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

JUN 1 1998

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Certified Mail

Ms. Julie Spagnoli
Bayer Corporation
8400 Hawthorn Road
P.O. Box 4913
Kansas City, MO 64120-0013

SUBJECT: HED RED Chapter for Isofenphos

Dear Ms. Spagnoli:

The Agency has completed its Human Health Effects chapter for isofenphos (copy enclosed). Please note, although no additional occupational and residential exposure data are required, you stated previously (personal communication with Ruby Whiters) that Bayer will have some exposure data in the near future. Therefore the Agency looks forward to receiving this information along with your comments within 30 days from receipt of this letter.

If you have any questions regarding this letter, please contact Ruby Whiters at (703) 308-8079.

Sincerely,

Jack Housenger
Associate Director
Special Review and
Reregistration Division

Enclosure



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

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**OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES**

MEMORANDUM

DATE: May 5, 1998

SUBJECT: ISOFENPHOS: HED Chapter for the Reregistration Eligibility Decision (RED) Document. Chemical No. 109401. Case No. 2345. Barcode D237260

FROM: Paula A. Deschamp, Risk Assessor
Reregistration Branch 2
Health Effects Division (7509C)

THROUGH: Alan P. Nielsen, Branch Senior Scientist
Reregistration Branch 2
Health Effects Division (7509C)

TO: Ruby Whiters/Walt Waldrop
Reregistration Branch III
Special Review and Reregistration Division (7508W)

The Human Health Assessment for the Reregistration Eligibility Decision (RED) Document for isofenphos is attached. This chapter includes the Hazard Assessment from Robert Fricke, the Occupational/Residential Exposure Assessment from Jonathan Becker, the Product and Residue Chemistry Assessment from Ken Dockter, Review of Isofenphos Incident Reports from Jerome Blondell/Monica Spann, and the Drinking Water Assessment from Nelson Thurman of EFED.

Isofenphos is an organophosphorus insecticide. Cumulative risk assessment considering risks from other pesticides having a common mechanism of toxicity is not addressed in this document.

The FQPA requirement to assess the potential for increased sensitivity of infants and children has been addressed by the HAZID (see Attachment 2). To assure that a consistent approach is used for all members of the organophosphorus class of chemicals, HED's FQPA Safety Committee will revisit isofenphos and all other members of this class later in the risk assessment/risk management process to determine the necessity and magnitude of any extra uncertainty factor to be applied to infants and children.

Attachments:
Attachment 1: HED RED Chapter. Paula A. Deschamp (05/05/98)
Attachment 2: HED HAZID Report. George Z. Ghali (1/13/98)
Attachment 3: Toxicology Chapter. Robert Fricke (05/05/98)
Attachment 4: Occupational and Residential Exposure Assessment. Jonathan Becker (2/18/98)
Attachment 5: Review of Isofenphos Incident Reports. Blondell and Span (3/4/98)
Attachment 6: Drinking Water Assessment for Isofenphos. Nelson Thurman (2/13/98)

RDI: BRSrSci:ANielsen



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# ISOFENPHOS HED RED CHAPTER
# EXECUTIVE SUMMARY

The Health Effects Division (HED) has conducted a health assessment for the active ingredient isofenphos [1-methylethyl-2-((ethoxy((1-methylethyl)amino)phosphinothioyl)oxy)benzoate] for purposes of making a reregistration eligibility decision. In making its determination of safety finding for health risks from non-occupational exposures, HED considered potential exposure of adults, infants, and children from : (i) lawn-care products containing isofenphos registered for use by homeowners; (ii) lawn-care products registered for use by professional lawn care services; and (iii) dietary exposure to isofenphos in the drinking water supply.

**Chemical Properties:** Isofenphos is a phenyl derivative, organophosphorous insecticide. Toxic effects of cholinesterase inhibition in plasma, red blood cells, and brain tissue have been reported in experimental animal studies. Isofenphos is nearly insoluble in water and has a relatively high vapor pressure. It is one of the more persistent organophosphorous pesticides in the first year of use; however, in subsequent years, persistence is likely to be reduced due to enhanced soil microbial degradation.

**Use/Usage:** Use sites supported by the basic producer, Bayer Corporation, include ornamental lawns and turf; ornamental plants, shrubs/trees; and outdoor commercial nurseries. There currently are no registered uses on agricultural food crops. Indoor and outdoor termiticide uses have recently been canceled. Isofenphos is used almost exclusively to treat subsurface lawn pests. Minor amounts are used for fire ant control. About 60% of isofenphos active ingredient produced annually is used on golf courses; the remainder is used on residential or public turf sites. Granular and liquid emulsifiable concentration formulations may be applied by both occupational and residential handlers although the use of some products is restricted to commercial handlers.

**Exposure, Frequency, Duration, and Magnitude:** Up to two applications per year are permitted and the maximum registered rate of 2 lb ai/A per application is recommended for efficacy. Based on the registered formulations and application equipment, exposure via both the dermal and inhalation routes is expected. In **occupational settings**, exposure durations for the mixer/loader/applicator are expected to be short- (1-7 days) and intermediate- (7-90 days) term. There is a potential for postapplication dermal exposure to occupational workers. In **residential settings,** exposure durations for mixing and applying lawn care products containing isofenphos will only be short term (1-7 days). There is a potential for post-application dermal exposure to adults, infants, and children entering and playing on treated lawns.

