl, sodium salt of) is a liquid herbicide which is an active ingredient in one currently registered product. It is a post-emergence heterocyclic nitrogen compound used to control selected broadleaf weeds and sedges (EPA, 1985a). In 1986, reported bentazon use totaled 214,913 pounds of active ingredient. While bentazon is registered for use on several crops, in 1986 the majority of reported use occurred on rice (213,656 pounds of active ingredient).

The acute rat oral and dermal LD₅₀ values are 1100 mg/kg and 2500 mg/kg, respectively (NIOSH, 1986). Sodium bentazon has been placed in Toxicity Category III by EPA based upon acute oral and dermal testing in the rat (EPA, 1985b). Animal metabolites include 2-amino-N-isopropyl benzamide (AIBA), 8-hydroxy-bentazon, 6-hydroxy-bentazon, and anthranilic acid. The oral LD₅₀ in SD rats for a 1:1 mixture of the hydroxy metabolites is 5780 mg/kg, while the oral ALD₅₀ (approximate median lethal dose) in NMRI mice for anthranilic acid is 1400 mg/kg (Hofmann, 1972 & 1974).

The oncogenicity potential of bentazon was investigated in two-year rat and mouse studies. Fischer 344/Du Crj rats (50/sex/group) were fed bentazon (93.3% purity) at levels of 0, 200, 800, 4000 ppm (Takehara, 1986). No oncogenic effects were observed. A NOEL of 200 ppm was established for effects which included reduced platelet counts in males treated with 800 ppm at 6 months, increased partial thromboplastin time in 800 and 4000 ppm males and females at 12 months, as well as thyroid weight increases in males at 800 and 4000 ppm. In a mouse study, B6C3F1 Crj mice (50/sex/group) were fed bentazon (93.9% purity) at 0, 100, 400, or 2000 ppm (Takehara, 1984). Limited evidence of oncogenicity was reported, based on a dose-related increase in hepatocellular adenomas (or adenomas + carcinomas)

in males. There was no evidence of increased hepatocellular carcinomas alone. A NOEL = 100 ppm was established for chronic effects, including testicular calcification and pancreatic islet cell hyperplasia in males receiving 400 ppm and above. Also, increased hepatocellular nodular hyperplasia was seen in the 2000 ppm females. An independent blind review of all liver and lung sections from this mouse study was conducted. The conclusion reached was that under the study conditions bentazon is not a carcinogen (Carlton, et al., 1987).

Teratology studies in the rat and rabbit reported adverse effects. Mated Wistar/HAN rats, 25/dose, were treated with bentazon (97.8% purity), by gavage, at dosages of 0, 40, 100, or 250 mg/kg on days 6 - 15 of gestation (Becker, 1987a). The maternal NOEL was >250 mg/kg, while the developmental NOEL = 100 mg/kg, based on increased resorption, decreased fetal weight, and increased incidence of delayed skeletal ossification at 250 mg/kg. In another study, mated chinchilla rabbits, 16/dose, were treated with 0, 75, 150, or 375 mg/kg/day on days 6 - 18 of gestation (Becker, 1987b). Maternal toxicity was not observed. The developmental NOEL was set at 375 mg/kg, based on increased resorption rate in the absence of maternal toxicity, observed at the 450 mg/kg dose in the pilot study.

Bentazon entered the risk assessment process at the California Department of Food and Agriculture under SB950 (Birth Defect Prevention Act of 1984), based on potential adverse effects identified in oncogenicity and teratogenicity studies.

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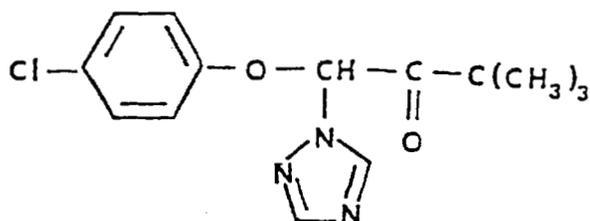
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TRIADIMEFON



Triadimefon (1-(4-chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)-2-butanone), a systemic fungicide, is an active ingredient in nine currently registered products. It is primarily used for control of powdery mildew on deciduous fruit, grains and vegetables, and rust diseases in many different crops. Triadimefon containing products are formulated as liquids (1 product), emulsifiable concentrates (1), granules (2), and wettable powders (5). In 1986, reported triadimefon use totaled 49,628 pounds of active ingredient. While triadimefon is registered for use on several crops, in 1986 the majority of reported use occurred on grapes (37,586 pounds of active ingredient).

