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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 1 4 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Thiodicarb - 114501**: Health Effects Division Risk Characterization Document for Extension of Time-Limited Tolerances of Thiodicarb in/on **Leafy Vegetables, Cabbage, Broccoli, and Cauliflower** (PP#7F3516).

Caswell: 900AA
DP Barcode: D230284

FROM: Felecia Fort, Chemist
Reregistration Branch I
Health Effects Division (7509C)

FA Fort

THROUGH: Whang Phang, Branch Senior Scientist
Reregistration Branch I
Health Effects Division (7509C)

8/14/97

TO: Tom Harris, Review Manager
Tina Levine, Branch Chief
Insecticide/Rodenticide Branch
Registration Division (7505C)

The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division of OPP has requested that HED evaluate toxicology and residue chemistry data and to perform dietary, and occupational risk assessments for the extension of temporary tolerances for thiodicarb uses on leafy vegetables, broccoli, cabbage, and cauliflower.

This is a highly unusual assessment because thiodicarb metabolizes to methomyl which is also a registered pesticide. This assessment will take into account both thiodicarb and methomyl. For dietary purposes, thiodicarb and methomyl will each be assessed separately. For the water risk, HED has determined the exposure and risk associated from methomyl only, since thiodicarb

conducted using thiodicarb when assessing exposure to mixer/loaders (handlers). However, since thiodicarb rapidly degrades to methomyl, post application (reentry intervals) assessments were conducted using methomyl. Thiodicarb does not have any residential uses.

Background

Rhone-Poulenc is petitioning for an extension of the time-limited tolerances for residues of thiodicarb and its regulable metabolite methomyl in/on leafy vegetables at 35 ppm and broccoli, cabbage, and cauliflower at 7 ppm. The existing tolerances for such residues in/on leafy vegetables, broccoli, cabbage, and cauliflower along with its associated registrations (EPA Reg. Nos. 264-378, 264-379, 264-530) expire 8/15/97 (40 CFR 180.407). The above tolerances were established as time-limited due to several outstanding toxicology data requirements. At this time all toxicology data have been submitted and reviewed except for an acute neurotoxicity study(81-8). All tolerances will be time-limited until this data gap is fulfilled. The time limitation allows for development and review of the data.

This petition is being examined with regard to the criteria set forth in the Food Quality Protection Act (FQPA). The Registrant submitted no new toxicology or residue chemistry data with this petition, but did include (1)chronic and acute dietary exposure and risk assessments for thiodicarb including both current and proposed uses, based on anticipated residues; (2)chronic and acute dietary exposure and risk assessments for methomyl and thiodicarb combined; and (3) a discussion of the impact of the FQPA on the above mentioned time-limited tolerances.

RECOMMENDATIONS

HED has evaluated the petition for the extension of time-limited tolerances for thiodicarb on leafy vegetables, broccoli, cabbage and cauliflower. At this time no additional concerns for exposure to infants and children are identified. Estimated aggregate chronic and acute risk from combined dietary, non-dietary and drinking water exposure for thiodicarb does not exceed HED's level of concern for the purposes of extending the time-limited tolerances.

RISK CHARACTERIZATION

Dietary Risk - Food(thiodicarb only)

A **chronic** dietary risk assessment was conducted using tolerance level residues and BEAD percent crop treated information. The chronic analysis indicates that exposure from the existing permanent, and time-limited tolerances for the U.S. population would account for 23% of the RfD. For females (13+ years, nursing), the subgroup with the highest exposure, 22% of the RfD would be utilized. For children(1 to 6 years old), and infants, 36% and 14%, respectively, of the RfD would be consumed. Therefore, chronic dietary risk considering

consumption of thiodicarb from food sources is not of concern.

To estimate **acute** dietary exposure, the registrant conducted Monte Carlo simulations for the overall U.S. population, women (13+ years, nursing), children (1 to 6 years), and infants. Acute dietary exposure estimates at the 99.9 percentile of exposure for the overall U.S. population, women (13+ years, nursing), children (1 to 6 years), and infants resulted in Margins of Exposure (MOEs) of 218, 222, 439, and 946, respectively. The results of the acute exposure analysis indicate that there are adequate Margins of Exposure (MOEs) for the population subgroup of concern, women of child bearing age, as well as for the overall U.S. population, infants and children from the application of thiodicarb.

A **cancer** assessment conducted for the total U.S. Population only, resulted in a MOE of 714. The MOE of 714 assumes all residues to be at tolerance level. Percent crop treated data was used in calculating the cancer MOE.

Dietary Risk-Water(methomyl only)

MOEs for acute risk are estimated to be 7001 for adults (males) and 2000 for children. Chronic water risks are estimated to be 9% RfD for adults, 33% RfD for children.

Occupational Risks

MOEs were calculated for mixer/loader (handler) applications for thiodicarb. MOEs were all above 100, the margin of exposure generally considered as HED's level of concern. Reentry intervals (REIs) based on methomyl and a 3 lb/A application resulted in a MOE of 352 on Day 1. Note: some treatments are applied at a 6 lb/A rate.

Non-occupational (residential) Risks

There are no residential or lawn uses of thiodicarb; therefore, a residential risk assessment is not appropriate.

Aggregate Exposure/Risk:

For **acute aggregate risk** from thiodicarb and methomyl combined, the dietary exposure number (6.57×10^{-3}) from the Novigen Monte Carlo analysis and the acute water exposure number (8.57×10^{-4}) were combined and resulted in

an aggregate exposure of 7.43×10^{-3}. When compared against the methomyl NOEL of 6 mg/kg/day the acute aggregate MOE for the general U.S. population is 807. Using the same formula, MOEs for children (1-6 years) and infants were 345 and 548, respectively.

For **chronic aggregate risk,** chronic exposures to methomyl from thiodicarb and methomyl applications and the chronic water exposure were combined and compared to the methomyl reference dose. Results of the chronic exposure analysis show that no single subpopulation exceeded 7% of the RfD. The two most significantly exposed subpopulations are non-nursing infants (<1 year old) and all infants with 6.5% and 5.2% of the RfD occupied, respectively. For the overall U.S. population, only 1.9% of the RfD was occupied.

No **aggregate cancer risk** assessment is required because methomyl is not a carcinogen and methomyl, rather than thiodicarb, per se, is expected in ground and surface water.

Detailed Considerations

Hazard Assessment for Thiodicarb

1. **Dietary Endpoint Selection**

   a) Acute Risk. The TES Committee recommended use of the developmental toxicity NOEL of 3 mg/kg/day, based on skeletal variations and decreases in pup body weights at the LOEL of 10 mg/kg/day, from an oral developmental toxicity study in the rat (Accession nos. 099377 and 099223). This risk assessment should evaluate acute dietary risk to females 13+ and older.

   b) Chronic Risk. RfD = 0.03 mg/kg/day. The RfD was established based on a 2-year rat feeding/carcinogenicity study (MRID Nos. 43308201, 43000501) with a NOEL of 3.3 mg/kg/day and an uncertainty factor of 100 based on increased incidence of extramedullary hematopoiesis in males and decreased red blood cell cholinesterase activity in females at the LOEL of 15 mg/kg/day.

   c) Cancer Risk. Thiodicarb has been classified as a Group B2 carcinogen by the Cancer Peer Review Committee (Peer Review Document dated 6/10/96), based on an increased incidence of liver tumors in male and female CD-1 mice at 1000mg/kg/day and testicular interstitial cell tumors in Sprague-Dawley rats at 60 mg/kg/day. A Q_1^* (low-dose extrapolation) was not considered appropriate because significant increases in the tumor incidences were observed only at the

highest tested dose in both species. In the mouse, the highest tested dose (1000 mg/kg) is the limit dose for a carcinogenicity study and it may have been excessive. Also there was no evidence of genotoxicity. The Cancer Peer Review Committee recommended that a non-linear methodology (MOE) be applied for the estimation of human cancer risk, with a point of departure set at the 5 mg/kg/day dose, the lowest tested dose in the mouse carcinogenicity study.

d) Infants and Children

I) Developmental Studies

Rat - From the rat developmental study (MRID Nos. 00043739, 00043740, 00043741, 00053254, 00053255, 00053256), the maternal (systemic) NOEL was 10 mg/kg/day, based on cholinergic clinical signs (tremors, inactivity) at the LOEL of 20 mg/kg/day. The developmental (pup) NOEL was 3 mg/kg/day, based on decreased fetal body weights and increased incidence of litters and fetuses with skeletal variations at the LOEL of 10 mg/kg/day.