**Hazard Identification:** Isofenphos technical material is acutely toxic via the oral and dermal routes (Toxicity Category I) and via the inhalation route (Toxicity Category II). It causes slight primary eye irritation (Toxicity Category III) and minimal primary dermal irritation. Isofenphos is not a dermal sensitizer. Acute studies conducted with selected isofenphos metabolites indicate that oral toxicity of the oxon analog is similar to isofenphos; other metabolites are slightly less toxic than isofenphos. In longer term studies (e.g. 2 year feeding, 90-day dermal, 15-day gavage) systemic LOELs have been based on inhibition of cholinesterase (ChE) in plasma, RBC, and brain tissues as well as compound-related clinical signs. Isofenphos is characterized as "Not Likely" to be carcinogenic in humans based on the absence of significant tumor increases in the mouse. In the two-generation reproduction study in rats and the prenatal developmental toxicity studies in rats and rabbits, there was no indication of increased sensitivity of the young animals to pre-and/or postnatal exposure to isofenphos.

**FQPA Safety Factor for Infants and Children:** The 10X factor for the enhanced sensitivity of infants and children (as required by FQPA) has been retained based on a weight-of-the evidence review of the toxicological database. Guideline subchronic delayed neurotoxicity studies in hens did not show any evidence of delayed neurotoxicity. However, several publications in the open literature did show evidence of delayed neurotoxicity.

**Dose/Response and Toxicological Endpoints for Risk Assessment**: Chronic (non-cancer) dietary endpoint effect: Small and emaciated pups and increased pup mortality (based on a 2 generational rat study)

**NOEL: 0.08 mg/kg/day**
**RfD: 0.00008 mg/kg/day**

Endpoint effects for all other exposure routes and exposure durations are based on plasma, RBC, and brain ChE inhibition from either an acute or a subchronic oral neurotoxicity study in rats. Both dermal and inhalation absorption are assumed to be 100%.

- Acute dietary NOEL not established; **LOEL=2 mg/kg/day**; the acceptable MOE is 3000
- Short Term Occupational/Residential NOEL not established ; **LOEL=2 mg/kg/day**; the acceptable MOE is 3000
- Intermediate-Term Occupational/Residential **NOEL=0.06 mg/kg/day**; the acceptable MOE is 1000



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**Combined Dermal and Inhalation Risk**: Because of the similarity of the endpoints identified both in dermal and inhalation exposure, e.g., cholinesterease inhibition, aggregate risk is expressed as follows:

$$\text{Combined Risk} = 1/[(1/MOE_{(dermal)} + 1/MOE_{(inhalation)})]$$

**Incident Reports:** Based on Poison Control Center data (1985-1992) there were a total of 351 isofenphos cases. Of these 47 cases involved occupational exposure, 194 involved adult non-occupational exposures, and 110 incidents involved children five years of age and under. Compared to other organophosphates and carbamates with 25 or more cases involving children, the isofenphos cases were half as likely as other reported cases involving children to be seen in health care facility or require hospitalization. Symptoms, however, occurred just as often for isofenphos, though there were no life-threatening cases reported in children under age six.

**Dietary and Residential/Occupational Exposure Databases:** Chronic (non-cancer) and acute dietary exposure to isofenphos in drinking water sources have been estimated by EFED using preliminary screening models for ground water (SCI-GROW) and surface water (GENEEC). These models provide upper bound estimates. Occupational and residential handler dermal and inhalation exposures were estimated using PHED Version 1.1 surrogate and chemical-specific data. Occupational postapplication exposures were estimated by a surrogate rangefinder assessment. Residential postapplication exposures were estimated using scenarios and assumptions from the Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments.

**Risks of Concern**: Occupational/residential combined dermal and inhalation MOEs of <3000 for short-term exposure and <1000 for intermediate exposure are considered to be of risk concern.

- Occupational handler combined dermal and inhalation baseline MOEs range from **0.30 to 250** for **short-term exposure** and from **0.0091 to 7.4** for **Intermediate-term exposure.** These MOEs are not mitigated by the addition of PPE or engineering controls except for one short-term scenario: Loading granules for tractor drawn/mechanical spreader application (MOE=4,300).

- Residential handler combined dermal and inhalation baseline MOEs range from **1.3 to 68** for short-term exposure.



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- Occupational and residential (adults and toddlers) postapplication dermal MOEs are all significantly less than the required MOE of 1000 except for incidental soil ingestion by a toddler where the MOE is 3000.

**Aggregate Exposure and Risk** (food, water and residential sources): Since residential exposure to isofenphos is a risk concern, a quantitative aggregate exposure assessment has not been conducted.

**Uncertainties Impacting Exposure and Risk Estimates:** Dermal and inhalation exposure estimates for occupational and residential handlers are based on surrogate exposure data from PHED V1.1. Assumptions regarding amount of isofenphos handled are believed to be reasonable and representative of central tendency exposures.

Postapplication dermal exposure estimates (occupational and residential) are based on the application rate recommended for turf and an assumed amount of isofenphos retained on turf. The assumed 10% dissipation rate per day may be a lower bound dislogeable residue estimate when compared to the anaerobic half-life reported in the available environmental fate data. Transfer coefficients for occupational reentry exposure levels are representative of central tendency exposures; however, the transfer coefficient for residential reentry exposure represents a high-end activity for adults.

Because there are no acceptable dermal toxicity or dermal absorption study data, acute toxicity via the oral and dermal routes have been compared. Dermal and oral toxicity via these routes are similar; therefore, a dermal absorption rate of 100% is assumed. Overall, the assumption of 100% dermal absorption likely results in an overestimation of risk.