Acute toxicity studies show triadimefon to be moderately toxic. The oral LD₅₀ is approximately 568 mg/kg for the male rat, 363 mg/kg for the female rat (Thyssen and Kimmerle, 1974). For dermal exposure, the LD₅₀ was found to be greater than 2000 mg/kg for rat (both sexes), and 1000 mg/kg for mouse (both sexes) (Nakazato, 1977). In a static spray inhalation study (4 hours) at 291 mg/m³, 11 of 20 exposed mice died, and the general health of other exposed animals, rats, hamsters and rabbits, was affected slightly (Thyssen and Kimmerle, 1974). EPA classified triadimefon in Toxicity Category II for wettable powder, and Category III for the granular and emulsifiable formulations.

Two study reports suggest triadimefon is a teratogen, although the results of these and a third teratogenicity study by oral gavage in the rat are somewhat conflicting (CDFA, 1988). A slight increased incidence of cleft palates (2/139) was observed at 100 mg/kg in a study in which triadimefon was administered to Sprague-Dawley rats (20/group) at 0, 10, 25, 50 or 100 mg/kg/day on days 6-15 gestation (Nagumo et al., 1981). Incidence of 14th rib occurred in 49% and 92% of the fetuses in mid- and high dose groups, respectively, compared with 11% in concurrent controls. Another study, in which Long

Evans rats received 0, 10, 30 or 100 or 0, 50, 75 or 100 mg/kg/day (20/group), also could not rule out a teratogenic effect (Machemer L. 1976). Cleft palate was observed in 4/211 fetuses at 100 mg/kg in the first experiment, and 1/183 at 100 mg/kg and 2/220 at 75 mg/kg in the second experiment. A third study, in which triadimefon was administered by gavage days 6 through 15 of gestation at dose levels of 0, 10, 30 and 90 mg/kg/day, revealed, at 90 mg/kg, a statistically significant increase only in rib anomalies (Unger et al., 1982).

One rat inhalation teratology study and two rabbit oral gavage teratology studies (Machemer 1976) had negative findings. In a study in which triadimefon was administered by inhalation₃ to Long Evans rats (20/group) at 0, 14.02, 33.20 or 113.66 mg/m³/6 hours on days 6-15 gestation, no fetal toxicity or teratogenicity was observed (Machemer and Kimmerle, 1976). A maternal toxicity NOEL (reduced body weight gain) was established at 14.02 mg/m³. One rabbit gavage study, in which 13 animals per group were exposed on 6-18 of gestation to 0, 5, 15, or 50 mg/kg/day, produced neither maternal nor developmental effects (Machemer, 1976). Another study explored dose levels of 0, 10, 30 or 100 mg/kg/day by gavage on days 6-18 of gestation with 12 rabbits/group (Roetz 1982). Complete resorptions in 3/12 inseminated dams at 100 mg/kg, compared with 1/12 in the control and none in the other groups were reported. A maternal NOEL (body weight gain during dosing), of 10 mg/kg, a fetotoxic NOEL of 30 mg/kg and a developmental NOEL \geq 100 mg/kg were established in this study.

In a 21-month dietary carcinogenicity study NMRI mice (50/sex/group) received 0, 50, 300, or 1800 ppm triadimefon (90% premix in Wessalon S (dispersed silicates)) (Bomhard & Hahnemann, 1986). Compound-induced pathological changes in the liver were observed at 300 ppm, with increased incidence and severity at 1800 ppm. Changes included single cell necrosis, Kupffer cell proliferation, hyperplasia, changed cell foci and an increase in adenomas at 1800 ppm (both sexes) interpreted as uncontrolled regeneration in response to repeated tissue damage rather than an oncogenic effect. There was no increased incidence of carcinomas. Changes in serum enzyme levels reflected liver damage attributed in the report to enzyme induction in an adaptive response. Data from two year feeding studies with triadimefon in the dog and rat are inadequate and inconclusive, although systemic effects of increased liver weights and liver enzyme levels were indicated consistently (CDFA, 1988).

Triadimefon has been evaluated in several mutagenicity assays all of which have shown negative results.

Triadimefon has entered the Risk Assessment process at the California Department of Food and Agriculture under SB950 (Birth Defects Prevention Act of 1984) because of the identification of possible teratogenic and chronic liver effects, with some indication of possible oncogenic potential.