Rabbit - From the rabbit developmental study (MRID Nos. 00159814, 40280001), the maternal (systemic) NOEL was 20 mg/kg/day, based on decreased body weight gain and food consumption at the LOEL of 40 mg/kg/day. The developmental (pup) NOEL was $\geq$40 mg/kg/day (highest dose tested).

Mouse - From the mouse developmental toxicity study (MRID nos. 00043742, 00043743, 00053257, 00053258), the maternal (systemic) toxicity NOEL was 100 mg/kg/day, based on increased mortality at the LOEL of 200 mg/kg/day. The developmental (pup) NOEL was $\geq$200 mg/kg/day (highest dose tested).

ii) Reproduction Studies

Rat - From the rat reproduction study (MRID Nos. 42381301, 42381302), the maternal (systemic) NOEL was 5 mg/kg/day), based on decreased body weight, weight gain and food consumption in both sexes at the LOEL of 15 mg/kg/day. The reproductive/developmental (pup) NOEL was 15 mg/kg/day, based on decreased fetal body weight and viability at the LOEL of 45 mg/kg/day.

2. **Occupational Exposure Endpoint Selection for Thiodicarb**:

a. There are no dermal absorption data available; therefore, a default of 100% dermal absorption is assumed.

b. For short term (1-7 day) or intermediate term (1 week to several months), **dermal** occupational and residential exposures:

This risk assessment is not required. No appropriate endpoint was identified. No treatment-related effects were observed at 1000 mg/kg/day in a 16-day repeated dose dermal toxicity study in rabbits (MRID 00043738). No dermal or systemic toxicity was observed at 1000 mg/kg/day in a 21-day dermal toxicity study in rats (MRID 00044967)..

c. For chronic (several months to lifetime), **dermal** occupational or residential exposures:

Chronic dermal toxicity endpoints were identified for thiodicarb. However, based on the current use patterns, chronic exposures to thiodicarb are not expected, and a chronic risk assessment is not necessary.

HED believes that a reasonable worst-case frequency of exposure would be six days per week for 2 - 3 months for harvesters working in crops where thiodicarb use is common. For nursery and greenhouse workers engaged in cultivation of herbaceous and woody ornamentals, a reasonable worst case frequency of exposure would be intermittent exposures of 2 - 3 weeks at a time, several times per year, but not continuous. This is representative of intermediate-term rather than chronic exposure

d. For **inhalation** (any duration) occupational or residential exposures:

Assuming 100% absorption, the LOEL to be used for risk assessment for thiodicarb is c 0.0048 mg/l, based on a 9-day dust inhalation study in rats. This was the lowest dose tested in this study. Effects seen at the LOEL of pinpoint pupils and tremors are clinical signs typically associated with cholinesterase effects. These effects were observed in both sexes. Using route-to-route extrapolation to calculate dose, this converts to a LOEL of less than 1.2 mg/kg/day.

NOTE: A hazard assessment for methomyl is provided as an addendum to this document (see Appendix I)

Dietary Exposure (Food)

1. The qualitative nature of the residue in plants is adequately understood based on soybean, tomato, cotton, sweet corn and peanut metabolism studies. The residues to be regulated

in plants are thiodicarb and its metabolite methomyl (S. Funk, 2/20/92, CBRS No. 8574, DP Barcode D168460).

2. The qualitative nature of the residue in animals is adequately understood based upon acceptable ruminant and poultry metabolism studies. The residues to be regulated in livestock are thiodicarb and its metabolite methomyl (D.Miller, 5/30/96, CBRS No. 14633, DP Barcode D208762).

3. Adequate analytical methodology is available for enforcement of tolerances of thiodicarb. Method I in the Pesticide Analytical Manual (PAM), Vol. II, is a GLC/sulfur specific flame photometric detector (FPD-S) method that has undergone a successful EPA method validation. The reported limit of detection is 0.02 ppm for plant commodities (D. Miller, 2/24/94, CBRS No.12305, DP Barcode D193543).

   An enforcement analytical method for livestock commodities is not necessary since there are no significant animal feed items associated with the subject crops.

4. Residues of thiodicarb or its metabolites are not expected to exceed 35 ppm in/on leafy vegetables and 7 ppm in/on broccoli, cabbage, and cauliflower as a result of this use (See Magnitude of the Residue-Crop Field Trials in Appendix II). **However, in accordance with 40 CFR § 180.41(c)(4), the time-limited tolerance for "leafy vegetables" should be modified to "leafy vegetables (except *Brassica* vegetables)."**

5. No processed commodities are associated with these uses.

6. Secondary residues in animal commodities are not expected from these uses.

7. There are no Codex, Canadian, or Mexican tolerances for thiodicarb in/on leafy vegetables, broccoli, cabbage or cauliflower. Therefore, there are no questions with respect to compatibility of U.S. tolerances with Codex MRLs.

Dietary Exposure (Water)

Use Pattern

Thiodicarb is a carbamate insecticide used in the control of all types of caterpillars on corn, cotton, soybeans, and vegetables. This use pattern may impact ground water and surface water, and ultimately drinking water. Therefore, an assessment of the risks posed to human health from the potential impact of the use of thiodicarb on drinking water is required. Data are available to assess the environmental fate of thiodicarb and its main degradate methomyl.

Ground Water

Thiodicarb breaks down rapidly in the environment to methomyl. Methomyl, the major degradate of thiodicarb, is very mobile and persists in the field for a time sufficient (field dissipation half life = 18 days) to leach into groundwater. This tendency is enhanced when soils are permeable and the water table is high. The Environmental Fate and Effects database, the Pesticides In Ground Water Database, and ground water monitoring studies were searched for monitoring data on thiodicarb and methomyl.

Water Exposure Estimates

Since, thiodicarb breaks down rapidly to methomyl, HED has estimated the exposure and risk associated with the highest methomyl residues detected in ground water monitoring studies and with the PRZM/EXAMS model numbers for surface water. An Environmental Fate profile is discussed in Appendix III.

The EFED-supplied estimate for methomyl/thiodicarb in ground water to be used in the acute exposure analyses is 20 ppb and is based on a small-scale prospective ground water study performed by DuPont. The EFED-supplied estimate for methomyl/thiodicarb in surface water is 30 ppb which is based on a worst-case PRZM/EXAMS run showing a concentration of 151 ppb in an agricultural farm pond and a DuPont ecological monitoring study showing a minimum 5-8 fold dilution factor (see D. Miller review, DP Barcode 238005). The use of the 5-fold dilution factor in estimating the concentration in surface water thus accounts for the high end of the possible range. The chronic estimated environmental concentration for methomyl is 26 ppb for surface water and 2 ppb for ground water (see Tier 2 Estmated Environmental Concentrations for Thiodicarb and Methomyl, N.Thurman, 5/29/97).

The following assumptions have been made to estimate exposure; water consumption is defined as all water obtained from the household tap that is consumed either directly as a beverage or used to prepare foods and beverages. For the adult male exposure calculation, the average adult body weight is assumed to be 70 kg, and it is assumed that the average adult consumes 2 liters of water (l)/day. For the and children's exposure, the average body weight is assumed to be 10 kg and the average water consumption is assumed to be 1 liter per day.

The other assumption inherent in this calculation is that water from the same source containing the same contaminant level is consumed throughout a 70-year lifetime. The second of these assumptions is extremely conservative, since most members of the U.S. population move at some time during their lifetime and do not live in the same area or drink from the same water source for a 70-year lifetime.

Exposure is calculated using the following formula for adults(males):

Exposure = (chemical concentration in ug/L in ground and/or surface water) x (10^{-3} mg/ug) ÷ (70 kg body weight) x (2L water consumed/day)

For children (1 to 6 years old), the exposure would be calculated using the following formula:

Exposure = (chemical concentration in ug/L in ground and/or surface water) x (10^{-3} mg/ug) ÷ (10 kg body weight) x (1L water consumed/day)

Adult (Male) Acute Exposure

Methomyl exposure (highest concentration detected in ground water) = (20 ug/L) x (10^{-3} mg/ug) ÷ (70 kg body weight) x (2L day) = 5.7×10^{-4} mg/kg/day.

Methomyl exposure (highest concentration modeled in surface water) = (30 ug/L) x (10^{-3} mg/ug) ÷ (70 kg body weight) x (2L day) = 8.57×10^{-4} mg/kg/day.

The highest exposure number will be used for acute water risk assessment for ug/L) x (10^{-3} mg/ug) ÷ (70 kg body weight) x (2L day) = 8.57×10^{-4} mg/kg/day.

