



5/17/00

MEMORANDUM

SUBJECT: Mevinphos: Revised Human Health Risk Assessment. Chemical I.D.
No. 015801. Case No. 0250. DP Barcode D266026.

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THRU: Whang Phang, Ph.D., Branch Senior Scientist
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TO: Joseph Nevola/Robert McNally (PM 60)
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Attached is the revised Human Health Risk Assessment for **Mevinphos** developed by the Health Effects Division. This revision incorporates any salient comments provided 12/7/99 by the registrant, AMVAC, on the 10/19/99 Preliminary Human Health Risk Assessment. As mevinphos is not an active ingredient in any product registered in the U.S., no occupational, residential, or drinking water exposure will occur. The only source of human exposure is via mevinphos residues in imported food. This risk assessment incorporates the salient portions of the following Reregistration Eligibility Decision chapters as well as several memoranda and HED committee reports: the Toxicology Chapter prepared by V. Dobozy (8/16/99; D251794), the Residue Chemistry Chapter prepared by W. Hazel (10/19/99; D259802), the anticipated residue/dietary risk memorandum by C. Olinger and F. Fort (10/18/99; D259803), the Hazard Identification Assessment Review Committee report by V. Dobozy and B. Tarplee dated 4/13/99, and the FQPA Safety Factor Committee report by B. Tarplee dated 9/28/99.

AMVAC Chemical Corp. is supporting tolerances for mevinphos residues in grapes and numerous vegetables to permit the importation of these commodities from Mexico. The current registrant in Mexico is an American Cyanamid Co. (AMCY) subsidiary in that country although AMVAC is reportedly planning to take over that registration. Note that mevinphos is reportedly also marketed in areas other than Mexico such as Europe,

Australia, Thailand, and The Republic of South Africa (personal communication with Ian Chart of AMVAC, 7/23/99). Mevinphos appears also to be used in South America as several monitored grape samples from Chile bore detectable residues although AMVAC claims not to "...currently supply mevinphos to Chile..." HED remains uncertain of the use directions to appear on Mexican labels. The current AMCY use directions do not agree with the parameters of the recent field trials conducted in Mexico. AMVAC claims that the Mexican label will be amended to reflect the Mexican field trial parameters and the AMCY Mexican subsidiary supports this.

The acute and chronic dietary risk assessments were quite refined. Refinements included the use of FDA and USDA/PDP monitoring data as the source of anticipated residues, correction for percent commodity imported and percent commodity treated, and a probabilistic acute assessment. Both acute and chronic dietary risks are below the Agency's level of concern.

cc: W. Hazel (HED), C. Olinger (HED), F. Fort (HED), List A Reg. Std. File, RF
RRB1:CM2:722J:WHazel:305-7677:wjh:5/16/00
RDI: W.Phang:5/16/00

INTRODUCTION

Mevinphos is a List A reregistration chemical and was the subject of a Registration Standard (3/31/88) which presented the regulatory decisions on the available data and specified additional data required for reregistration purposes. Due to concerns over agricultural worker exposure and safety, EPA was prepared (6/30/94) to issue a Notice of Intent to Suspend all mevinphos registrations. Instead, AMVAC requested voluntary cancellation of all its U.S. registrations for products containing mevinphos. The Agency granted this request effective 7/1/94 (59 FR 38973, 8/1/94); this cancellation order was later amended (60 FR 17357, 4/5/95) to extend the distribution, sale, and use of AMVAC's mevinphos-containing products to 11/30/95. As all registered uses of mevinphos in the U.S. were canceled, the Agency subsequently proposed revoking all mevinphos tolerances (60 FR 30393, 8/2/95). In its proposal, the Agency also noted that a preliminary acute dietary risk assessment based upon the available data indicated a concern for acute exposure to mevinphos, particularly for infants and children.

In response to this proposal, AMVAC requested (letter dated 10/31/95) that the Agency not revoke tolerances for mevinphos residues in/on selected fruits and vegetables as AMVAC was supporting the continued use of mevinphos in Mexico on commodities that are imported into the U.S. The uses being supported include the following crops: broccoli, cabbage, cauliflower, celery, cucumbers, grapes, lettuce (head and leaf), melons, peppers, peas (succulent), spinach, squash (summer), strawberries, and tomatoes. AMVAC also provided (letter dated 11/20/95) its own acute dietary exposure analysis for mevinphos residues based upon the crop uses they were continuing to support.