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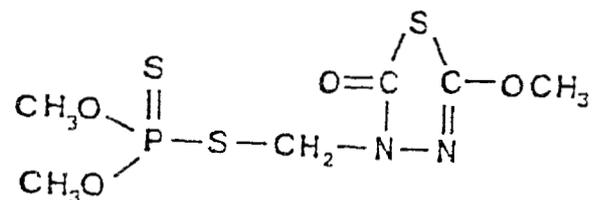
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METHIDATHION



Methidathion (O,O-dimethyl phosphorodithioate S-ester with 4(mercaptomethyl)-2-methoxy-delta-2-1,3,4-thiadiazolin-5-one), an organophosphate insecticide, is an active ingredient in one currently registered product formulated as an emulsifiable concentrate. In 1986, reported methidathion use totaled 306,927 pounds of active ingredient. While methidathion is registered for use on several crops, in 1986 the majority of reported use occurred on just three crops: oranges (76,004 pounds of active ingredient), almonds (39,562), and cotton (38,619).

Methidathion is a cholinesterase inhibitor. The acute rat oral and dermal LD₅₀ values are 46.1 and 1663 mg/kg, respectively (EPA, 1988). Methidathion is a restricted use pesticide in California, and has been placed in toxicity Category I for oral effects, and in Category II for dermal effects.

The oncogenic potential of methidathion has been investigated in rat and mouse studies. Sprague Dawley rats (80/sex/group) were treated with methidathion (97.3%) at concentrations of 0, 4, 40, or 100 ppm, for two years in a chronic/oncogenicity dietary study (Yau et al., 1986). The NOEL for chronic toxicity was 4 ppm (0.4 mg/kg), based on effects observed in both sexes, including skin lesions with inflammation and ulceration, transient neurological effects, altered blood parameters, altered biochemical parameters, reduced liver weights, and alveolar foamy macrophages. Statistically significant decreases were noted in plasma, red blood cell, and brain cholinesterase levels in animals receiving methidathion concentrations equal to or greater than 40 ppm. No oncogenic effects were observed. In a chronic/oncogenicity study with mice, however, possible oncogenic effects were observed (Goldenthal, 1986). Charles

River CD₁ mice (50/sex/group) were fed technical methidathion (purity not stated) at 0, 3, 10, 50, or 100 ppm. The male mice treated with 50 and 100 ppm methidathion exhibited increased frequencies of hepatocellular adenomas and carcinomas, as well as nonneoplastic hepatic and biliary changes, while increased frequencies of nonneoplastic hepatic changes were seen in females at 100 ppm. A statistically significant decrease in red cell cholinesterase values was observed in males receiving 100 ppm at 3 and 12 months of study. In females, a statistically significant decrease in red cell cholinesterase activity was noted at 3, 6, 12, 18, and 24 months of study at the 100 ppm level, and at 3, 6, 18, and 24 months of study at the 50 ppm level. Both sexes receiving 100 ppm exhibited statistically significant decreases in brain cholinesterase activity at 3, 6, 12, 18, and 24 months of study. Males receiving 50 ppm exhibited a statistically significant decrease of brain cholinesterase activity at 6 months of study, and females receiving 50 ppm also had a decrease at 24 months of study. The NOEL for chronic effects was 10 ppm (approx. 1.5 mg/kg), based on cholinesterase inhibition in both sexes at 50 and 100 ppm, as well as increased male mortality at 100 ppm, and discolored urine in males receiving 50 and 100 ppm.

Chronic toxicity was examined in rat and dog two-year feeding studies. Methidathion (purity not stated) was administered to Charles River CD albino rats (25/sex/group) for two years at concentrations of 0, 4, 16, or 64 ppm in the diet (Johnston, 1967a). Decreased body weight gain was seen in male rats receiving 64 ppm, from week 8 on, and from week 56 in males receiving 4 or 16 ppm. Both sexes fed the 64 ppm concentration exhibited red blood cell (RBC) cholinesterase activity at 30-40% of control values. Plasma cholinesterase activity was not affected. Also, brain cholinesterase activity in both sexes receiving 64 ppm was 35% of control values. Females in the 16 and 64 ppm groups had decreased adrenal-to-body weight ratios, with decreased ovary-to-body weight ratios seen at 64 ppm. Increased kidney ratios were seen in males receiving 16 and 64 ppm. The NOEL is <4 ppm based decreased weight gain. In the dog study, methidathion (purity not stated) was administered to dogs (3/sex/group) for two years at concentrations of 0, 4, 16, or 64 ppm in the diet, 6 days/week (Johnston, 1967b). Mean RBC cholinesterase values were marginally decreased only in the 64 ppm group (both sexes). Plasma and brain cholinesterases were not affected. Some increases in serum alkaline phosphatase and sulfobromophthalein retention were seen in the 16 and 64 ppm groups, with markedly elevated activity of serum glutamic-pyruvic transaminase observed. Dark liver pigmentation, some hepatic cell, and slight upper nephron tubular cell

pigmentation were observed in the 64 ppm group. A NOEL of 4 ppm (approx. 0.1 mg/kg) was reported for these effects.