Children (1 to 6 years old) Acute Exposure

Methomyl exposure (highest concentration detected in ground water) = (20 ug/L) x (10^{-3} mg/ug) ÷ (10 kg body weight) x (1L day) = 2.0×10^{-3}mg/kg/day.

Methomyl exposure (highest concentration modeled in surface water) = (30 ug/L) x (10^{-3} mg/ug) ÷ (10 kg body weight) x (1L day) = 3.0×10^{-3} mg/kg/day.

The highest exposure number will be used for acute water risk assessment for ug/L) x (10^{-3} mg/ug) ÷ (10 kg body weight) x (1L day) = 3.0×10^{-3} mg/kg/day.

Adult (Male) Chronic Exposure

Methomyl exposure (average concentration detected in ground water) = (2 ug/L) x (10^{-3} mg/ug) ÷ (70 kg body weight) x (2L day) = 5.7×10^{-5} mg/kg/day.

Methomyl exposure (average concentration detected in surface water) = (26 ug/L) x (10^{-3} mg/ug) ÷ (70 kg body weight) x (2L day) = 7.4×10^{-4} mg/kg/day.

The highest exposure number will be used for chronic water risk assessment = 7.4×10^{-4}.

Children's(1 to 6 years old) Chronic Exposure

Methomyl exposure (average concentration detected in ground water) = (2 ug/L) x (10^{-3} mg/ug) ÷ (10 kg body weight) x (1L day) = 2.0 x 10^{-4} mg/kg/day.

Methomyl exposure (average concentration modeled in surface water) = (26 ug/L) x (10^{-3} mg/ug) ÷ (10 kg body weight) x (1L day) = 2.6 x 10^{-3} mg/kg/day.

The highest exposure number will be used for acute water risk assessment for children = 2.6 x 10^{-3}.

Drinking Water Risk

Thiodicarb breaks down rapidly in the environment to methomyl and methomyl is the pesticide that was monitored in ground water and surface water studies. The methomyl acute dietary endpoint is used for the acute dietary risk from water and is based on the maternal toxicity NOEL of 6 mg/kg/ day from the rabbit developmental toxicity study. For calculating the MOE, an extra safety factor of 3 will be used in addition to the 100 (MOE = 300) due to the lack of acute and subchronic neurotoxicity studies as well as the severity of effects seen in the rabbit developmental toxicity study.

Acute Risk-Water

NOEL//Exposure = MOE

Adult (male) MOE = 6 mg/kg/day ÷ acute water exposure (8.57 x 10^{-4}mg/kg/day) = 7001

Children's MOE = 6 mg/kg/day ÷ acute water exposure(3 x 10^{-3} mg/kg/day) =2000

Chronic Risk- Water

The chronic dietary endpoint, the RfD, is 0.008 mg/kg/day for methomyl, and is used to calculate the chronic dietary risk. The RfD was established based on a 2-year dog feeding/carcinogenicity study with a NOEL of 2.5 mg/kg/day and an uncertainty factor of 100 to account for both inter-species extrapolation and intra-species variability. An additional uncertainty factor of 3 was applied to account for the lack of acute and subchronic neurotoxicity studies.

The chronic dietary risk from ground and surface water is expressed as a percentage of the RfD through the following formula:

chronic water exposure mg/kg/day ÷RfD mg/kg/day X 100 = % RfD

%RfD Adult (male) = $7.4 \times 10^{-4} \div 0.008$ mg/kg/day x 100 =9%RfD

%RfD Children(1 to 6 years) = $2.6 \times 10^{-3} \div 0.008$ mg/kg/day x 100 =33%RfD

Occupational and Residential Exposure

An occupational and/or residential exposure assessment is required for an active ingredient if (1) certain toxicological criteria are triggered and (2) there is potential exposure to handlers (mixers, loaders, applicators, etc.) during use or to persons entering treated sites after application is complete. Thiodicarb has been determined to be a carcinogen and there is potential exposure.

Summary of Use Patterns and Formulations

Thiodicarb, is an insecticide used on terrestrial food and non-food crops. The registrations associated with this risk assessment (264-379, 264-378, and 264-530) are formulated as a water dispersible granular/dry flowable (80% a.i.) and a flowable concentrate (3.2 lb/gal.). Thiodicarb is applied using a variety of equipment including fixed-wing aircraft, helicopters, groundboom sprayers, and chemigation techniques. Application rates vary up to one pound active ingredient per acre depending on the formulation and the target crop. Thiodicarb is applied to a wide variety of food and non-food sites including: broccoli, cabbage, cole crops, leafy vegetables, corn, cotton, soybeans, citrus fruits, rights-of-way/fencerows/hedgerows/drainage systems, ornamental herbaceous and nonflowering plants, at commercial nurseries and greenhouses by professionals, and ornamental and/or shade trees.

Non-occupational/Residential Exposure

There are no residential lawn or garden uses for thiodicarb; therefore, non-occupational exposure of thiodicarb is insignificant.

Epidemiological Information

The following data bases have been consulted for poisoning incident data for

thiodicarb: (1) OPP Incident Data System (IDS), (2) Poison Control Centers, (3) California Department of Food and Agriculture (replaced by the Department of Pesticide Regulation in 1991), and (4) National Pesticide Telecommunications Network (NPTN).

There is very little information available on incidents related to use of thiodicarb from any of the available data bases consulted by HED. However, almost no usage by commercial pesticide applicators has been reported for thiodicarb products in California from 1982 - 1993 (the period reviewed). HED concludes that the lack of incident reports reflects the absence of any significant usage in California.

Handler Exposures and Assumptions

Dermal exposure was not considered since no dermal, short- or intermediate-term endpoints were identified.

However, there are potential inhalation exposures to mixers, loaders, applicators, and other handlers during usual use-patterns associated with thiodicarb uses on leafy vegetable, broccoli, cabbage, and cauliflower. Based on the use patterns, seven major exposure scenarios were identified for thiodicarb: (1a) mixing/loading wettable powders for aerial/chemigation application; (1b) mixing/loading wettable powders for groundboom application; (2a) mixing/loading liquids for aerial/chemigation application; (2b) mixing/loading liquids for groundboom application; (3a) mixing/loading dry flowables for aerial/chemigation application; (3b) mixing/loading dry flowables for groundboom application; (4) applying sprays with a fixed-wing aircraft; (5) applying sprays with a helicopter; (6) applying sprays with groundboom equipment; and (7) flagging aerial spray applications.

Inhalation exposure estimates (developed using PHED Version 1.1 surrogate data) are presented in Table 1. No chemical-specific data were submitted. Table 2 presents the corresponding risk assessment (MOEs) for inhalation exposures. Table 3 summarizes the caveats and parameters specific to each exposure scenario and corresponding risk assessment.

Table 1. Inhalation Exposures of Thiodicarb

Exposure Scenario (Scen #)	Baseline Inhalation Unit Exposure (μg/lb ai)[a]	Application Rate (lb ai/acre)[b]	Daily Acres Treated[c]	Daily Inhalation Exposure (mg/day)[d]
Mixer/Loader Exposure				
Mixing/Loading Wettable Powder for Aerial and Chemigation Application (1a)	43.4	1	350	15.19
Mixing/Loading Wettable Powder for Groundboom Application (1b)			80	3.47
Mixing/Loading Liquids for Aerial and Chemigation Application (2a)	1.2	1	350	0.42
Mixing/Loading Liquids for Groundboom Application (2b)			80	0.096
Mixing/Loading Dry Flowable for Aerial and Chemigation Application (3a)	0.77	1	350	0.27
Mixing/Loading Dry Flowable for Groundboom Application (3a)			80	0.062
Applicator Exposure				
Fixed-wing Aerial Spray Application (4)	See Eng. Controls	1	350	See Eng. Controls
Helicopter Spray Application (5)	See Eng. Controls	1	350	See Eng. Controls
Groundboom Spray Application (6)	0.7	1	80	0.056
Flagger Exposure				
Flagging Aerial Spray Application (7)	0.28	1	350	0.098

a Baseline inhalation exposure represents no respirator.

b Application rates are maximum values found in the thiodicarb labels [EPA Reg. Nos. 264-343, 264-378, 264-379, 264-530].

c Daily acres treated values are from EPA estimates of acreage that could be treated in a single day for each exposure scenario of concern.

d Daily inhalation exposure (mg/day) = Exposure (μg/lb ai) * (1mg/1000 ug)conversion * Appl. Rate (lb ai/A) * Acres Treated