**Determination of Safety:** The margin of exposure (MOEs) estimated for all non-dietary/non-occupational (residential) exposure scenarios indicates that there is a risk concern for currently registered uses of isofenphos. These MOE calculations were based on inhibition of plasma, erythrocyte and brain ChE activity in an acute neurotoxicity study in the rat. HED cannot conclude with reasonable certainty that no harm will result to infants and children from residential exposure to isofenphos from playing on treated lawns or from incidental nondietary ingestion of isofenphos from hand-to-mouth transfer, or from ingestion of isofenphos-treated turfgrass.



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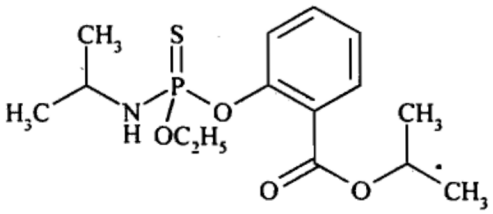
# III. SCIENCE ASSESSMENT

## A. Physical and Chemical Properties Assessment

### 1. Identification of Active Ingredient

Isofenphos is a colorless oily liquid with a boiling point of 120 C and a vapor pressure of 0.22 mPa at 20 C [4 x $10^{-6}$ mm Hg at 20 C; Merck Index]. Isofenphos is nearly insoluble in water (23.8 mg/kg at 20 C), but is miscible with n-hexane, dichloromethane, 2-propanol, ether, benzene, cyclohexanone, acetone, alcohol, kerosene and toluene.



Empirical Formula: $C_{15}H_{24}NO_4PS$
Molecular Weight: 345.40
CAS Registry No.: 25311-71-1
Shaughnessy No.: 109401

### 2. Manufacturing-Use Products

A search of the Reference Files System (REFS) conducted 1/27/97 identified a single isofenphos manufacturing-use product registered under Shaughnessy No. 109401: the Bayer Corporation 91.7% technical (T; EPA Reg. No. 3125-326). Only the Bayer 91.7% T/TGAI is subject to a reregistration eligibility decision. Based on available manufacturing, composition, and impurity information, there is no significant potential for formation of impurities of special concern which could constitute a potential exposure/risk problem.

### 3. Product Chemistry Data

All pertinent data requirements are satisfied for the isofenphos T/TGAI except for OPPTS GLNs 830.1800, 830.6313, and 830.7050. Provided that the registrant submits the data required in the Product Chemistry Data Summary Table (Appendix 1) for the isofenphos 91.7% T/TGAI, and either certifies that the suppliers of beginning materials and the manufacturing process for the isofenphos MP have not changed since the last comprehensive product chemistry review or submits a complete updated product



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chemistry data package, HED has no objections to the reregistration of isofenphos with respect to product chemistry data requirements.

## B. Human Risk Assessment

### 1. Hazard Assessment

The toxicological data base for isofenphos is adequate to support reregistration. Although the requirements for long-term chronic dietary, oncogenicity, subchronic (90-day) feeding studies have been waived based on the intended use patterns (terrestrial, non-food and residential outdoor) for isofenphos, available data from these studies are summarized in this hazard assessment.

All of the acute studies with isofenphos have been satisfied. Technical isofenphos was found to be acutely toxic when administered by oral, dermal or inhalation routes of exposure. Isofenphos produced moderate to slight irritation in the eye and dermal irritation studies, and did not induce dermal sensitization in guinea pigs. Additional acute toxicity studies were conducted with selected isofenphos metabolites. While oral toxicity of the oxon analog was similar to isofenphos, the des-isopropyl and des-
isopropyl oxon analogs were slightly less toxic. The ester chloride is essentially non-toxic. It should be noted that none of the isofenphos metabolites were identified the in the rat metabolism study; they were in all likelihood present as intermediary metabolites.

The dermal toxicity in the rabbit was evaluated in two 21-day studies with formulated products [Oftanol 5G (5% granular preparation of isofenphos) and Oftanol 2 Insecticide (22% emulsion of isofenphos)] and in one subchronic, 90-day, study with technical isofenphos (92.1%). The LOEL was established by the inhibition of plasma cholinesterase (ChE) activity with the 21-day study with the granular preparation and inhibition of plasma, erythrocyte and brain ChE activities in both the 21-day study with the emulsion and 90-day study with technical isofenphos. In all three studies, there were no signs of dermal irritation.

The chronic toxicity of isofenphos was evaluated in a two-year feeding study in the dog and a combined chronic feeding/oncogenicity study in the mouse. In the dog study, clinical signs of cholinergic toxicity were observed. In the mouse study, no clinical signs, change in body weights or clinical pathology could be attributed to treatment; the tumor profiles of the treated animals were comparable to that of the control animals. In these studies, the LOEL was based on the inhibition of plasma and erythrocyte ChE in the dog and plasma ChE in the mouse.



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Developmental and reproductive toxicity studies with isofenphos were carried out in the rabbit and rat. No maternal or fetal toxicity was observed in the rat developmental toxicity study. In the rabbit developmental study, maternal toxicity was limited to increased mortality, decreased body weight and body weight gain, and decreased food consumption. The reproductive toxicity study in the rat revealed clinical signs in parental animals and pup mortality. The LOELs for the developmental and reproductive toxicity studies in the rat were established by the inhibition of plasma, erythrocyte and brain ChE activities and for the rabbit developmental toxicity study by the inhibition of plasma and erythrocyte ChE activities.