Reproductive effects of methidathion were examined in a 3-generation rat study. Albino rats (strain not noted - 10 males, 20 females/group) were fed 0, 4, or 32 ppm methidathion (40% wettable powder) (Woodard Research, 1966). A brief summary with one data table reported a NOEL of 4 ppm for decreased weanling survival, which was observed in all generations fed 32 ppm of methidathion. In a separate two-generation reproduction study, methidathion was fed to male and female rats in concentrations of 0, 5, 25, or 50 ppm (15 males and 30 females/dose group (Becker, 1987). The reproductive NOEL was 5 ppm based on decreased survival and body weights of offspring in the 25 and 50 ppm groups; however, the parental NOEL was determined to be 5 ppm based on decreased weight gain, food consumption, and organ weights.

Sprague Dawley rats were used to test the teratogenicity potential of methidathion (Fritz, 1976). Methidathion (no purity stated) was administered by gavage to female rats on days 6 - 15 of gestation, at doses of 0 mg/kg to 24 rats, 1 mg/kg to 28 rats, 2.5 mg/kg to 23 rats, or 5.0 mg/kg to 21 rats. A NOEL for maternal toxicity was established of 1 mg/kg for decreased body weight gain and food intake, and tremors (no cholinesterase-related information stated). The developmental NOEL was 2.5 mg/kg for incompletely ossified fifth sternbrae. Information was insufficient to fully assess possible adverse effects. No adverse developmental effects were reported in a rabbit teratology study in which females were treated with 0, 2, 6, or 12 mg/kg/day (p.o.) of methidathion on gestation days 7 - 19 (Hummel et al., 1987). Maternal toxicity was seen in the does treated with 12 mg/kg/day.

Chromosome mutation studies presented equivocal evidence for a possible adverse effect. Two micronucleus studies and one dominant lethal assay were negative (CDFA, 1988). However, when methidathion (purity not stated) was administered to Chinese hamsters (4/sex/dose) by gavage, at a single dose of 0, 17, 34, or 68 mg/kg, sister chromatid exchange (SCE) frequency was elevated ($P < 0.01$) at the intermediate dose.

Methidathion has been classified by EPA as a Group C oncogen (possible human carcinogen) based on the positive carcinogenic effects found in male mice (Federal Register, 1988). EPA has established an ADI of 0.001 mg/kg body weight/day, based on the cholinesterase and liver effects in the two-year dog study (Johnson, 1967b). FAO/WHO has set an ADI of 0.005 mg/kg body weight/day (FDA, 1981).

Methidathion entered the risk assessment process at the California Department of Food and Agriculture under SB950 (Birth Defect Prevention Act of 1984) based on potential adverse effects identified in combined oncogenicity/chronic toxicity, and mutagenicity studies.

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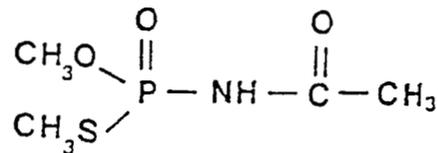
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ACEPHATE



Acephate ((O,S-dimethyl acetylphosphoramidothioate) is an insecticide which is an active ingredient in 24 currently registered products. Acephate containing products are formulated as emulsifiable concentrates (5 products), wettable powders (5), dusts (1), liquids (1), granules (1), soluble powders (4), and six miscellaneous products such as baits. In 1986, reported acephate use totaled 449,616 pounds of active ingredient. While acephate is registered for use on a wide range of crops, in 1986 the majority of reported use occurred on just three crops: cotton (202,857 pounds of active ingredient), lettuce (108,832), and beans (71,703).

Acephate has relatively low acute toxicity to laboratory animals via oral, dermal or inhalation routes of exposure. An oral LD₅₀ of 945 mg/kg has been measured for the male rat, and of 866 mg/kg for the female rat (Cavalli and Spence, 1970). The dermal LD₅₀ for the male rabbit is greater than 10,000 mg/kg, and an inhalation LC₅₀ (4 hr) in Sprague-Dawley rats (both sexes) was measured at a nominal concentration of 61.7 mg/L (Rittenhouse et al., 1979). Methamidophos (O,S-dimethyl phosphoramidothioate), an impurity found in up to 1% of technical acephate, is formed also by soil or plant (but not by animal) degradation of acephate (Lee, 1972). An insecticide in its own right, methamidophos is a more potent cholinesterase inhibitor, with an oral LD₅₀ in rat of 18-21 mg/kg (Berg, 1988). Acephate has been classified in Toxicity Category III for oral and dermal exposure, and Toxicity Category IV for inhalation exposure (EPA, 1987).