A preliminary human health risk assessment for mevinphos, dated 10/19/99, was the first step in the Reregistration Eligibility Decision (RED) process. This document is the revised human health risk assessment amended to respond to the 12/7/99 AMVAC comments provided on the preliminary risk assessment. As all mevinphos-containing products registered in the United States have been cancelled, human exposure to this pesticide is strictly through the consumption of imported foods. Accordingly, this risk assessment involves consideration of only the hazard component of the risk and food sources of dietary exposure. Probabilistic assessment of acute dietary risk has been conducted using the DEEM™ Software based on anticipated residue data and percent crop imported/treated data. Chronic dietary risk was estimated using DEEM™, anticipated residue data, and mevinphos usage data. Both dietary assessments are considered to be highly refined. Residential and occupational exposures as well as dietary exposure through drinking water are not expected because there is no domestic use of mevinphos. Therefore, aggregate acute and chronic risks are attributable only to food sources of dietary exposure.

EXECUTIVE SUMMARY

The Health Effects Division (HED) of EPA's Office of Pesticide Programs has evaluated the mevinphos toxicology and residue chemistry databases. Although the databases have several deficiencies, they are sufficient upon which to base a human health risk assessment for mevinphos.

Mevinphos [methyl 3-[(dimethoxyphosphinyl)oxy]butenoate] is a contact/systemic organophosphate insecticide that was previously registered in the United States by AMVAC Chemical Corporation under the trade name Phosdrin[®] for use on fruit and vegetable crops, cereal grains, and non-grass animal feed crops. There are presently no registered uses of mevinphos in the United States. However, AMVAC continues to support the use of mevinphos in Mexico as a broadcast foliar application to selected fruits and vegetables that can be imported to the U.S.

Mevinphos residues of concern in plants consist of the α - and β -isomers of mevinphos (40 CFR §180.157). Based upon the available animal metabolism data, HED concluded that quantifiable residues of mevinphos are unlikely to transfer from treated crops to livestock [CFR 40 180.6(a)(3)]; therefore, tolerances for mevinphos residues in livestock commodities are not required.

Several submissions of data have been received since the Registration Standard was issued. The information contained in this document outlines the current hazard and dietary exposure assessments with respect to the reregistration of mevinphos.

As with other organophosphates, the principal toxic effects induced by mevinphos are related to its ability to inhibit cholinesterase (ChE) activity. Mevinphos is one of the more potent cholinesterase inhibitors based on the acute oral, dermal, and inhalation study results (Toxicity Category I; see Table 1). The acute toxicity endpoint was based on plasma and brain ChE inhibition and clinical signs observed at 2.0 mg/kg/day, the Lowest Observed Adverse Effect Level (LOAEL); the No Observed Adverse Effect Level (NOAEL), used in acute dietary risk assessment, was 0.1 mg/kg/day. The chronic toxicity endpoint was based on plasma and brain ChE inhibition observed at the LOAEL of 0.35 mg/kg/day in a 2-year oral rat study; the NOAEL used in chronic dietary risk assessment was 0.025 mg/kg/day in this study. Upon applying the appropriate uncertainty factors, the derived Reference Doses (RfDs) used in risk assessment are 0.001 mg/kg/day for acute dietary and 0.00025 mg/kg/day for chronic dietary assessments. **It is the very low numerical values (high toxicity) of the hazard components of the risk that are driving the dietary assessments.** Mevinphos does not pose a cancer hazard to humans. There was no evidence of sensitivity to fetuses relative to adult animals in developmental toxicity studies. There was some indication of increased sensitivity of offspring treated postnatally in the range-finding study associated with the two-generation rat reproduction study. Although mevinphos is a

potent ChE-inhibitor, no structural neuropathological effects were observed in an acute rat neurotoxicity study. However, a published study indicates alteration of neurological parameters in humans exposed to mevinphos for 28 days. In its 12/7/99 letter, AMVAC disagrees that there was increased sensitivity of offspring in the two-generation rat reproduction study and cites this as the reason the Agency is requiring a developmental neurotoxicity study. HED notes that there were clinical signs of toxicity and increased acute lethality when offspring in the range-finding study were treated from postnatal day 21 to 28, necessitating a delay in dosing to day 28 in the definitive study. Regarding the developmental neurotoxicity study, there are other reasons it is being required than results of the range-finding study, for example, mevinphos is neurotoxic in mammals.