Acute and subchronic neurotoxicity studies in the rat and acute and subchronic delayed neurotoxicity in the hen were also carried out. For the acute and subchronic neurotoxicity studies, clinical signs consistent with ChE inhibition were observed, but the LOEL was established by the inhibition of plasma, erythrocyte and brain ChE activity. In an acute delayed neurotoxicity study (graded as non-guideline by the Agency because of insufficient number of hens) and in a guideline subchronic delayed neurotoxicity, no evidence of delayed neurotoxicity was observed.

The metabolism of isofenphos in the rat revealed that essentially all of the administered dose was accounted for in the excreta, cage wash and total body. The major route of elimination was in the urine. Four major urinary metabolites were identified as 1,2-isoproxycarbonyl-phenly sulfate; 2-hydroxy-hippuric acid; 2,5-dihydroxy-isoproxycarbonyl-phenyl glucuronide; and 2-isoproxycarbonyl-phenyl glucuronide. Of the two fecal metabolites isolated, one was identified as isopropyl-salicylate and the other as unmetabolized parent compound.

In addition to studies submitted to the Agency, several open literature publications have been reviewed. A publication included a human exposure accident and four publications dealing with some of the *in vitro* and *in vivo* effects of isofenphos in the hen. These studies have been used, in part, to support the Hazard Identification Assessment Review Committee's recommendation for a developmental neurotoxicity study in the rat and retention of the 10X uncertainty factor as required by Food Quality Protection Act (FQPA).

**a. Acute Toxicity**

Acute toxicity studies provide information on the potential for health hazards that may arise as a result of short-term exposure. These data provide a basis for precautionary labeling, protective clothing requirements, and for calculation of agricultural reentry intervals. Sufficient data are available to evaluate the acute toxicity

of isofenphos via oral, dermal or inhalation routes of administration. The acute toxicity data requirements 81-1 through 81-6 study in the rat are satisfied.

Results of acute toxicity studies, primary eye and dermal irritation studies and dermal sensitization study for isofenphos, technical, are summarized in the table below. The median lethal dose ($LD_{50}$) for acute oral toxicity in rats was approximately 39 to 45 mg/kg (mg isofenphos/kg body weight) in males and 28 to 32 mg/kg in females; these $LD_{50}$ values place isofenphos in Toxicity Category I for both males and females. Isofenphos was less toxic to mice, with oral $LD_{50}$ values of 127 mg/kg in males and 91.3 mg/kg in females (Toxicity Category II). A dermal toxicity study in the rat yielded $LD_{50}$ values of 191 mg/kg in the male and approximately 70 mg/kg in the female, both values resulted in Toxicity Category I for dermal exposure. Acute inhalation exposure to isofenphos resulted in a median lethal aerosol concentration of ( $LC_{50}$) of 0.21 to 0.525 mg/L in males and 0.144 to 0.273 mg/L in females, resulting in Toxicity Category II for both sexes. The primary eye irritation study in the rabbit showed slight conjunctival redness at 24 hours (Toxicity Category III), with complete clearing by 48 hours. Dermal application of isofenphos to rabbits produced very slight to well-defined erythema within 24 hours post-dosing, with complete recovery by 72 hours [primary dermal irritation score (PDIS = 0.42, Toxicity Category IV). Isofenphos did not induce dermal sensitization in guinea pigs.

**Acute Toxicity of Isofenphos, Technical**

| Study Type | Animal | Results | Tox Cat | MRID No |
|---|---|---|---|---|
| 81-1: Acute Oral | Rat | Male 38.7 (34.3-43.7) mg/kg<br>Female 28.0 (25.3-30.9) mg/kg | I | 96659 |
| | | Male 45 (39-53) mg/kg<br>Female 32 (28-36) mg/kg | I | 96657 |
| | Mice | Male 127 (113-143) mg/kg<br>Female 91.3 (84.9-98.2) mg/kg | II | 96659 |
| 81-2: Acute Dermal | Rat | Male 191 (143-256) mg/kg<br>Female 70 (estimated) mg/kg | I | 420300-01 |
| 81-3: Acute Inhalation | Rat | Male 0.525 mg/L (est)<br>Female 0.273 (0.199-0.374) mg/L | II | 416099-01 |
| | | Male 0.21 mg/L<br>Female 0.14 mg/L | II | 96659 |
| 81-4: Primary Eye Irritation | Rabbit | Slight conjunctival redness at 24 hrs | III | 416099-11 |
| 81-5: Primary Dermal Irritation | Rabbit | PDIS = 0.42 | IV | 416099-04 |
| | | PDIS = 0.69 | IV | 248241 |
| 81-6: Dermal Sensitization | Guinea Pig | Negative | N/A | 96657 |



(10)

Acute oral toxicity studies in the rat were also performed on selected isofenphos metabolites (table below). The acute oral $LD_{50}$ values of the oxygen metabolite (oxon) was 38 and 17 mg/kg for males and females, respectively, which were comparable to the $LD_{50}$ of the parent compound in males (38 to 45 mg/kg) but lower in females (28 to 32 mg/kg). Compared to the parent compound, the des-isopropyl oxon and des-isopropyl metabolites were both less toxic than the parent compound, with $LD_{50}$ values of 86 and 111 mg/kg, respectively, in males, and 50 and 194 mg/kg, respectively, in females. The chloride ester metabolite of isofenphos was non-toxic ($LD_{50}$ > 5000 mg/kg, Toxicity Category IV) in the male rat.