Acephate has been classified as a Category C carcinogen (possible human carcinogen) based on data from a two-year oncogenicity mouse study and several mutagenicity assays (EPA, 1987). Acephate was presented in the diet at concentrations of 0, 50, 250 or 1000 ppm to CD-1 mice (75/sex/group) for 104 weeks, and it produced a significant increase in hepatocellular carcinomas (12/76, or 15.8% vs. 1/75, or 1.3%), and hyperplastic nodules (13/34, or 38.2% vs. 1/31 or 3.2%) in 1000

ppm treated females when compared with controls (Jefferson et al., 1982). Compound related increases in these proliferative lesions were not seen in females at 50 ppm or 250 ppm nor in males. Other dose-related nonneoplastic lesions observed in males and females at the mid- and high dose levels were hepatocyte hypertrophy, karyomegaly and intranuclear inclusions. No tumorigenic findings have been reported in other species tested. Acephate was administered to Sprague-Dawley rats, 80/sex/dose level, at concentrations of 0, 5, 50 or 700 ppm in the diet for 2 years (Auletta and Hogan, 1981). Significantly lower body weights in males at the high dose and consistent cholinesterase inhibition at the low and mid-dose levels were the only adverse effects noted. Calculation of a chronic LOEL of 5ppm (0.25 mg/kg) was based on inhibition of cholinesterase activity in plasma, RBC and brain (EPA, 1987). Similar results occurred in Beagle dogs (4/sex/ group) given 0, 10, 30 or 100 ppm acephate in the diet for 2 years (Hartke et al., 1972). Cholinesterase depression was observed in both sexes at the high dose level, but no other adverse effects were seen. The NOEL was determined to be 30 ppm in the diet (equivalent to 0.75 mg/kg bw/day), based on inhibition of plasma, RBC and brain cholinesterase activity.

In vitro mutagenicity studies indicate that acephate can induce gene mutations, sister chromatid exchanges, and DNA repair (CDFA, 1988). Multiple reports show acephate was weakly mutagenic in Salmonella typhimurium at concentrations of 5.0 mg/plate and above, especially in strain TA100, with and without activation (CDFA, 1988). In the mouse lymphoma assay, three reports indicated dose-dependent increases in mutation frequency at the TK locus at concentrations greater than 1.0 mg/ml without S-9, and 2.0 mg/ml with S-9 (Kirby P.E. et al.; 1982, Jotz et al., 1980). A study in Chinese hamster ovary cells reported increased SCE's at 500 ug/ml without S-9, and 5000 ug/ml with S-9 (Evans et al., 1980). Comparison of differential toxicity in repair proficient versus repair deficient strains of Salmonella suggest an adverse effect on cell viability via a defective recombinant repair pathway (Mortelmans and Riccio, 1981). Additionally, S. cerevisiae strains D3 and D7 both showed increased mitotic recombination, mitotic crossing-over or gene conversion with acephate exposure, lending support to these data (Mortelmans et al., 1981, and Simmon, 1979). Increased unscheduled DNA synthesis (UDS) was measured in WI-38 human fibroblasts, without activation, at 1000 ug/ml and above (Simmon, 1979). In vivo studies for dominant lethality and bone marrow chromosome aberrations were negative (Eisenlord, 1982, and Esber, 1982).

The FAO/WHO Joint Meeting on Pesticide Residues in food (JMPR) established an acceptable daily intake (ADI) in man for

acephate of 0-0.003 mg/kg bw, based on data from lifetime studies in the mouse, rat and dog (FAO/WHO, 1987).

Acephate has entered the risk assessment process at the California Department of Food and Agriculture under SB950 (Birth Defects Prevention Act of 1984) because of the identification of possible oncogenic and mutagenic effects. Cholinesterase inhibition in chronic studies was also a consideration for selection of this compound as a candidate toxic air contaminant.