Table 2. Inhalation Risk from Thiodicarb

Exposure Scenario (Scen #)	Baseline Inhalation Dose (mg/kg/day)[a]	Baseline Inhalation MOE[b]	PPE Inhalation Unit Exp. (ug/lb ai)	PPE Inhalation Dose (mg/kg/day)[a]	PPE Inhalation MOE (mg/kg/day)[b]	Engineering Controls Inhalation Unit Exp.(ug/lb ai)	Engineering Controls Inhalation Dose (mg/kg/day)[a]	Engineering Controls Inhalation MOE[b]
Mixer/Loader Risk								
Mixing/Loading Wettable Powder for Aerial and Chemigation Application (1a)	0.217	6	8.68 (Dust/ Mist Respirator -- five fold PF)	0.043	28	0.24 (Water Soluble Packets)	0.0012	1,000
Mixing/Loading Wettable Powder for Groundboom Application (1b)	0.05	24		0.01	120	NA	NA	NA
Mixing/Loading Liquids for Aerial and Chemigation Application (2a)	*0.006*	*200*	NA	NA	NA	NA	NA	NA
Mixing/Loading Liquids for Groundboom Application (2b)	0.0014	857	NA	NA	NA	NA	NA	NA
Mixing/Loading Dry Flowables for Aerial and Chemigation Application (3a)	0.0039	308	NA	NA	NA	NA	NA	NA
Mixing/Loading Dry Flowables for Groundboom Application (3b)	0.00089	1348	NA	NA	NA	NA	NA	NA
Applicator Risk								
Fixed-wing Aircraft Spray Application (4)[c]	See Eng. Controls	See Eng. Controls	See Eng. Controls	See Eng. Controls	See Eng. Controls	0.068	0.00034	3,529
Helicopter Spray Application (5)[c]	See Eng. Controls	See Eng. Controls	See Eng. Controls	See Eng. Controls	See eng. Controls	*0.0018*	*0.000009*	133,333
Groundboom Application (6)	0.0008	1,500	NA	NA	NA	NA	NA	NA
Flagger Risk								
Flagger for Aerial Spray Applications (11)	0.0014	857	NA	NA	NA	NA	NA	NA

NA Not applicable since the MOE already exceeded 100.

[a] Baseline Inhalation Dose (mg/kg/day) = daily inhalation exposure (mg/day) / 70 kg.

[b] Inhalation MOE = NOEL (mg/kg/day) / Daily Inhalation Dose (mg/kg/day). Where NOEL = 0.00480 mg/L; route-to-route extrapolation = [(0.0048 mg/L/day * 1 * 8.46 L/hr * 6 hr * 1) / (0.190 kg)] = NOEL of **1.2** mg/kg/day.

[c] Only closed cockpit data are available for scenarios 4 and 5.

Table 3. Exposure Scenario Descriptions for Uses of Thiodicarb

Exposure Scenario (Number)	Data Source	Standard Assumptions[a] (8-hr work day)	Comments[b]
Mixer/Loader Exposure			
Mixing/Loading Wettable Powder (1a and 1b)	PHED V1.1	350 acres for aerial and chemigation, 80 acres for groundboom.	**Baseline:** "Best Available" grades: Inhalation = ABC grades. Inhalation = 44 replicates. Medium confidence in inhalation data. **Engineering Controls (water soluble packets):** "Best Available" grades: Inhalation = All grades. Inhalation = 15 replicates. Low confidence in Inhalation data. PHED data were used for baseline and engineering controls data. An 80% PF was added to the PPE scenario only to simulate a dust/mist respirator.
Mixing Liquid Formulations (2a and 2b)	PHED V1.1	350 acres for aerial and chemigation, 80 acres groundboom.	**Baseline:** "Best Available" grades: Inhalation acceptable grades. Inhalation = 85 replicates. High confidence in inhalation data. PHED data were used for baseline, no PFs were necessary.
Mixing/Loading Dry Flowable Formulations (3a and 3b)	PHED V1.1	350 acres for aerial and chemigation, 80 acres groundboom.	**Baseline:** "Best Available" grades: Inhalation acceptable grades. Inhalation = 23 replicates. High confidence in inhalation data. PHED data were used for baseline, no PFs were necessary.
Applicator Exposure			
Fixed-wing Aircraft Application (4)	PHED V1.1	350 acres	**Engineering controls:** "Best Available" grades: Inhalation = ABC grades. Inhalation = 23 replicates. Medium confidence in inhalation data. PHED data were used for baseline, no PFs were necessary.
Helicopter Application (5)	PHED V1.1	350 acres	**Engineering controls:** "Best Available" grades: Inhalation = acceptable grades. Inhalation = 3 replicates. Low confidence in inhalation data. PHED data were used for baseline, no PFs were necessary.
Groundboom Application (6)	PHED V1.1	80 acres	**Baseline:** "Best Available" grades: Inhalation = acceptable grades. Inhalation = 22 replicates. High confidence in inhalation data. PHED data were used for baseline, no Pfs were necessary.
Flagger Exposure			
Flagger (7)	PHED V1.1	350 acres	**Baseline:** "Best Available" grades: Inhalation = acceptable grades. Inhalation = 18 replicates. High confidence in inhalation data. PHED data were used for baseline, no PFs were necessary.

[a] Standard Assumptions based on an 8-hour work day as estimated by HED. BEAD data were not available.

[b] "Best Available" grades are defined by EPA SOP for meeting Subdivision U Guidelines. Acceptable grades are matrices with grades A and B data. Data confidence are assigned as follows:

[c] High= grades A and B and 15 or more replicates, Medium = grades A, B, and C and 15 or more replicates, Low= grades A, B, C, D, and E or any combination of grades with less than 15 replicates

Post Application Exposure & Assumptions

A dislodgeable foliar residue (DFR) study was conducted for thiodicarb on lettuce, MRID 43198102. In this study, residues of both thiodicarb and its breakdown product, methomyl, were measured. However, since thiodicarb breaks down rapidly to methomyl, only methomyl residues were included in the risk assessment. Four applications of thiodicarb were made to head lettuce at a rate of 0.75 pounds active ingredient (ai) per acre at 7-day intervals for a total application of 3.0 pounds active ingredient per acre. Four trials were conducted: two at Imperial Valley, California, and two at San Joaquin Valley, California. Residue samples were taken before and after each application and on days 1, 5, 7, 10, 14 and 18 following the last application. A review of the QA/QC results for this study indicate that the laboratory, field, and storage recoveries were all within an acceptable range of 70 to 120 percent. At the Imperial Valley site, the Spring application (March/ April of 1993) residue data were not used by EPA for this assessment because of a rain event that affected residue results. The residues from the other three test runs were averaged.

HED has estimated 1,000 cm^2/hr to represent the transfer coefficient for crops with relatively low potential for dermal transfer during routine post-application activities. HED believes the transfer coefficient is a reasonable worst-case value. The following crops are considered to have relatively low potential for post-application dermal transfer: broccoli, cabbage, other cole crops, lettuce and other leafy vegetables, cotton, and soybeans.

HED believes the lettuce DFR study *overestimates* potential methomyl residues in lettuce and other leafy vegetables since the seasonal application rate used in the study with head lettuce was twice the labeled rate. The label states that application to lettuce and other leafy vegetables should not exceed 1.5 pounds active ingredient per acre per season, but the study was conducted at 3 pounds active ingredient per acre per season.

HED believes the DFR study *underestimates* the potential methomyl residues following thiodicarb applications to cole crops which include broccoli, cabbage and cauliflower for several reasons: (1) these crops have an application rate (single application) greater than the 0.75 pounds ai per acre rate used in the study; (2) labels recommend applications to many crops more frequently than once per week as was used in the study; and (3) several crops have seasonal maximum rates of greater than the 3.0 pounds ai per acre applied in the study. For example, for cole crops, the label allows application of 1.0 pounds ai per acre as often as needed up to a seasonal rate of 6.0 pounds ai per acre. HED has determined that methomyl residues on these crops are likely to be higher than those reported in the DFR study on lettuce. Table 4 lists maximum application rates, application frequency, and maximum seasonal application rates by crop.

Table 4: Maximum Application Rate, Application Frequency, and Seasonal Rates for Thiodicarb

CROP	Maximum Application Rate (lb ai/acre	Frequency of Application	Maximum Seasonal Rate (lb ai/acre)
Lettuce Study (MRID 43198102)	0.75	7 days	3.0
Lettuce & other Leafy Vegetables	0.75	as needed	1.5
Broccoli & other Cole Crops	1.0	as needed	6.0

Using the DFR data from the lettuce study and estimated transfer coefficients, HED has estimated exposure, dose, and MOEs for post-application activities. The results are presented in Table 5.