The Food Quality Protection Act (FQPA) of 8/3/96 requires that a 10-fold safety factor be applied to risk assessments to protect against the potential increased sensitivity of infants and children unless there is evidence supporting reduction of this factor. In the case of mevinphos, hazard and exposure considerations led to the conclusion that this factor should be retained for all population subgroups for the chronic dietary risk assessments. In the case of acute risk assessments, the FQPA safety factor was reduced to 3X for infants, children, and females of child-bearing age (13+ years) and removed (reduced to 1X) for all other subpopulations. Thus the acute and chronic RfDs must be divided by the relevant FQPA safety factor to derive the respective Population Adjusted Doses (PADs): **the aPAD for infants, children, and females (13+ years) is 0.0003 mg/kg/day; the aPAD for all other subpopulations is 0.001 mg/kg/day; and the cPAD is 0.000025 mg/kg/day for all population subgroups.** These are the hazard components to be used in the dietary risk assessments, i.e., the target or allowable level of dietary exposure to mevinphos in units of mg/kg/day.

Dietary risk assessments reflect highly refined exposure estimates. The exposure components consisted of anticipated residues derived largely from FDA Surveillance Monitoring Data and USDA/Pesticide Data Program (PDP) monitoring data although field trial data were used in some cases. Generally, anticipated residues were adjusted by percent crop imported and percent crop treated figures. A Tier 3 probabilistic/Monte Carlo type of acute dietary risk assessment was conducted. These refined dietary exposure values were then compared to the aPAD and cPAD to estimate dietary risk. **Acute risks to all population subgroups were $\leq 17\%$ of the aPAD and chronic risks to all population subgroups were $\leq 1.7\%$ of the cPAD; the most highly exposed population subgroup for both durations of exposure was children (1-6 years). These dietary risks are below the Agency's level of concern.**

Aggregate exposure is comprised solely of food sources as there are no drinking water or residential exposures to mevinphos. Thus, acute and chronic dietary (food only) assessments of risk are identical to the corresponding aggregate risks. **These aggregate risks are below the Agency's level of concern.**

As there is no registered use of mevinphos-containing products in the United States, an occupational risk assessment is not necessary.

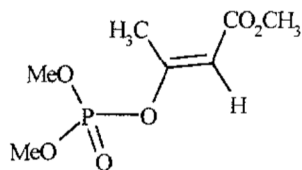
The mevinphos database, while not being complete, is adequate for the conduct of this preliminary human health risk assessment. The following confirmatory toxicology data remain outstanding: (i) neurotoxic esterase (NTE) data on the hen are required to support the hen delayed neurotoxicity study (OPPTS 870.6100); (ii) *in vivo* cytogenetic assay and data to upgrade the unscheduled DNA synthesis assay; (iii) subchronic neurotoxicity study in the rat (received by the Agency and currently under review); and (iv) developmental neurotoxicity study in the rat. In its 12/7/99 letter, AMVAC argues that the hen NTE should not be required because an acceptable acute delayed neurotoxicity study is available and due to the other neurotoxicity information available. It is policy to require NTE data for organophosphates, according to the July 7, 1998 HIARC report. In the case of mevinphos, "the lack of NTE data in an otherwise acceptable negative hen study is not considered a major data gap but rather is characterized as the need for confirmatory data (i.e., data to confirm that an effect on NTE does not occur)". Regarding the *in vivo* cytogenetic assay and data to upgrade the unscheduled DNA synthesis assay, AMVAC stresses that definitive oncogenicity studies in mice and rats are available that demonstrate that mevinphos does not induce tumor formation and that these two screening-level mutagenicity studies would offer no additional information of import to the safety assessment. The full compliment of testing, including genetic toxicology is required by law to satisfy FIFRA requirements. **In this case**, however, nothing would be gained from pursuing genetic toxicology testing in light of the negative response for a carcinogenic effect and the absence of reproductive effects that would suggest a heritable concern. The requirement to submit fully acceptable studies to satisfy the 1991 mutagenicity test guidelines is, therefore, waived for mevinphos.

The following residue chemistry data remain outstanding to permit reassessment of the established tolerances: label use information detailing how mevinphos will be used in Mexico; additional storage stability data; additional field trials (conducted largely in Mexico) on broccoli, cabbage, celery, lettuce, peas (succulent), peppers, spinach, squash (summer), strawberries, and tomatoes; and either grape and tomato processing studies or rationale supporting the contention that processed products of grapes and tomatoes from countries having mevinphos registrations will not be imported by the U.S. In its 12/7/99 letter, AMVAC disagrees with the Agency's contention that the terms of an earlier agreement between AMVAC and the Agency have not been met. Although the agreed-upon number and location of field trials have been conducted, other terms of the agreement have not been met or have been obscured due to: (i) Green Giant monitoring data not being provided to HED even, as opposed to AMVAC's statement, for the first year; (ii) a different formulation being used in the Mexican field trials than was used in the trials conducted in the U.S.; (iii) the residues resulting from the trials conducted in the U.S. being higher than those conducted in Mexico in many cases; (iv)