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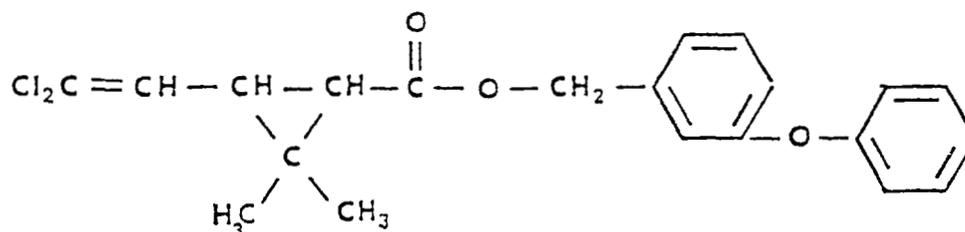
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PERMETHRIN



Permethrin (3-(phenoxyphenyl)methyl +/- cis, trans 3-(2,2-dichloroethenyl-2,2-dimethylcyclopropanecarboxylate) is an insecticide which is an active ingredient in 138 currently registered products. Permethrin containing products are formulated as emulsifiable concentrates (27 products), wettable powders (7), dusts (6), liquids (46), granules (2), and 50 miscellaneous products such as baits. In 1986, reported permethrin use totaled 122,857 pounds of active ingredient. While permethrin is registered for use on a wide range of crops, in 1986 the majority of reported use occurred on just three crops: lettuce (65,095 pounds of active ingredient), pistachios (9,748), and celery (8,886).

Permethrin is a synthetic pyrethroid insecticide (FDA, 1981). The acute rat oral LD₅₀ toxicity values range from 333 to 4000 mg/kg. The toxicity appears to be solvent influenced, as well as dependent on the cis:trans ratio of the material tested. The cis isomer is more stable, more acutely toxic, and less readily eliminated.

Reproductive effects were examined in a 3 generation study in rats (Hodge et al., 1977). Wistar rats (12 males/24 females/group) were fed permethrin (purity range 94.0-98.9%; cis:trans 36:61 to 44:55) at concentrations of 0, 500, 1000, or 2500 ppm. Adverse effects observed in pups at weaning included neonatal toxicity with eye (buphthalmos with persistent pupillary membranes) effects seen in F_{1b} and subsequent litters at 1000 and 2500 ppm. Liver^{1b} effects (centrilobular hypertrophy) were seen in F_{3b} pups at all doses, and kidney effect mainly in female F_{1b} and F_{3b} pups, were induced at 2500 ppm. Tremors were seen in parents at 2500 ppm and occasionally at 1000 ppm, and in offspring at 1000 ppm. Although these were clearly related to administration of permethrin, they were transient, and no evidence of neuropathy was found in F₁ males exposed in utero and treated for one

year. A parental NOEL of 500 ppm was reported with the neonatal NOEL < 500 ppm.

The potential of permethrin for oncogenicity and chronic toxicity has been examined in several studies. Wistar rats (60/sex/group) were fed permethrin (no purity stated) in dosages of 0, 10, 50, or 250 mg/kg/day in a two year chronic/oncogenicity study (McSheehy, 1980). A NOEL was reported of 10 mg/kg based on liver hypertrophy. No oncogenic effects were reported. A second chronic/oncogenicity study was conducted in which Wistar rats (60/sex/group) were fed permethrin (purity range 93.1-98.9%; cis:trans ratio range 36:62 to 44:55) at concentrations of 0, 500, 1000, or 2500 ppm for two years (Richards, 1977). A NOEL of 500 ppm was reported based on liver hypertrophy with associated increases in liver weight, microsomal enzyme activity, and smooth endoplasmic reticulum, at 1000 and 2500 ppm.

In an oncogenicity study, Long-Evans rats (60/sex/group) were fed permethrin (no purity stated; cis:trans ratio 40:60) for two years at concentrations of 0, 20, 100, or 500 ppm (Braun, 1977). No significant signs of toxicity were reported. An increase ($p \leq 0.05$) in ovary weights at 500 ppm was noted, as well as elevated mean glucose values at 500 ppm in females at 18 and 24 months, and males at 24 months of study. In a mouse study, permethrin (no purity stated; cis:trans ratio 25:75) was fed to CFLP mice (100/sex in controls, 75/sex/test group) at dosages of 0, 10, 50, or 250 mg/kg/day for 91 weeks (James, 1980). While the incidence of lung tumors in high dose females was statistically significant in relation to controls, the values fall within the historical data range for controls. At 250 mg/kg, female kidney weights were increased, as were liver weights in males. Another mouse study was conducted in which Alderly Park albino mice (70/sex/group) were fed permethrin (purity range 94.0-98.9%; cis:trans ratio 40:60) at concentrations of 0, 250, 1000, or 2500 ppm for 98 weeks (Hart, 1977). Increased liver weights, smooth endoplasmic reticulum proliferation, and increased eosinophilia of centrilobular hepatocytes were observed in females receiving 1000 and 2500 ppm. In a chronic dog study, permethrin (92.5% purity; 32.3:60.2 cis:trans ratio-nominal) was administered by gelatin capsules with corn oil, to beagles (6/sex/group) for 52 weeks at concentrations of 0, 5, 100, or 2000/1000 (reduced after 2 days) mg/kg (Litchfield, 1982). A NOEL of 5 mg/kg was reported based on liver hypertrophy, adrenal alterations and decreased weight gain in both sexes.