Potential average daily exposure (ADE) is calculated as follows:

$$\textit{Potential ADE} = \frac{\textit{DFR (ug/cm}^2\textit{) x Transfer Coefficient (1,000 cm}^2\textit{/hr) x Work Day (8 hr)}}{\textit{Unit Adjustment from ug to mg (1000ug)}}$$

Table 5: Worker Reentry Exposure to Methomyl Residues Following Thiodicarb Application (Application rate of 0.75 lb for 4 applications at 7 day intervals for a total of 3.0 lb per acre per season)

Days After Treatment	Best Fit DFR (μg/cm^2)[a]	Tc (cm^2/hr)[b]	Exposure (mg/day)[c]	Dose (mg/kg/day)[d]	MOE[e]
1	0.1242	L[f] 1,000	0.994	0.0142	**352**

[a] The average foliar dislodgeable residues from the lettuce study MRID No. 431981-02, also used as a surrogate for other crops. DFR (μg/cm^2) was derived by converting the measured DFR data into log normal then running a linear regression equation to estimate the dissipation over time.

[b] Transfer coefficients estimated by HED.

[c] Exposure (mg/day) = [(Best Fit DFR x Transfer Coefficient (1,000 cm^2/hr)) / 1,000 μg/mg] x 8 hrs/day

[d] Dose (mg/kg/day) = Exposure (mg/day) / 70 kg.

[e] MOE = methomyl NOEL (5 mg/kg/day) / Dose (mg/kg/day)

[f] L = crops with potentially low dermal transfer to post-application entry workers

Occupational and Residential Risk Characterization

Risk Estimates For Handler Exposures

Inhalation

The daily inhalation dose is calculated using the following formula. A body weight of 70 kilograms is used in these calculations to represent the average body weight of an adult handler.

Daily Inhalation Dose (mg ai/kg body weight/day) =
Daily Inhalation Exposure (mg ai/day) / Body Weight (kg)

These calculations of daily inhalation dose of thiodicarb received by handlers are used to assess the inhalation risk to those handlers. Inhalation MOEs are calculated using the following formula:

MOE = NOEL (mg/kg/day) / Daily Inhalation Dose (mg ai/kg bw/day)

To calculate the handler inhalation MOEs for thiodicarb, a LOEL of 1.2 mg/kg/day is used.

The calculations estimating inhalation risk indicate that the MOEs are 100 or greater at **baseline** for the following scenarios:

- (2a) mixing/loading liquids for aerial and chemigation applications;
- (2b) mixing/loading liquids for groundboom application;
- (3a) mixing/loading dry flowables for aerial and chemigation application;
- (3b) mixing/loading dry flowables for groundboom application;
- (7) flagging liquid aerial applications.

The calculations estimating inhalation risk indicate that the MOEs are 100 or greater with **PPE** (a dust/mist respirator) for the following scenario:

- (1b) mixing/loading wettable powder for groundboom application.

The calculations estimating inhalation risk indicate that the MOEs are 100 or greater with **engineering controls** for the following scenarios:

- (1a) mixing/loading wettable powder for aerial and chemigation application;

- (4) applying liquid sprays with a fixed-wing aircraft; and,
- (5) applying liquid sprays with a helicopter.

NOTE: (4) and (5) Only enclosed cockpit data are available as *baseline* and *PPE* for applying liquid sprays with a fixed-wing aircraft and with a helicopter.

Risk From Post-Application Exposures

Potential average daily dose (ADD) is calculated using the following formula:

$$Potential\ ADD = \frac{Exposure\ (mg/day)}{70\ kg.}$$

Because the toxicity data are from a dermal study, dermal absorption is not factored.

Post-application MOEs are calculated using the following formula:

$$MOE = \frac{NOEL}{ADD}$$

There is no short- or intermediate-term dermal endpoint of concern for thiodicarb, and a post-application inhalation risk assessment is not warranted since thiodicarb degrades rapidly to methomyl; therefore, only the toxicity concerns pertaining to methomyl are considered in the post-application risk assessment. For methomyl, the short- and intermediate-term NOEL for dermal toxicity is 5 mg/kg/day.

A study was conducted on dislodgeable foliar residues following applications of thiodicarb to lettuce (MRID 43198102). Both thiodicarb and methomyl residues are reported in the study. EPA estimated reasonable worst-case transfer coefficients for crops with potentially low dermal transfer during post-application activities, as well as for crops with potentially medium to high dermal transfer during post-application activities. The resulting calculations indicate that MOEs equal or exceed 100 for crops with potentially low dermal transfer, on the day following application (24 hours).

Note that HED believes the calculations *overestimate* risk following applications to lettuce and other leafy vegetables, since they are based on a seasonal application rate of 3.0 pounds per acre and the maximum allowable seasonal rate for these crops is 1.5 pounds per acre.

Note also that HED believes that the calculations *underestimate* risk following

applications to cole crops as noted in Table 4, these crops have (1)higher maximum application rates than the 0.75 pound per acre rate applied in the DFR study, (2) shorter (more frequent) application intervals than the once-per-week interval used in the DFR study, and (3) higher maximum seasonal application rates than the 3.0 pounds per acre applied in the DFR study. However, for the purpose of these time-limited tolerances, HED considers the Margin of Exposure of 352 to be adequate. Considerations of post application risk from these underestimated risk will be discussed at the issuance of the thiodicarb RED chapter.

Additional Occupational/Residential Exposure Studies

Handler Studies

Based on the risk assessment of the current uses of thiodicarb, additional handler exposure studies are not required at this time.

Post-Application Studies

Additional studies may be required pending the outcome of discussions on post-application risk.

Dietary Risk Assessment and Characterization

Thiodicarb

Acute Dietary Risk.

To estimate acute dietary exposure, the registrant conducted Monte Carlo simulations for the overall U.S. population and women 13 years and older, children 1 to 6 years of age, and infants. These analyses included residues from field trial studies, consumption data from the 1989 through 1992 USDA Continuing Survey of Food Intake by Individuals (CSFII), and information on the percentages of the crop treated were utilized.

Food consumption data from the USDA's CSFII conducted from 1989 through 1992 were used to estimate dietary exposure. The USDA provided statistical weights that permitted the data from the various years of the survey to be combined.

For the acute analysis, field trial residues were used for all crops. In compliance with the EPA's guidance document, residue distributions from field studies conducted at maximum label conditions (e.g. maximum number of applications, maximum application rate, and minimum preharvest intervals) were used for foods considered to be single-serving commodities (e.g. cabbage, broccoli, lettuce); mean field trial residues were used for blended/processed commodities (e.g. cottonseed meal, soybean oil).

Processing factors were calculated for cottonseed meal, cottonseed oil, and soybean oil. These factors were used in conjunction with the mean field trial residues to estimate residue levels in the processed commodities.

Residue values were adjusted for the percent of the crop estimated to be treated with thiodicarb. These percentages were provided by the Agency's Biological and Economic Analysis Division (BEAD). . The maximum percentage reported for a particular crop was used in the acute exposure analyses. Percent crop treated information was not provided for swiss chard, parsley, cress, and endive. The percent crop treated for spinach was assumed for these crops.

Acute exposure estimates to thiodicarb were compared against the developmental NOEL of 3 mg/kg/day from a rat developmental study in which decreased pup body weight was observed. Because of the effects observed, the population subgroup of concern is women of child-bearing age. For the overall U.S. population, children 1 to 6 years of age, and infants acute exposure estimates were compared against the maternal NOEL of 10 mg/kg/day from a rat developmental study based on clinical signs of tremors and inactivity.

The Margin of Exposure (MOE) is a measure of how close the high end exposure comes to the NOEL (the highest dose at which no effects were observed in the laboratory test), and is calculated as the ratio of the NOEL to the exposure (NOEL/exposure = MOE). Generally, acute dietary margins of exposure greater than 100 tend to cause no dietary concern to the Agency when results are compared to animal-derived data. The For thiodicarb, EPA has decided that an MOE equal to or greater than 100 is considered to be protective. Although there is a data gap (acute neurotoxicity study), EPA has determined that this is simply a confirmatory study. Other than this study, the database is complete. While tremors and inactivity were observed in one developmental study, other instances of neurotoxic behavior have not been observed in the remaining studies. MOEs for acute dietary exposure were calculated using the estimates at the 99.9 percentile of exposure for groups of concern. The acute exposure MOEs for the application of thiodicarb are presented below in Table 6.