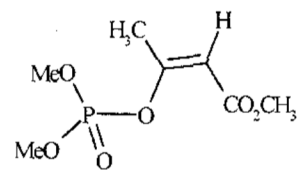
the Agency still not knowing the use directions to appear on the Mexican label(s); (v) the parameters of the field trials not agreeing with the current Mexican label; (vi) most positive monitoring samples of grapes having originated in Chile; and (vii) the Import Tolerance Guidelines specifying additional field trials than were conducted in Mexico. HED disagrees with AMVAC's contention that it is inappropriate for the Agency to require additional field trial data from major crop producing/exporting countries, even if AMVAC does not currently market mevinphos in those countries. AMVAC has chosen to support the mevinphos tolerances in/on major children's foods, crops that are largely imported during certain times of the year, and most of which are frequently consumed raw. HED stresses that these requirements are in accordance with the Draft Import Tolerance Guidance. We also stress that a tolerance is not country-specific, i.e., the U.S. is capable of regulating use of a pesticide in the U.S. but cannot control (or possibly even be knowledgeable of) expansion of uses to additional countries. These and other considerations lead the Agency to reassess the need for additional field trials in spite of the 1996 agreement with AMVAC. A grape processing study and a waiver from the requirement of a tomato processing study have apparently been submitted but have not yet been received by HED.

PHYSICAL/CHEMICAL PROPERTIES

Mevinphos [methyl 3-[(dimethoxyphosphinyl)oxy]butenoate] is a contact/systemic organophosphate insecticide. All U.S. registrations containing mevinphos have been voluntarily cancelled. However, AMVAC wishes to support tolerances in/on several vegetable and fruit crops to permit the export of mevinphos-treated crops from Mexico to the U.S. The chemical structures of the two mevinphos isomers as well as several properties and identifying characteristics of mevinphos are presented below. HED has inserted AMVAC's suggested hydrolytic stability (below) received in the 12/7/99 letter.



Alpha (cis) isomer



Beta (trans) isomer

Mevinphos

Physical Properties:

| | |
|---------------------------------|---|
| Physical state. | Liquid |
| Boiling point. | 99-103 C |
| Solubility. | Miscible with water, acetone, benzene, ethanol, xylene |
| Vapor pressure. | 3×10^{-3} mmHg |
| Octanol/H ₂ O coeff. | 1.1-1.7 |
| Stability. | Hydrolytic $t_{1/2}$ at pH 7 = 29 days (α) and 63 days (β) |

Other Identifying Characteristics and Codes:

| | |
|--------------------|---|
| Empirical Formula. | C ₇ H ₁₃ O ₆ P |
| Molecular Weight. | 224.16 |
| CAS Registry No. | 7786-34-7 |
| Chemical I.D. No. | 015801 |

HAZARD ASSESSMENT

The Toxicology Chapter of the RED was prepared by V. Dobozy (8/16/99; D251794). The mevinphos data base is not complete; however, there are sufficient data from the available studies for selecting acute and chronic dietary endpoints for an **import tolerance**.

Mevinphos is an organophosphate (OP) insecticide; its mode of toxic action is the inhibition of cholinesterase (ChE). In all studies in which ChE was measured, the Lowest Observed Adverse Effect Level (LOAEL) was based on either clinical signs of OP toxicity, plasma ChE inhibition or brain ChE inhibition (ChEI). In some studies, including both short-term and chronic administration, all three effects were seen at the LOAEL. Red Blood Cell (RBC) ChEI was not the basis for establishing any of the effect levels.

Mevinphos is a potent cholinesterase inhibitor at very low doses to rodents and rabbits. Female rats are more sensitive than males in many of the reviewed studies. The rat is more sensitive than the mouse; however, this finding could be due to the method of oral administration. The chemical was administered by gavage in the rat studies but in the diet with the mouse carcinogenicity study. A bolus administration could have produced more toxicity than the gradual consumption of the chemical in the diet.

Mevinphos is acutely toxic to rats by the oral, dermal and inhalation routes (Toxicity Category I). Mevinphos acute toxicity is summarized in Table 1. Acute Primary eye and skin irritation studies could not be conducted due to acute toxicity. Mevinphos is

not a dermal sensitizer. There was no evidence of delayed neurotoxicity in the hen study. A confirmatory neurotoxic esterase (NTE) study is required. Evidence of neurotoxicity was observed in most of the studies; however, there was no evidence of alterations in structural neuropathological (gross and histopathology) measurements in an acute neurotoxicity study in rats. A subchronic neurotoxicity study is required due to findings in a human study in the literature in which neurological parameters were altered in men exposed to mevinphos for 28 days; this study has been submitted and is currently in review.