The five rat and mouse studies described were considered by EPA in setting a non-oncogenic NOEL of 5/mg/kg/day used for ADI determination (CDFA, 1988). The FIFRA Scientific Advisory

Panel (SAP) reviewed the available rat and mouse studies in 1981, concluding that although a low oncogenic potential was present in mice, and no oncogenic potential was shown in rats, the likelihood of oncogenicity in humans was small (Federal Register, 1982).

EPA has established an ADI of 0.05 mg/kg body weight/day derived from rat and mouse chronic/oncogenicity studies based on liver effects (CDFA, 1988). FAO/WHO has set an ADI of 0.03 mg/kg body weight/day (FDA, 1981). EPA has classified permethrin as a Group C oncogen (possible human carcinogen) based on tumors in female mice (Chemical Regulation Reporter, 1987).

Permethrin entered the risk assessment process at the California Department of Food and Agriculture under SB950 (Birth Defect Prevention Act of 1984) based on the potential adverse effects identified in chronic toxicity and reproduction studies.

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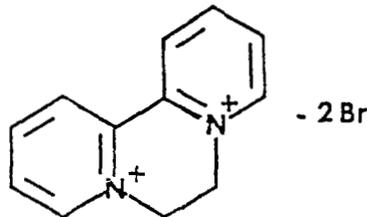
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DIQUAT DIBROMIDE



Diquat dibromide (1,1'-ethylene-2,2'-dipyridinium dibromide) is a contact herbicide and plant growth regulator which is an active ingredient in thirty currently registered products formulated as liquids and emulsifiable concentrates. In 1986, reported diquat dibromide use totaled 48,494 pounds of active ingredient. The majority of reported use occurred on rights of way (31,233 pounds of active ingredient) and landscape maintenance (10,477).

The toxicity displayed by diquat is due to the cation. While little metabolism is observed in animals, a small amount of the metabolite TOPPS (1,2,3,4-tetrahydro-1-oxypyrido-2H-[1,2-a]-5-pyrazinium ion) monopyridone (II) is excreted in the urine. EPA has classified diquat as a Category I chemical based on its acute dermal toxicity. The oral rat LD₅₀ is 400-440 mg/kg, while the dermal rat LD₅₀ is between 50-100 mg/kg. Available data indicate acute symptoms of oral and/or dermal exposure include ulceration, gastric mucosa irritation, and severe dehydration. The type of lung injury and compound accumulation in lung tissue observed in paraquat rat toxicity is not found with diquat poisoning, although inhalation exposure can produce non-specific respiratory distress.

Nephrotoxicity, hematological changes and cataract formation have been observed in two rat dietary studies (Colley et al, 1985; Rogerson et al, 1978) and one dog study (Hurst, 1966). A NOEL for cataract formation was established for the rat of 0.22 mg/kg/day and 1.7 mg/kg/day for the dog. No compound-related cataracts were seen in mice (Ben-Dyke et al, 1975).

In a teratology study, albino mice were treated (32-34/dose) with 0, 1, 2, or 4 mg/kg/day of analytical grade diquat by gavage for days 6-15 of gestation. Litters showed increases in skeletal anomalies, including exencephaly, and variant sternebrae at the 4 mg/kg dose; however, maternal

toxicity was seen at all doses (Palmer et al, 1978). No adverse effects were exhibited in a Sprague-Dawley rat teratology study with 32% w/v diquat ion fed at concentrations of 0, 125, and 500 ppm for days 1-20 of gestation (Moore and Wilson, 1973), or in a rabbit study in which 100% purity diquat dibromide monohydrate was administered at levels of 0, 1.25, 2.5 and 5.0 mg/kg/day on days 1-28 of gestation (Palmer and Pratt, 1974).