Table 6. Acute Exposure MOEs from the Application of Thiodicarb

Group of Concern	Exposure	NOEL	MOE
U.S. Population	0.013792	10 mg/kg/day	218
Woman 13 years and older	0.013500	3 mg/kg/day	222
Children 1 to 6	0.022758	10 mg/kg/day	439
Infants	0.010575	10 mg/kg/day	946

The results of the acute exposure analyses indicate that there are adequate Margins of Exposure for the overall U.S. population, the population subgroup of concern, women of child bearing age, as well as for the, infants and children from the application of thiodicarb (D. Miller, D238005, 8/8/97).

Chronic Dietary Risk.

A Dietary Risk Evaluation System (DRES) chronic exposure analysis was performed using tolerance level residues and BEAD percent crop treated information to estimate the Anticipated Residue Contribution (ARC) for the general population and 22 subgroups.

Using existing thiodicarb tolerances and % crop treated information result in a ARC which represents 23%, 14%, and 36% of the RfD for the U.S. general population, infants, and children (1 to 6 years old). A total of 22% of the RfD is occupied by females (13+ years, nursing) which is the highest exposed subgroup. If more refined estimates of dietary exposure were made (i.e., use of anticipated residues) lower chronic risks would be estimated. However, Even including the pending tolerances and the higher tolerance for cottonseed, chronic dietary risk from food sources is not of concern.

Cancer Risk

The Cancer Peer Review Committee recommended that a non-linear methodology (MOE) be applied for the estimation of human cancer risk. The Cancer Peer Review Committee has determined that the NOEL of 5 mg/kg/day be used as the point of departure for estimating human risk (For additional details on cancer risk, please see pages 4 and 5). Cancer MOEs are estimated by dividing the NOEL of 5 mg/kg/day, by the chronic exposure. The assessment was conducted for the Total U.S. Population only.

Exposure = ARC
= 0.007 mg/kg/day

MOE = NOEL ÷ Exposure
= 5 mg/kg/day ÷ 0.007 mg/kg/day
= 714

The MOE of 714 assumes all residues be at tolerance level. BEAD percent crop treated information was used in estimating the chronic exposure from thiodicarb.

FQPA Considerations

Aggregate Exposure

In examining aggregate exposure, FQPA directs EPA to take into account available

information concerning exposures from pesticide residues in food and other exposures or which there is reliable information. These other exposures include drinking water and non-occupational exposures, e.g., to pesticides used in and around the home. Risk assessments for aggregate exposure consider both short-term and long-term (chronic) exposure scenarios considering the toxic effects which would likely be seen for each exposure duration.

Thiodicarb is a food use chemical. There are no residential (non-occupational) uses of thiodicarb; therefore, the considerations for aggregate exposure are those from food and drinking water.

Acute Risk

The registrant provided an acute dietary Monte Carlo distributional risk assessment which utilized combined residues of methomyl from the application of thiodicarb and residues of methomyl from the application of methomyl . The methomyl acute dietary NOEL of 6 mg/kg/day was used to calculate the MOE.

Since methomyl, rather than thiodicarb, per se is expected in ground and surface water as a result of thiodicarb applications, an acute aggregate risk from thiodicarb residues includes only risks from food. This assessment is discussed in the previous section under risk characterization for thiodicarb.

Acute exposures to methomyl residues from all sources (food and water, from thiodicarb and methomyl applications) will be aggregated and compared to the methomyl acute dietary NOEL. Using exposure estimates provided by the registrant, EPA estimated MOEs which are shown below in Table 7.

Table 7: EPA-calculated Margins of Exposure (MOEs) for Various U.S. Subpopulations Based on Acute Effects and 24-hour intervals (NOEL = 6 mg/kg BW/day)--FOOD AND WATER .

Population Group	Food		Food and Water Combined	
	24 hour interval		24 hour interval	
	mg/kg BW/day	MOE	mg/kg BW/day	MOE
U.S. Population				
95th percentile	0.000349	17192	0.001206	4975
99th percentile	0.001099	5460	0.001956	3067
99.9th percentile	0.006577	912	0.007434	807
Infants				
95th percentile	0.000215	27907	0.003215	1866
99th percentile	0.000874	6865	0.003874	1549
99.9th percentile	0.007940	756	0.01094	548
Children 1-6 years	0.000482	12448	0.003482	1723
95th percentile	0.002108	2846	0.005108	1175
99th percentile	0.014396	417	0.017396	345
99.9th percentile				

Overall, these estimates are likely to be a conservative estimate of the Margin of Exposure. For example, it assumes that residues, when present, are present as a result of application at the maximum permitted level and observance of the minimum PHI. No reduction as a result of transport time from farm gate to consumer is assumed to occur. Also, no further reduction of residues through washing, peeling, or cooking at the producer or consumer level is assumed to occur. We conclude that sufficient margins of exposure exist at various high-end percentile exposure levels of interest (e.g., 95th, 99th, and 99.9th percentile values) and that there are no acute concerns associated with potential residues of thiodicarb and/or methomyl in foods or drinking water (see D. Miller, D238005, 8/8/97).

Chronic Aggregate Risk

Chronic exposures to methomyl residues from all sources (food and water, from thiodicarb and methomyl applications) will be aggregated and compared to the methomyl reference dose. Therefore aggregate chronic risk for thiodicarb residues includes only risks from food and is shown in the previous section.

Results of the chronic exposure analysis show that no single subpopulation exceeded 7% of the RfD. The two most significantly exposed subpopulations are non-nursing infants (< 1 year old) and all infants with 6.5% and 5.2% of the RfD occupied, respectively. For the overall U.S. population, only 1.9% of the RfD was occupied (see D. Miller, D238005, 8/8/97). The aggregated chronic exposure is shown in Table 8 below.

Table 8. Chronic Aggregate Exposure

Population Subgroup	Dietary %RfD[a]	Water %RfD	Total[b]
U. S. General	1.9	9	11
Children (1 to 6)	2.7	33	36
Infants	6.5	33	40

[a] Dietary %RfD includes methomyl residues from application of thiodicarb and methomyl

[b] Although the Novigen chronic analyses incorporated exposure to both food and water, water concentrations were assumed in their analyses to be 4 ppb. The Agency believes that 26 ppb is a more appropriate estimate. Therefore, chronic water exposure were calculated independently by the Agency using the 26 ppb estimate. The total exposure reflected here incorporates both of these estimates and therefore slightly overestimates the chronic risk.

Carcinogenic Aggregate Risk

No aggregate cancer risk assessment is required because methomyl is not a carcinogen and methomyl, rather than thiodicarb, per se, is expected in ground and surface water.

Cumulative Exposure To Substances with Common Mechanism of Toxicity.

Section 408(b)(2)(D)(v) of the Food Quality Protection Act requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodologies to resolve the complex scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical specific data, much of which may not be presently available.

Although at present the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments, there are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

EPA does not have, at this time, available data to determine whether thiodicarb has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, EPA has not assumed that thiodicarb has a common mechanism of toxicity with other substances.

However, the Agency has determined that thiodicarb has a metabolite which is a registered pesticide, methomyl. Therefore, methomyl residues resulting from applications of both thiodicarb and methomyl will be considered in a cumulative risk assessment and

compared to appropriate toxicological endpoints for methomyl. This is described to some extent in the aggregate exposure section of this time-limited tolerance. These cumulative risks will be addressed further in the HED RED chapter for both thiodicarb and methomyl.

Determination of Safety for Infants and Children

FFDCA section 408 provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for pre-and post-natal toxicity and the completeness of the database unless EPA determines that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA risk assessments either directly through use of a MOE analysis or through using uncertainty (safety) factors in calculating a dose level that poses no appreciable risk to humans. EPA believes that reliable data support using the standard MOE and uncertainty factor (usually 100 for combined inter- and intra-species variability)) and not the additional tenfold MOE/uncertainty factor when EPA has a complete data base under existing guidelines and when the severity of the effect in infants or children or the potency or unusual toxic properties of a compound do not raise concerns regarding the adequacy of the standard MOE/safety factor.

For purposes of assessing the pre- and post-natal toxicity of thiodicarb, EPA has evaluated at least two developmental and one reproduction study. Based on current toxicological data requirements, the data base for thiodicarb, relative to pre- and post-natal toxicity is complete. However, as EPA fully implements the requirements of FQPA, additional data related to the special sensitivity of infants and children may be required.