There was no evidence of prenatal developmental toxicity or increased quantitative or qualitative fetal susceptibility in rats or rabbits. There was evidence of a qualitative increase in postnatal susceptibility in the range-finding study for the two-generation reproduction study. Due to the lethality in offspring treated by gavage on postnatal day (PND) 21 in the range-finding study, the timing of the direct treatment in the definitive two-generation reproduction study was delayed from PND 21 to PND 28. In the two-generation reproduction study, there was evidence of reproductive effects in both males and females in the F₁ generation. Offspring effects were seen at the same dose as the adult effects. A developmental neurotoxicity study (with extended postnatal treatment) is required based on the finding of qualitative increased susceptibility in the range-finding study.

There are no acceptable chronic toxicity studies in nonrodents. A waiver of the chronic toxicity study in dogs was granted due to emesis at low doses. In the mouse carcinogenicity study, there was no evidence of an increased incidence of neoplasms at doses that were adequate for testing the carcinogenic potential of the chemical. In the rat combined chronic toxicity/carcinogenicity study, evidence of chronic toxicity was limited to clinical signs of toxicity and ChEI. Female rats had significant increasing trends in liver adenomas ($p < 0.05$) and adenomas and/or carcinomas combined ($p < 0.01$); however, there were no statistically significant differences in the pair-wise comparisons of the dosed groups with controls. Therefore, it was determined that Mevinphos does not pose a cancer hazard to humans. The mutagenicity data base is not complete. The available data do not unequivocally demonstrate that mevinphos is genotoxic: mevinphos was weakly mutagenic in *Salmonella typhimurium* (with or without activation), equivocally mutagenic in a mammalian cell forward gene mutation assay, and significantly clastogenic in mammalian cells without activation.

In the rat, mevinphos is readily absorbed from the GI tract and is eliminated primarily as expired CO₂ or secondarily in the urine. The fraction of urinary excretion was increased with increasing doses. Four urinary metabolite fractions were isolated from female and male rats and the metabolite pattern was similar between sexes. None of the metabolites are of toxicological concern.

Table 1 contains the acute toxicity results which are especially important for labeling

purposes. As mevinphos is only applied outside the U.S., these data are presented largely for informational purposes.

Table 1. Acute Toxicity of Mevinphos

| Guideline No. | Study Type | MRID #(S). | Results | Toxicity Category |
|---------------|-----------------------------------|------------|---|-------------------|
| 81-1 | Acute Oral - Rat | 40570701 | LD ₅₀ = 3.5 mg/kg (M) 2.3 mg/kg (F) 2.8 mg/kg (M+F) | I |
| 81-2 | Acute Dermal - Rabbit | 40570702 | LD ₅₀ = 51 mg/kg (M) 60 mg/kg (F) 54 mg/kg (M+F) | I |
| 81-3 | Acute Inhalation - Rat | 40600001 | LC ₅₀ = 0.012 mg/L (M) 0.0073 mg/L (F) 0.0098 mg/L (M+F) | I |
| 81-4 | Primary Eye Irritation | Waived | | |
| 81-5 | Primary Skin Irritation | Waived | | |
| 81-6 | Dermal Sensitization - Guinea pig | 40570703 | non-sensitizer | |

DOSE RESPONSE AND HAZARD ENDPOINT SELECTION

A summary of the mevinphos toxicology studies and hazard dose and toxicity endpoint selections made by the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) is provided in the HIARC report by V. Dobozy dated 4/13/99. Table 2 contains a summary of the doses and toxicity endpoints selected for use in the human health risk assessments.