A possible oncogenic effect was reported in a Charles River CD rat study in which concentrations of diquat at 0, 5, 15, 75, and 375 ppm were administered. Positive dose-related trends were found in incidences of osteosarcoma and thyroid follicular adenoma in males at the 375 ppm dose; however, using the Fisher exact test, these results were not statistically significant (Colley et al, 1985). A dietary Charles River CD-1 mouse study tentatively reported no oncogenic effect up to 300 ppm pending examination of additional histopathological data (Ben-Dyke et al, 1975). Mutagenicity studies reported forward mutations were observed in S. typhimurium and mouse L5178Y cells, while human lymphocyte experiments provided evidence of chromosomal aberrations (Richardson et al, 1986).

EPA has set an ADI of 0.005 mg/kg bw, mainly based on diquat's dermal toxicity and its potential as a cataractogenic agent, while FAO/WHO has established an ADI of 0-0.0036 mg/kg bw. The ACGIH TLV-TWA is 0.5 mg/m³ due to the potential for inducing cataract formation, as well as the dermal, oral, and inhalation toxicity.

A risk assessment document will be prepared on diquat at California Department of Food and Agriculture because of potential adverse effects, including cataract formation and nephrotoxicity, identified in oncogenicity/chronic toxicity and mutagenicity studies under SB950 (Birth Defect Prevention Act of 1984).

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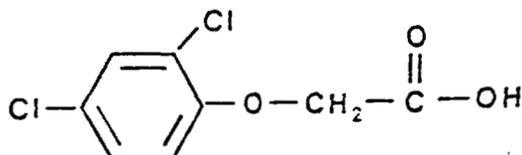
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2,4-D



2,4-D (2,4-dichlorophenoxyacetic acid), a widely used selective herbicide, is an active ingredient in numerous currently registered products. Included in this category are the free acid, the salts (principally amine salts), and the esters. The dimethylamine salt is the most heavily used. In 1986, reported 2,4-D, dimethylamine salt use totaled 540,205 pounds of active ingredient. The majority of reported use occurred on landscape maintenance (192,319 pounds of active ingredient), wheat (118,359), and barley (49,754).

While data exist on acute toxicity of these different compounds, there is very little, if any, information available on chronic or reproductive toxicity, oncogenicity and mutagenicity, except for the free acid form. This summary, therefore, will concentrate on the adverse health effects which have been associated with the acid form of 2,4-D.

2,4-D is only moderately toxic on an acute basis. The oral LD₅₀ for 2,4-D in the rat ranges between 375-800 mg/kg, while the dermal LD₅₀ for the rabbit is greater than 2 g/kg. The inhalation LC₅₀ (4 hours) for the rat is greater than 21.1 mg/l.

A potential oncogenic effect was observed in a chronic study in F344 rats (60/sex/group) which were fed 0, 1, 5, 15, or 45 mg/kg/day of 2,4-D (Serota, 1984). There was an increased incidence of brain tumors (astrocytomas) in the male rats treated with 45 mg/kg/day and kidney effects were reported at 5 mg/kg/day and higher dosages. No tumors were reported in mice (C57BL) fed dosages of 2,4-D of 0, 149, or 323 mg/kg/day for 78 weeks (IARC, 1977); however, due to the small sample size (18/sex/group), definitive conclusions from this study could not be made. In addition to the animal data on oncogenicity, a recent epidemiological study reported an increased incidence of non-Hodgkin's lymphoma (NHL) in farmers who had been exposed to phenoxyacid herbicides (principally 2,4-D) (Hoar et al., 1986). In this population-based case control study, a random sample of 200 men from 297 cases of NHL

were chosen and white men from the general population of Kansas served as controls. A significant trend ($p=.02$) in risk for NHL with increasing years of herbicide use and with number of days of herbicide exposure per year ($p=.0004$) was reported. Further oncogenicity studies are being conducted on 2,4-D, and currently it is designated as a Class C carcinogen (possible human carcinogen) by EPA.

Adverse reproductive effects have been reported in rats in a 2 generation study where the animals were fed 0, 5, 20, or 80 mg/kg/day (Rodwell, 1984). Gestation survival was low and litter loss was high in the 80 mg/kg group. There were decreased weight gains in the dams at this dose; however, these changes appear to be associated with litter losses. The high dose was discontinued after Flb due to fetal toxicity. Preliminary studies do not indicate that 2,4-D is teratogenic (IARC, 1977; Rodwell, 1983).

2,4-D will be entering the risk assessment process at California Department of Food and Agriculture under SB950 (Birth Defects Prevention Act of 1984), based on the potential adverse effects identified in the oncogenicity/chronic toxicity study and in the reproductive study.

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