Developmental and Reproductive Effects

The effects observed in the thiodicarb developmental and reproduction studies can be summarized as follows:

In a rat developmental toxicity study, pregnant Charles River CD COBS rats were administered thiodicarb via gavage on gestation days 6-19 at dose levels of 0 (vehicle 0.5% methocel), 10, 20, and 30 mg thiodicarb/kg body weight/day. In another rat developmental toxicity study, pregnant Fisher 344 rats were dosed via the diet on (1) gestation days 6 to 15 or (2) gestation days 0-20 at dose levels of 0.5, 1.0, 3.0, and 100 mg thiodicarb (>99%)/kg body weight/day. When these two studies are considered together, the maternal toxicity NOEL is 10 mg/kg/day, and the maternal toxicity LOEL is 20 mg/kg/day, based on clinical signs (tremors, inactivity). The developmental toxicity NOEL is 3 mg/kg/day, and the LOEL is 10 mg/kg/day, based on decreased fetal body weights and increased incidence of litters and fetuses with developmental variations which included unossification of sternebrae #5 and/or #6 and other sternebrae (MRIDs 00043739, 00043740, 00043741, 00053254, 00053255, 00053256).

In a developmental toxicity study, artificially-inseminated New Zealand white rabbits were administered thiodicarb via gavage on gestation days 6 through 19 at dose levels of 0 (vehicle, 0.5% aqueous methylcellulose), 5, 20, and 40 mg thiodicarb (93%)/kg body weight/day. The maternal toxicity NOEL was 20 mg/kg/day, and the maternal toxicity LOEL was 40 mg/kg/day, based on reduced body-weight gain and food consumption. The developmental toxicity NOEL was 40 mg/kg/day, the highest dose tested (MRIDs 00159814, 40280001).

In a developmental toxicity study, Charles River CD-1 mice were administered thiodicarb on gestation days 6 through 16 via gavage at dose levels of 0 (vehicle 0.5% methocel), 50, 100, and 200 mg thiodicarb/kg body weight/day. The maternal toxicity NOEL was 100 mg/kg/day, and the maternal toxicity LOEL was 200 mg/kg/day, based on increased mortality. The developmental toxicity NOEL was 200 mg/kg/day, the highest dose tested (MRIDs 00043742, 00043743, 00053257, 00053258).

In a two-generation reproduction study, Crl:CD®BR/VAF/Plus® rats were fed doses of 0, 5, 15, and 45 mg/kg/day thiodicarb. The reproductive/developmental toxicity NOEL is 5 mg/kg/day, and the reproductive/developmental toxicity LOEL is 15 mg/kg/day, based on decreased fetal body weight and viability. The systemic NOEL is 5 mg/kg/day and the systemic LOEL is 15 mg/kg/day, based on decreased body weight/gain and food consumption in both sexes (MRIDs 42381301, 42381302, 42735101).

There is no unequivocal evidence of additional sensitivity to offspring following pre- and/or postnatal exposure to thiodicarb. In the two-generation reproduction study in rats, reproductive/developmental effects in pups (decreased body weight and viability) were observed only at dietary levels which were toxic in the parental animals, as evidenced by decreased body weight and food consumption. In the prenatal developmental toxicity studies in mice and rabbits, no developmental toxicity was observed, even at maternally toxic doses. In rats, two prenatal developmental toxicity studies were conducted, and based on the combined results of these studies, the developmental NOEL of 3 mg/kg/day was determined. This developmental NOEL was based upon decreased fetal body weight and increased incidence of delayed ossification in the sternebrae and was lower than the maternal NOEL of 10 mg/kg/day, which was based upon clinical signs of tremors and inactivity. Although these results are indicative of an additional sensitivity of offspring to prenatal exposure to thiodicarb, an uncertainty factor is not recommended for the following reasons. The results are derived from two separate studies, using two different strains of rat (Sprague-Dawley and Wistar), which could alter the fetal response to prenatal exposure. Additionally, the developmental NOEL was identified in the second prenatal study, while all other NOELs and LOELs were identified in the first study. The dose level at which the developmental NOEL was established is, in many ways, an artifact of dose selection, since the next higher dose was 33 times greater than that which demonstrated no fetal effects. If a wide spectrum of dose levels had been selected for testing in this strain of rat, it is very possible that no indication of additional fetal sensitivity would have been observed. Without adequate confidence in the assessment of additional sensitivity, the use of an additional uncertainty factor is not recommended.

Uncertainty Factor

Based on the considerations outlined above, and the absence of any incident or epidemiological data for thiodicarb, the Agency concludes that an additional uncertainty factor to account for any special sensitivity to infants and children is not warranted for the thiodicarb risk assessment.

cc with Attachments: RCAB Files, PP#3516, F. Fort
RDI: W. Phang(8/13/97), K. Boyle(8/8/97)
Felecia Fort:CM#2:(703)305-7478:7509C:Room 804S

APPENDIX I: HAZARD ASSESSMENT FOR METHOMYL

1. Occupational Exposure Endpoint Selection:

   a. A dermal absorption rate of 32% was calculated based on the LOEL of 16 mg/kg/day established in the developmental toxicity stuyd in rabbits ())131257) and the LOEL of 50 mg/kg/day established in the 21-day dermal study in rabbits (41251501). In the developmental toxicity study, the LOEL was based on clinical signs indicative of neurotixicity and in the 21-day dermal toxicity study, the LOEL was based on decreases in plasma and brain cholinesterase activity. The 32% dermal absorption rate will be used for the chronic risk assessment since an oral (dietary) study was selected for this exposure scenario.

   b. For short term (1-7 day) or intermediate term (1 week to several months), **dermal** occupational and residential exposures:

      For short and intermediate term occupational or residential exposure, brain ChE inhibition in both sexes at 50 mg/kg/day (LOEL) from a 21-day dermal toxicity study in rabbits (MRID# 41251501) was selected as an endpoint. A NOEL of 5 mg/kg/day will be used for risk assessment. An MOE of 100 should be adequate for this risk assessment because there are not data gaps for dermal exposure and the 2-day dermal toxicty study showed a less toxic effect than in the acute dietary study.(death).

   c. For chronic (several months to lifetime), **dermal** occupational or residential exposures:

      For chronic occupational or residential exposure, renal toxicity in both sexes manifested as swollen/irregular epithelial cells of the proximal convoluted tubules as well as an increase in the amount of pigment in the cytoplasm of these cells at 10.0 mg/kg/day (LOEL) from a 2-year feeding study in dogs (MRID#00007091) was selected as an endpoint. A NOEL of 2.5 mg/kg/day will be used for risk assessment. It is noted that this study/dose was used to establish the RfD. For calculating the MOE, an extra safety factor of 3 will be used in addition to the 100 (i.e., MOE -300) due to the lack of acute and subchronic neurotoxicity studies (data gaps). Unlike thiodicarb, the two neurotoxicity studies on methomyl are critical data gaps based on the fact that neurotoxicity has been demonstrated in animals studies in two species (dog, rabbit) and by both the oral and dermal routes of exposure. The dose of 2.5 mg/kg/day should be corrected for 32% dermal absorption for this risk assessment.

   d. For **inhalation** (any duration) occupational or residential exposures:

      For short, intermediate, and long term inhalation exposure, mortality and clinical signs of neurotoxicity at 0.182 mg/L from an acute inhalation study in rats (MRID# 42140102) was selected as an endpoint. This risk assessment will be performed only if inhalation exposure is greater than 1% of total dermal and inhalation exposure. The risk due to dermal

2. Dietary Endpoint Selection

   a) Acute Risk. The TES Committee (meeting of October 9, 1996) recommended use of the maternal toxicity NOEL of 6 mg/kg/day, based on mortality in the does on days 1-3 after dosing at the LOEL of 16 mg/kg/day, from an oral developmental toxicity study in the rabbit (MRID No. 00131257). For calculation of the MOE, the Committee recommended use of an additional uncertainty factor of 3 (i.e., MOE = 300), due to the lack of acute and subchronic neurotoxicity studies (data gaps) and the severity of the effects (mortality within 1-3 days). Since the NOEL used in estimating the MOE is based on maternal toxicity, it was used on all populations.

   b) Chronic Risk. RfD = 0.008 mg/kg/day (10/25/96). The RfD was established based on 2-year dog feeding study (MRID No. 00007091) with a NOEL of 2.5 mg/kg/day (100 ppm in diet) and an uncertainty factor of 300(due to the lack of acute and subchronic neurotoxicity studies (data gaps)) based on renal toxicity (swollen/irregular epithelial cells of the proximal convoluted tubules, increased pigment deposition at the LOEL of 10 mg/kg/day (400 ppm) and .

c) Cancer Risk. Methomyl has been classified as a Group E (no evidence of carcinogenicity) by the RfD/Cancer Peer Review Committee (10/25/96).

d) Infants and Children

i) *Developmental Studies*

Rat - From the rat developmental toxicity study (MRID 00008621), the maternal (systemic) toxicity NOEL was 9.4 mg/kg/day (100 ppm in the diet), based on decreased body weight gain and food consumption at the LOEL of 33.9 mg/kg/day (400 ppm). The developmental (pup) toxicity NOEL was $\geq$ 33.9 mg/kg/day (400 ppm), the highest dose tested.