Table 2. Mevinphos Doses and Endpoints for Risk Assessment.

| EXPOSURE SCENARIO | DOSE (mg/kg/day) | ENDPOINT | STUDY |
|---|---|---|---|
| Acute Dietary | NOAEL= 0.1 mg/kg/day UF = 100 | increased incidence of clinical signs, changes in the majority of the FOB parameters and decreased plasma and brain cholinesterase in males and females | Acute Neurotoxicity Study in Rats (MRID 42985401) |
| | Acute RfD = 0.001 mg/kg (General Population) Acute RfD for Females 13+ not proposed Acute PAD = 0.0003 mg/kg/day for females 13+, infants, and children (FQPA 10X reduced to 3X) Acute PAD = 0.001 mg/kg/day for the general population (FQPA 10X removed) | | |
| Chronic Dietary | NOAEL = 0.025 mg/kg/day UF = 100 | decreased plasma and brain cholinesterase activity in males and females | Combined Chronic Toxicity/Carcinogenicity Study in Rats (MRID 43088601) |
| | | Chronic RfD = 0.00025 mg/kg/day Chronic PAD = 0.000025 mg/kg/day (FQPA 10X retained) | |
| Short-Term (Dermal and Inhalation) | NOAEL= | Not required - import tolerance only | -- |
| Intermediate-Term (Dermal and Inhalation) | NOAEL= | " | -- |
| Long-Term (Dermal and Inhalation) | NOAEL= | " | -- |

FQPA Safety Factor

The Food Quality Protection Act (FQPA) of 8/3/96 requires that a 10-fold safety factor be applied to risk assessments to protect against the potential increased sensitivity of infants and children unless there is evidence supporting reduction of this factor. The FQPA Safety Factor Committee met on 5/3/99 and 8/23/99 to evaluate the hazard and exposure data for mevinphos as bases for making a recommendation on the magnitude of the FQPA Safety Factor. Hazard and exposure considerations led the FQPA Safety Factor Committee, in its 9/28/99 report, to recommend that the 10X FQPA Safety Factor be retained for chronic risk assessments for all population subgroups. In the case of acute risk assessments, the FQPA safety factor was reduced to 3X for infants, children, and females of child-bearing age (13+ years) and reduced to 1X for all other subpopulations. The rationale for retention of an FQPA

Safety Factor and the basis for selection of the applicable population subgroups is:

- The toxicology database for mevinphos is incomplete (subchronic neurotoxicity study in rats is lacking);
- A developmental neurotoxicity study in rats (with an expanded protocol) has been required by the HIARC which may provide additional information on possible adverse effects of mevinphos on the developing organism; and
- There is evidence of qualitative increased postnatal susceptibility in the range-finding study for the two-generation reproduction study.

When assessing **Acute Dietary Risk to Females 13-50 and to the Infants and Children Subgroups, the Safety Factor can be reduced to 3x** since no increased susceptibility was observed following *in utero* exposure to rats or rabbits in the developmental studies (which could potentially occur after a single dose); and the concern for this exposure scenario is the uncertainty associated with the data gap for the developmental neurotoxicity study (as opposed to the increased susceptibility seen in offspring after repeated oral exposures in the range-finding study for the 2-generation reproduction study). The developmental neurotoxicity study is designed to evaluate neurotoxic effects on the mother and fetus from the time of implantation of the fertilized egg into the wall of the uterus through birth. This study may provide additional information that could be used to further characterize the effects of mevinphos on the developing organism. **For all other population subgroups, the Safety factor may be reduced to 1X.**

When assessing the **Chronic Dietary Exposure, the Safety Factor should be Retained at 10x for All Population Subgroups** since there is concern for increased susceptibility of the young demonstrated after repeated oral exposures in the range-finding study for the 2-generation reproduction study (which is designed to assess the effects of the pesticide on male and female reproductive processes, from egg and sperm production and mating through pregnancy, birth, nursing, growth and development, and maturation); and since there are data gaps in the toxicology data base for the subchronic neurotoxicity study and the developmental neurotoxicity study in rats. As previously stated, the developmental neurotoxicity study may provide additional information that could be used to further characterize the effects of mevinphos on the developing organism.

To derive the acute and chronic Population Adjusted Doses (PADs), the acute and chronic RfDs (0.001 and 0.00025 mg/kg/day, respectively) must be divided by the relevant FQPA Safety Factor: **the aPAD for infants, children, and females (13+ years) is 0.0003 mg/kg/day; the aPAD for all other subpopulations is 0.001 mg/kg/day; and the cPAD is 0.000025 mg/kg/day for all population subgroups.** These are the hazard components to be used in the dietary risk assessments, i.e., the target or allowable level of dietary exposure to

mevinphos in units of mg/kg/day.

DIETARY EXPOSURE AND RISK ASSESSMENT

Food Sources of Dietary Exposure

Tolerances for residues of mevinphos in/on raw agricultural plant commodities (RACs) have been established under 40 CFR §180.157 and range from 0.2 ppm in/on citrus fruits, cucumbers and tomatoes to 2 ppm in/on watercress. A 4 ppm tolerance has also been established for residues in dehydrated parsley, which is the only processed commodity having a tolerance for mevinphos residues. No tolerances have been established for mevinphos residues in animal commodities. Recently submitted U.S. and Mexican field trial data are presented in the 10/19/99 W. Hazel review. The residue chemistry database is summarized and deficiencies outlined in the Residue Chemistry Chapter of the RED (W. Hazel, 10/19/99, D259804).