**Acute Oral Toxicity of Isofenphos Metabolites in the Rat (MRID No.: 96657)**

| Metabolite | $LD_{50}$ (95% Conf Interval) | | Tox Cat |
|---|---|---|---|
| Oxygen analog | Male<br>Female | 38 (31-48) mg/kg<br>17 (14-22) mg/kg | I |
| Des-isopropyl | Male<br>Female | 111 (83-148) mg/kg<br>194 (155-224) mg/kg | II |
| Des-isopropyl oxygen analog | Male<br>Female | 86 (69-108) mg/kg<br>50 (44-56) mg/kg | Male: II<br>Female: I |
| Ester Cl | Male | > 5000 mg/kg | IV |

### b. Subchronic Toxicity

Subchronic toxicity testing is used to provide information on possible health hazards likely to arise from repeated exposures over a limited period of time (90-days). These studies are used to help identify target organs and can be used to select the dose levels for chronic studies.

Based on the use pattern for isofenphos, the data requirements for subchronic feeding studies in the rat [§82-1(a)] and dog [§82-1(b)] have been waived. However, acceptable 21-day dermal studies with isofenphos formulations (Oftanol 2 and Oftanol 5W) in the rabbit and a subchronic dermal toxicity study with technical isofenphos in the rabbit were available for review.

#### 21-Day Dermal Toxicity Studies in the Rabbit with End-Use Products

In one 21-day dermal toxicity study (MRID No.: 40917101, HED Doc No: 007246), New Zealand White rabbits (5/sex/dose) were treated with Oftanol 2 Insecticide (22% a.i. in an emulsion) at dose levels of 0, 2.5, 10 or 40 mg/kg/day, six hours/day, five days/week, for 21 days. No treatment-related changes were noted in mean body weights or food consumption. No signs of dermal irritation were observed during the study. In high-dose females, plasma ChE activity measured at weeks 1, 2, and 3 was significantly ($p \leq 0.05$) inhibited by 21%, 24%, and 22%, respectively, while erythrocyte ChE was inhibited by 16% (not significant), 27% and 22%, respectively. At terminal sacrifice, brain ChE activity of high-dose females was significantly ($p \leq 0.05$) inhibited by 29%. Although ChE activity of high-dose males was inhibited, the value was not statistically significant.

**Based on the results of this study (inhibition of plasma, erythrocyte and brain ChE in females) the LOEL was established at 40 mg/kg/day; the NOEL was established at 10 mg/kg/day in females.**

In another 21-day dermal toxicity study (MRID No.: 40217401, HED Doc No: 006607), New Zealand White rabbits (5/sex/dose) were treated with Oftanol 5G (5% granular preparation) at dose levels of 0, 1000, 2250, or 5050 mg/kg/day (equivalent to 0, 50, 113, or 253 mg a.i./kg/day) for 6 hours per day, 5 days/week for 3 weeks. Plasma and erythrocyte ChE activities were measured at the start of the study and after 1, 2, and 3 weeks of treatment; brain ChE was measured at terminal sacrifice. Body weights and food consumption were not affected by treatment. No signs of dermal irritation were observed during the study. After three weeks of treatment, plasma ChE of mid- and high-dose males were each inhibited by 19%, while mid- and high-dose females, by 16% and 18%, respectively. Erythrocyte ChE activity was significantly inhibited in mid- and high-dose females (20% and 16%, respectively) after two weeks of treatment. Brain ChE activity was not inhibited at any dose level.

**Based on the results of this study [inhibition of plasma (males and females) and erythrocyte (females only) ChE activity] the LOEL was established at 113 mg a.i./kg/day in both sexes; the NOEL was established at 50 mg a.i./kg/day.**

**Subchronic Dermal Toxicity**

In a subchronic dermal toxicity study (MRID No.: 42891702, HED Doc No.: 011204), male and females New Zealand white rabbits (10/dose/sex) were exposed to isofenphos (92.1%) at doses of 0, 2, 10 or 50 mg/kg/day, 6 hours/day, 5 days/week for 13 weeks. Plasma and erythrocyte ChE activities were measured on study days 28/29 (males/females); at terminal sacrifice (day 89) plasma, erythrocyte and brain ChE activities were measured.



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All animals survived to terminal sacrifice without the appearance of any treatment-related clinical signs. Body weights and food consumption were also unaffected by treatment. Although statistically significant hematological and clinical chemistry changes were noted, none were outside of the historical control range, and therefore not considered to be biologically significant.

At the interim evaluation, plasma ChE activities were statistically significantly decreased, relative to the concurrent control values, in mid- and high-dose males (35% and 60%, respectively) and high-dose females (61%). Erythrocyte ChE activities were statistically lower than control values in high-dose males (46%) and mid- and high-dose females (44% and 74%, respectively). At terminal sacrifice, statistically significant decreases were noted in plasma ChE of mid- (37% in males and 21% in females) and high- (58%, males; 62% in females) dose animals, and, erythrocyte ChE of mid- (32% in males and 48% in females) and high- (71% in males and 77% in females) dose animals. Brain ChE activity was inhibited by 38 and 57% in mid- and high-dose males, respectively and by 63% in high-dose females.

At terminal sacrifice, gross pathological findings in the control, low-, mid- and high-dose animals included light red to yellow discoloration of the adipose tissue in 0/10, 1/10, 1/10 and 4/10 males, respectively, and 0/10, 3/10, 3/10, and 4/10 females, respectively. Histopathological examination, however, did not reveal any treatment-related changes in either the adipose tissue or any other tissue examined.