Rabbit - From the rabbit developmental toxicity study (MRID 00131257), the maternal (systemic) toxicity NOEL was 6 mg/kg/day, based on mortality and clinical signs at the LOEL of 16 mg/kg/day. The developmental (pup) toxicity NOEL was $\geq$ 16 mg/kg/day, the highest dose tested.

ii) Reproduction studies

Rat - From the 2-generation rat reproduction study (MRID), the maternal (systemic) toxicity NOEL was 3.75 mg/kg/day (75 ppm), based on decreased body weight and food consumption and altered hematological parameters at the LOEL of 30 mg/kg/day (600 ppm). The reproductive toxicity NOEL was 3.75 mg/kg/day (75 ppm), based on decreased mean number of live pups and decreased mean offspring body weights.

APPENDIX II

For the purposes of reregistration, thiodicarb is a List B chemical.

Magnitude of the Residue - Crop Field Trials

The following summary of residue field trial data are reproduced from previous CBTS reviews as noted below. No new residue data were presented with this revised petition.

Broccoli

Broccoli trials reported are from 5 locations (California (2), Iowa, Mississippi, and Texas. The Iowa trial was harvested at 1, 3, and 14 days following 8 applications at 0.5 lb/ai/A. The Texas trial used only the 3.2 F formulation applied at label maximum but sampled only at 14 days; California trials were sampled at 7 and 14 days. Only one California trial included aerial application. Texas data at 14 days are slightly less in residue quantity (0.15 to 0.27 ppm) as compared to California(#2) (0.46 to 0.67) or California (#1) (0.71 to 1.0 ppm), and more than Mississippi (0.07 to 0.11 ppm) or Iowa (<0.02 to 0.13 ppm at 8 X 1.0 lb/ai/A applications). Residues ranged from 0.77 to 5.0 ppm by ground application and a maximum of 5.6 ppm from aerial application which were applied according to the proposed use.

Cabbage

Cabbage trials reported are from 11 locations (Alabama, California(2), Florida, North Carolina(2), New York, Ohio, Pennsylvania, Wisconsin and Mississippi) All applications were by ground equipment with the exception of the California (#2) trial. Sampling and analyses were with and without wrapper leaves. Regardless of formulation; 3.2F or 80DF, or method of application, ground or air; the residues of thiodicarb in cabbage, with wrapper leaves, ranged rom 0.04 ppm in Pennsylvania to 5.3 ppm in North Carolina, following applications in accordance with the proposed use.

Cauliflower

Cauliflower trials reported are from 4 locations (California(2), Mississippi, and New York. The New York trial included only a single sampling at a 14-day PHI following 6 X 1.0 lb /ai/A applications. At 14 days the New York analyses were 1.7, 1.9, and 4.1 ppm. In the other trials, at 7-day PHI, residues ranged from <0.04 ppm to 2.3 ppm.

Leafy Vegetables

Two applications at a rate of 0.75 lb ai/A were applied to celery, spinach, leaf and head lettuce. Data was submitted for all four seasons of the year for each crop and were harvested per normal cultural practices. Data was submitted for 6-8 states per crop in differing soils and varieties (a minimum of 9 trials per crop). Residues were as follows:

Celery	0.07 - 23 ppm
Spinach	<0.04 - 25 ppm
Leaf Lettuce	<0.04 - 18 ppm
Head Lettuce	<0.04 - 22 ppm

APPENDIX III

1. Environmental Fate Profile

Thiodicarb is a non-persistent, but highly mobile compound in soil and water environments. It degrades rapidly to methomyl. Methomyl is moderately persistent and highly mobile in soil and water environments.

The HED Metabolism Committee has determined that the residues of concern for thiodicarb include the parent and methomyl. Environmental fate profiles for thiodicarb and methomyl are given below:

	Thiodicarb	Methomyl
Solubility:	19 ppm (22°C)	5.8×10^4 ppm (20°C)
Hydrolysis:	12 hours (pH = 9)	30 days (pH = 9)
	32 days (pH = 7)	stable (pH = 7)
	78 days (pH = 5)	stable (pH = 5)
Photolysis (water) t½:	7.6 days	1 day (pH = 5)
Photolysis (soil) t½:	37 days	34 days
Soil t½ (aerobic):	1.5 days (pH = 5.4)	11-45 days
Soil t½ (anaerobic):	N/A	7-14 days
Aquatic (aerobic):	N/A	3.5-5 days (20°C)
Aquatic t½ (anaerobic):	< 3 hours	N/A
Mobility: Kd =	0.16-14 ml/gm (mobile)	0.23-1.4 ml/gm (highly mobile)

2. Monitoring Data: Ground Water

The EFGWB One-Liner database, the "Pesticides in Ground Water Database", ground water monitoring study, and miscellaneous data were searched for monitoring data on thiodicarb and methomyl residues. No data on thiodicarb residues in ground water are available. Limited data on methomyl residues in ground water are available. In New Jersey, selected domestic, irrigation and public supply wells were monitored for methomyl residues in 1989. Residues were detected in the 5 out of 120 wells sampled, and concentrations were "trace", 0.5 ppb, 0.6 ppb, 0.8 ppb, and 1.0 ppb using a detection limit of 0.5 ppb. The average detection was 0.6 ppb (assuming "trace" was equal to one-half of the detection limit) for samples with detections, i.e., not including non-detects). This is also the median concentration. The wells were approximately 80 feet deep and the detections represented non-point sources of contamination. In New York, methomyl was detected every year in Suffolk County drinking water wells from 1982 to 1994. Residues were detected in 81 out of 20,955 wells sampled, and concentrations ranged from 1 to 20 ppb with a detection limit of 1.0 ppb. The average concentration was 3 ppb for samples with detections, i.e., not including non-detects.

Monitoring data from a small-scale prospective ground water monitoring study in Cook County, Georgia ranged from 0.110 to 0.428 ppb with a detection limit of 0.1 ppb. The average concentration for the samples with detections was 0.288 ppb.

The highest single concentration of methomyl detected in ground water was 20 ppb. The highest averaged concentration detected in any one study was 3 ppb (New York), and the overall average concentration from all of the studies is 1 to 2 ppb.

3. Monitoring Data: Surface Water

The EFGWB One-Liner database, the U.S. EPA's "STORET Database", and miscellaneous data were searched for monitoring data on thiodicarb and methomyl residues in surface waters. No data on thiodicarb residues in surface water are available. Limited data on methomyl residues in surface water are available. The South Florida Water Management District (Miles and Pfeuffer 1994) collected samples every two to three months from 27 surface water

sites within the SFWMD from November 1988 through November 1993 and analyzed them for multiple pesticides. Approximately 810 samples (30 sampling intervals X 27 sites sampled/interval) were collected from the 27 sites from November 1988 through November 1993. Methomyl was detected in only one sample at a concentration of 1.9 ug/L. Detection limits generally ranged from 1.9 to 20 ug/L.

In 1994, Washington State collected surface water samples in April, June, and October from 8 sights (for a total of 24 samples) and analyzed them for multiple pesticides including methomyl. Methomyl was not detected in any of the 1994 samples above an approximate quantification limit of 0.04 ug/L. However, methomyl was detected at a concentration of 0.088 ug/L in a 1993 sample collected from a site (Salmon Creek) not resampled in 1994.

A search of STORET for methomyl in surface water by S. Mostaghimi revealed 9 detections in 3849 samples collected over 37 states. Five detections were in California (0.67, 0.33, 0.23, 0.15, and 0.13 ug/L), 3 were in Texas (1, 0.38 and 0.12 ug/L), one was in Pennsylvania (0.19 ug/L), and one was in Washington (0.9 ug/L). The ratio of detects to samples and detection limits are listed for each of the 37 states in the attached table. Most of the detection limits were well below 1 ug/L.

The highest single concentration of methomyl detected in surface water was 2 ppb. The highest averaged concentration detected in any one study was 0.5 ppb (Texas) and the overall average concentration from all of the studies is below 1 ppb.

HEALTH CRITERIA

The Office of Drinking Water has established a life-time health advisory (HA) for methomyl at 200 ppb, and 1 and 10-day HAs of 300 ppb for methomyl. There are no established health criteria for thiodicarb.

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