Mevinphos residues of concern in plants include the α - and β -isomers of mevinphos (DP Barcode D189713, S. Knizner, 7/29/93). Based upon the available animal metabolism data (DP Barcode D183036 and D189714, S. Knizner, 2/1/93 and 8/16/93), HED concluded that residues of mevinphos are unlikely to transfer to livestock tissues from treated feed items [CFR 40 180.6(a)(3)]; therefore, tolerances for mevinphos residues in livestock commodities are not required. Adequate data collection and enforcement methods are available to detect mevinphos residues in plant commodities. The chemical names and structures of α - and β -mevinphos are depicted in the section on Physical/Chemical Properties.

The mevinphos dietary exposure analyses were based largely on PDP (grapes and tomatoes) and FDA (all other crops except head lettuce and cabbage) monitoring data. Only import monitoring data were used for these dietary exposure assessments. Field trial data were used in the cases of head lettuce and cabbage. Available field trial and monitoring data included all residues of regulatory and toxicological concern, i.e., the α - and β -isomers of mevinphos. Both acute and chronic dietary exposure assessments included correction for percent of crop imported and percent crop treated figures provided by OPP's Biological and Economic Analysis Division (BEAD; 8/10/99 and 9/27/99 D. Widawsky reports). Residues were typically below the limit of detection (LOD), between the LOD and the limit of quantitation (LOQ), or at or just above the LOQ. The monitoring data indicate that residues of mevinphos in fruits and vegetables are significantly lower than the established tolerances. As grape and tomato processing studies were not available, default concentration factors were used in the dietary exposure assessments; submission of such studies would permit risk refinement. A grape processing study and request for a waiver from the tomato processing study requirement has reportedly been submitted but has not yet been received by HED. Refer to the 10/18/99 C. Olinger/F. Fort review (D259803) for details of the dietary exposure and risk analyses.

HED conducts dietary risk assessments using the Dietary Exposure Evaluation Model (DEEM™), which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For chronic dietary risk assessments, the three-day average of consumption for each subpopulation is combined with average residues in commodities to determine average exposure in mg/kg/day. For refined acute dietary risk assessments, the entire distribution of consumption events for individuals is multiplied by a distribution of residues to obtain a distribution of exposures in mg/kg/day; this is a probabilistic analysis, referred to as "Monte Carlo," with risk at the 99.9th percentile of exposure reported.

In the acute dietary exposure assessment, risk at the 99.9th percentile of exposure is reported since the probabilistic analysis was highly refined using residue distribution files adjusted by the proportion of U.S. consumption of each food that has been treated. **Estimated acute dietary exposure and risk are below HED's level of concern for mevinphos.** At the 99.9th percentile of exposure, the most highly exposed population subgroup is children (1-6 years), with 17% of the aPAD consumed. Estimated acute dietary exposure to the general U.S. population is much lower, corresponding to 2% aPAD (Table 3).

Estimated chronic dietary exposure and risk for mevinphos are significantly below HED's level of concern. The most highly exposed population subgroup is children (1-6 years), with an estimated exposure corresponding to 1.7% of the cPAD. Estimated dietary exposure to the general U.S. population is even lower, corresponding to 0.8% cPAD (Table 3).

Table 3. Mevinphos Acute and Chronic Dietary Exposure and Risk Estimates.¹

| Population Subgroup | Acute Assessment 99.9th %-ile of Exposure | | | Chronic Assessment | | |
|--------------------------------------|--|--------|-------|-------------------------|----------|-------|
| | Exposure (mg/kg/day) | aPAD | %aPAD | Exposure (mg/kg/day) | cPAD | %cPAD |
| General US Population | 2.40e-05 | 0.001 | 2 | <1.0e-06 | 0.000025 | 0.8 |
| All infants (<1 year) | 1.50e-05 | 0.0003 | 5 | <1.0e-06 | 0.000025 | 0.7 |
| Children 1-6 years | 5.50e-05 | 0.0003 | 17 | <1.0e-06 | 0.000025 | 1.7 |
| Children 7-12 years | 2.90e-05 | 0.0003 | 9 | <1.0e-06 | 0.000025 | 1.0 |
| Females 13-19 (not preg./nursing) | 2.10e-05 | 0.0003 | 6 | <1.0e-06 | 0.000025 | 0.6 |
| Females 20+ years | 2.10e-05 | 0.0003 | 6 | <1.0e-06 | 0.000025 | 0.8 |
| Females 13-50 years | 2.00e-05 | 0.0003 | 6 | <1.0e-06 | 0.000025 | 0.7 |
| Males 13-19 years | 2.30e-05 | 0.001 | 2 | <1.0e-06 | 0.000025 | 0.6 |
| Males 20+ years | 1.80e-05 | 0.001 | 2 | <1.0e-06 | 0.000025 | 0.7 |