Statistically significant increases in absolute liver weights and the absolute and relative adrenal weights were observed in high-dose males. The study author attributed the increases in adrenal weights to "incipient stress-related functional hypertrophy of the renal cortex as a reaction to marked inhibition of ChE activities in this dose group".

**Based on the results of the study, the NOEL for systemic toxicity was established at 50 mg/kg/day. The LOEL for systemic toxicity was not established.**

**Based on the results of the study (inhibition of plasma and erythrocyte ChE in males and females and brain ChE in males), the LOEL for ChE inhibition was established at 10 mg/kg/day. The NOEL for ChE inhibition was established at 2 mg/kg/day.**

**c. Chronic Toxicity/Carcinogenicity**

Chronic toxicity and carcinogenicity studies are used to assess the toxicity resulting from repeated exposure to a pesticide over a long period of time. These studies are designed to identify toxic and carcinogenic effects which are manifested only after a

long latent period or are cumulative in nature. The results of these studies are designed to permit the determination of a no-observed-effect level, which may be used to characterize the potential risk of the pesticide to human health.

Sufficient toxicity data are available on isofenphos to assess the chronic toxicity and carcinogenic potential of isofenphos.

**1) Chronic (2-year feeding) Toxicity Study in the Dog:** In a 2-year study (MRID Nos.: 00083067, 92085010, 43198001, HED Doc Nos.: 009748, 012340), dogs (4/sex/dose) were fed diets containing isofenphos (89.3%) at dietary concentrations of 0 (basal diet), 3 ppm (males, weeks 1 to 83, females weeks 1 to 104), 2 ppm (males, weeks 84 to 104), 15 ppm (weeks 1 to 104), 75, ppm (weeks 1 to 53), 150 ppm (weeks 54 to 99), or 300 ppm (weeks 100 to 104) (equivalent to 0, 0.09, 0.45, or 4.24 mg/kg/day in males, 0, 0.1, 0.53, or 3.43 mg/kg/day in females). During the study, the high-dose level was progressively increased until clear clinical signs of toxicity were observed.

Compound-related clinical signs were observed in high-dose males and females. These animals exhibited vomiting, loose feces and signs of weakness, with males being more severely affected than females. At week 28, one high-dose male showed signs of anorexia, which persisted through the end of the study, while in another signs of anorexia appeared during the final weeks of the study. At week 88, hind limb weakness was observed in one of the affected males; by week 98, this animal became unsteady and showed additional clinical signs (drowsiness, salivation and immobility). The other high-dose male also exhibited weakness and gait abnormalities at week 100; at the end of week 100, this dog exhibited paresis of the hind limbs, trembling, sticky fur coat, salivation and protruding tongue. The clinical condition of the two high-dose males deteriorated following the increase in dose to 300 ppm at week 100. One of these high-dose males died during study week 104 and the other was sacrificed in moribund condition just prior to terminal sacrifice. These deaths were attributed to severe inhibition of ChE.

During the first 78 weeks of the study, body weight gains of the treated animals were comparable of control values. Overall (weeks 0 to 104) body weight gains by high-dose males, relative to concurrent control values, were decreased by 56%. Body weight gains by low- and mid-dose males and all treated females were comparable to control values.

Clinical pathological evaluations during the study included hematology, clinical chemistry and urinalysis. For high-dose animals, mean alkaline phosphatase activity was significantly increased by 166% in males and 70% in females after 66 weeks of



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treatment, and, 266% in males and 104% in females after 92 weeks of treatment. No treatment-related changes were noted in any of the urinalysis parameters. Slight decreases were noted in the erythrocyte counts, hematocrits and hemoglobin concentration of high-dose males. The values were, however, all within the historical control ranges for these parameters, and therefore, not considered to be biologically relevant.

Plasma and erythrocyte ChE activities were measured at the start of the study and after 14, 39, 79 and 104 weeks of treatment. At terminal sacrifice (week 104), brain ChE was also measured. After 39 weeks treatment at 75 ppm, plasma and erythrocyte ChE activities were markedly inhibited in males (74% and 60%, respectively) and females (46% and 34%, respectively). Increasing the dietary concentration of isofenphos in the high-dose diet to 150 ppm, resulted in further inhibition of plasma ChE (93% in males and 76% in females) and erythrocyte ChE (72% in males and 37% in females) activities. With the increase in the concentration of isofenphos in the high-dose diet to 300 ppm at the end of the study, severe inhibition of plasma ChE (89% in males and 87% in females), erythrocyte ChE (89% in males and 85% in females) and brain ChE (67% in both males and females) activities were observed. Treatment at 15 ppm resulted in significant inhibition of plasma ChE activities by 18 to 48% in males and 31% to 45% in females. Erythrocyte ChE activity was decreased in males (9% to 19%, not significant), while activity in females was unaffected by treatment.

**Based on the results of this study (decreased body weight gains in males and clinical signs in males and females), the LOEL for systemic toxicity was established at 75/150/300 ppm (4.24 mg/kg/day in males and 3.43 mg/kg/day in females); the NOEL was established at 15 ppm (0.45 mg/kg/day in males and 0.53 mg/kg/day) in females.**

**Based on the results of this study (plasma and erythrocyte ChE inhibition at week 39) the LOEL for ChE inhibition was established at 15 ppm in males (0.45 mg/kg/day) and females (3.43 mg/kg/day); the NOEL was established at 3 ppm (0.09 mg/kg/day in males and 0.1 mg/kg/day) in females.**

**2) Chronic Feeding and Oncogenicity Study in Mice:** Although the data requirement for carcinogenicity studies has been waived because of the intended use pattern for isofenphos, the Hazard Identification Assessment Review Committee reviewed a chronic feeding/carcinogenicity study in the mouse. In this study (MRID No.: 000000, HED Doc. No.: 002490), male and SPF female mice (40/sex/dose) were fed diets containing isofenphos (89.3%) at 0 (basal diet), 1, 10, or 100 ppm.

No treatment-related effects were noted in clinical signs, mortality, body weights, food consumption or routine clinical pathology. Plasma ChE activity was decreased at 10 ppm (74% in males and 78% in females) and 100 ppm (89% in males and 92% in females). Erythrocyte ChE activities were unaffected by treatment, while brain ChE activities were decreased by 46% in males and 31% in females.

Isofenphos was not carcinogenic under the conditions of this study. The tumor profiles of the treated animals were comparable to control values.

**Based on the results of this study (plasma ChE inhibition in males and females), the LOEL for ChE inhibition was established at 10 ppm (1.5 mg/kg/day, estimated). The NOEL was established at 1 ppm (0.15 mg/kg/day, estimated).**

**The LOEL for systemic toxicity and carcinogenicity was not established, while the NOEL was established at 100 ppm (15 mg/kg/day, estimated).**

**d. Developmental Toxicity Studies**

Developmental studies are designed to identify potential adverse effects in developing organisms resulting from the mother's exposure to the test material during pre-natal development. Acceptable data from rat and rabbit developmental studies satisfy the data requirements for guideline 83-3(a) and (b), respectively.

**1) Developmental Toxicity Study in the Rat**: In a developmental toxicity study (MRID No.: 42381201, HED Doc No.: 009740), pregnant CD Br rats (40/dose) were gavaged with isofenphos (91.4%) at doses of 0, 0.05, 0.45 and 4.0 mg/kg/day from gestation days (GDs) 6 to 15.

At the high-dose level, clinical signs of ChE inhibition (consisting of tremors and ear twitching) were observed in one animal on GD 13 and two other animals on GD 14. No other abnormal clinical signs were observed.

Of the parameters measured to assess developmental toxicity, mean pre-implantation losses of 4.5% and 3.1% were observed at the 0.5 and 4.0 mg/kg/day dose levels, respectively. Since these effects were lower than the control value of 21%, they were not considered to be toxicologically significant.

Fetal observations (viability indices, body weight or incidences of external, visceral and skeletal abnormalities) were not affected by treatment.



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On GDs 16 (1 day postdosing) and 20 (5 days postdosing), maternal plasma, erythrocyte and brain ChE activities were evaluated; fetal brain ChE activity was measured on GD 20. On GD 16, plasma, erythrocyte and brain ChE activities were inhibited by 32, 20 and 16%, respectively, in mid-dose animals and 62, 73 and 71%, respectively, in high-dose animals. On the day 20 evaluations, maternal brain ChE activity was still significantly inhibited by 9.6% and 39% in mid- and high-dose animals respectively; erythrocyte ChE was significantly inhibited by 59% in high-dose animals. Fetal brain ChE activity was not affected by treatment.

**Based on the results of this study (clinical signs of ChE inhibition), the LOEL for systemic toxicity in maternal animals was established at 4.0 mg/kg/day; the NOEL was established at 0.45 mg/kg/day.**

**Based on the results of this study (plasma, erythrocyte and brain ChE inhibition), the LOEL for ChE inhibition in maternal animals was established at 0.45 mg/kg/day; the maternal NOEL was established at 0.05 mg/kg/day.**

**The LOEL for fetal toxicity was not established (> 4.0 mg/kg/day); the fetal NOEL was established at 4.0 mg/kg/day.**

**2) Developmental Toxicity Study in the Rabbit:** In another developmental toxicity study (MRID No.: 42382801& 42499601, HED Doc No.: 009896) study, New Zealand White rabbits (20/dose) were orally gavaged with isofenphos (91.4%) at dosages of 0, 0.25, 1.25, and 7.5 mg/kg/day, throughout the organogenesis period [gestation days (GDs) 6 to 18].

Clinical observations during the study revealed treatment-related effects at the high-dose level. Three does in the 7.5 mg/kg/day group died during the study, one on day 18 and two others on day 19. Two of the three animals had soft stools, diminished stool output and perianal soiling observed during the clinical evaluations.

At 7.5 mg/kg/day, statistically significant decreases in mean maternal body weights were observed on gestation days 19 (6.2%), 21 (7.1%) and 29 (6.0%). The mean body weight gain of these animals for gestation days 6 through 19 was only 0.02%, compared to the control value of 0.19% (an 89% decrease).

Necropsies were performed on animals which died during the study and all surviving animals on day 29. Incidental findings were limited to the high-dose group and included stomach erosions in two animals that died during the study and another at scheduled sacrifice. No statistically significant differences in caesarean section data were observed.

Fetal observations consisted of evaluation of body weight, viability indices, and incidences of external or visceral and skeletal abnormalities; fetal ChE activity was not measured. The mean fetal body weights of the treated animals were comparable to control values. Statistically significant observations were limited to an increase in the incidence of abnormal hyoid body or arch in the in high-dose fetuses (91%) compared to controls (76%). The litter incidence this skeletal abnormality, however, was not significantly different from the control group.

No developmental toxicity was present at the highest dose tested (7.5 mg/kg/day).