¹ The acute Population Adjusted Dose (aPAD) is 0.0003 mg/kg/day for infants, children, and females 13+ years; 0.001 mg/kg/day for U.S. Population and all other subgroups; the chronic PAD (cPAD) is 0.000025 mg/kg/day.

The chronic and acute analyses do not take into consideration the potential for reduction of mevinphos residues in cooked/canned/processed products since there are no chemical-specific cooking studies. HED will refine the mevinphos dietary exposure analyses if such data become available. Additional refinements could include the conduct of grape and tomato processing studies to derive mevinphos-specific processing factors.

Drinking Water Sources of Dietary Exposure

Products containing mevinphos are not registered for use within the United States. Therefore, no contamination of drinking water sources is expected. As a result, drinking water is not a contributor to the aggregate risk and a water assessment has not been conducted.

AGGREGATE EXPOSURE AND RISK ASSESSMENT

Acute Aggregate Exposure and Risk

Acute aggregate risk consists solely of food sources of dietary exposure because dietary exposure through drinking water to mevinphos is not expected. Acute dietary (food only) risks and, hence, acute aggregate risks do not exceed the Agency's level of concern as the most exposed population subgroup, children (1-6 years), has a risk that is 17% of the aPAD (Table 3) based on highly refined exposure estimates.

Aggregate short-term and intermediate-term exposures were not estimated because there are no residential exposures to mevinphos expected based on the use pattern.

Chronic Aggregate Exposure and Risk

In the case of chronic aggregate risk, food sources of dietary exposure are the only contributor because drinking water exposure is not expected. Chronic (food only) risks and, hence, chronic aggregate risks are below the Agency's level of concern. The most exposed subpopulation is, again, children (1-6 years) at 1.7% of the cPAD (Table 3); these risk values are based on highly refined dietary exposure estimates.

OCCUPATIONAL AND RESIDENTIAL EXPOSURE AND RISK ASSESSMENT

Products containing mevinphos are not registered for use within the United States. Therefore, no occupational or residential exposure is expected. As a result, these risk assessments have not been conducted.

ENDOCRINE DISRUPTER EFFECTS

The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR71541). The Program uses a tiered approach and anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of mevinphos and its end-use products for endocrine effects may be required.

CUMULATIVE EXPOSURE AND RISK

EPA has determined that mevinphos has a common mechanism of toxicity with other members of the organophosphate class of pesticides. However, the Agency is in the process of developing methodology to conduct a cumulative risk assessment. At this time, therefore, EPA will not conduct a cumulative risk assessment.

DATA NEEDS

The following confirmatory data requirements have been identified for mevinphos:

Toxicology

- 870.6100 Neurotoxic esterase (NTE) data on the hen are required to support the hen delayed neurotoxicity study
- 870.6200 Subchronic neurotoxicity study in rats
- 870.6300 Developmental neurotoxicity study in rats (with expanded protocol to extend the postnatal treatment period and to measure ChE inhibition in offspring)

Residue Chemistry - Tolerances Cannot be Reassessed Until the Following are Submitted:

- 860.1200 Directions for Use: Label directions for the American Cyanamid/AMVAC product registered in Mexico once it is revised to be in agreement with the submitted Mexican field trial data parameters
- 860.1380 Storage stability data are needed to support existing field trial data as well as new field trials to be conducted (these data have been received for existing studies but have not yet been reviewed)
- 860.1500 Additional field trials are necessary in the major countries exporting the following crops to the U.S.: broccoli, cabbage, celery, lettuce, peas (succulent), peppers, spinach, squash (summer), strawberries, and tomatoes
- 860.1520 Grape and tomato processing studies must be conducted. Alternatively, rationale supporting the contention that processed products of grapes and tomatoes from countries having mevinphos registrations will not be imported by the U.S. These studies would also permit risk refinement. A grape processing study as well as a waiver request for the tomato processing study have apparently been submitted although HED has not yet received them.



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