Plasma, erythrocyte and brain ChE activities were measure in maternal animals; fetal ChE activities was not determined. Plasma and erythrocyte cholinesterase activities were measured before treatment and on gestation days 19 (1 day post-treatment) and day 29 (11 days post-treatment); brain cholinesterase activity was measured on day 29. On gestation day 19, plasma and erythrocyte ChE activities were inhibited by 31% and 55%, respectively, in mid-dose animals and 69% and 88%, respectively, in high-dose animals. On day 29, plasma ChE activities were comparable to control values, while erythrocyte and brain ChE activities were both significantly inhibited in mid- (25% and 11%, respectively) and high- (48% and 22%, respectively) dose animals.

**Based on the results of this study (increased incidence of mortality, decreased body weight and body weight gain, and decreased food consumption), the LOEL for systemic toxicity in maternal animals was established at 7.5 mg/kg/day, and the NOEL, at 1.25 mg/kg/day.**

**Based on the results of this study (inhibition of plasma, erythrocyte, and brain ChE activities), the LOEL for ChE inhibition was established at 1.25 mg/kg/day; the NOEL was established 0.25 mg/kg/day.**

**Based on the results of this study, the LOEL for developmental toxicity was not established (> 7.5 mg/kg/day), the NOEL was established at 7.5 mg/kg/day.**

**e. Reproductive Toxicity**

The objective of multigeneration reproduction studies is to determine the general effects of a test material on overall reproductive capability of parental animals and the growth and development of the offspring.

In a two-generation, two litter reproduction study (MRID 41609902, HED Doc. No.: 012311) isofenphos (92.9%) was administered to Bor strain:WISW (SPF Cpb) rats

(25/sex/dose) at dietary levels of 0, 1, 5, or 25 ppm (achieved doses of 0, 0.08 to 0.16, 0.44 to 0.69, or 2.21 to 3.92 mg/kg/day).

Evaluation body weights, body weight gains, food consumption, and reproductive indices did not reveal any treatment-related effects in either sex of either generation throughout the study. However, females in the high-dose group had increased mortality (12%, $F_0$ females) and increased absolute ovarian weights ($F_0$, 9%; $F_{1b}$, 12%; $p \leq 0.05$).

Reproductive toxicity was demonstrated at 5 ppm as treatment-related increases in the number of litters with small to very small pups ($F_{1b}$) and emaciated pups ($F_{2b}$). For the $F_{1b}$ mid-dose litters, treatment-related reductions were noted in the lactation index (35% vs. 64% for controls, $p \leq 0.01$) and in mean litter sizes were decreased at days 14 (3.1 vs. 5.8 for control, $p \leq 0.01$), 21 (3.0 vs 5.7 for controls, $p \leq 0.01$), and 28 (3.1 vs. 5.7 for controls, $p \leq 0.01$) . The lactation index was also decreased for the mid-dose $F_{2b}$ litters (71% vs. 90% in controls, $p \leq 0.01$).

At 25 ppm, treatment-related increases in the numbers of litters with small to very small pups ($F_{1a}$ and $F_{1b}$), cold pups ($F_{1b}$ and $F_{2b}$), and emaciated pups ($F_{2b}$) were observed. For the high-dose $F_{1a}$ and $F_{1b}$ litters, treatment-related increases were noted in the number of deaths between days 5 and 28, with related reductions in the mean litter sizes on days 14 to 28 ($F_{1a}$, 47%, $p \leq 0.01$) and 7 to 28 ($F_{1b}$, 34 to 60%, $p \leq 0.01$ or $\leq 0.05$), number of pups alive on day 28, and lactational indices ($F_{1a}$: 47% vs. 88% for controls, $p \leq 0.01$; $F_{1b}$: 12% vs. 64% for controls, $p \leq 0.01$). In addition for the $F_{1b}$ litters, a treatment-related reduction in the viability index was noted (76% vs. 97% for controls, $p \leq 0.01$). For the high-dose $F_{2b}$ litters, treatment-related reductions in the viability index (92% vs. 99% for controls, $p \leq 0.01$) and lactation index (70% vs. 90%, $p \leq 0.01$) were observed. For both generations, the total number of pups born was reduced at the high-dose; this was because of increased mortality of the $F_0$ dams and their offspring (only nine $F_{1b}$ females were available for mating) resulting in a smaller number of females which gave birth. A treatment-related reduction in pup body weights during lactation was also noted at the high-dose ($F_{1a}$, 11 to 19% $p \leq 0.01$ or 0.05; $F_{1b}$, 23 to 29%, $p \leq 0.01$).

Plasma, erythrocyte and brain ChE activities were determined on male and females $F_{1b}$ rats after the second mating (males) or after the $F_{2b}$ pups had been weaned (females). Inhibition of plasma (19% in males and 27% in females), erythrocyte (7% females only) and brain (27% in males only) ChE activities were observed in mid-dose animals. At the high-dose level, plasma, erythrocyte and brain ChE activities were inhibited by 54%, 16% and 27%, respectively, in males, and 80%, 26%, and 32%, respectively, in females.

**Based on the results of this study (inhibition of plasma and erythrocyte ChE in both sexes and brain ChE in males), the LOEL for ChE inhibition was established at 5 ppm (0.44 to 0.69 mg/kg/day), and the NOEL, at 1 ppm (0.08 to 0.16 mg/kg/day).**

**The LOEL for reproductive toxicity was established at 5 ppm (0.44 to 0.69 mg/kg/day) based on clinical signs of toxicity (small to very small and emaciated pups) and increased pup mortality (reductions in the lactation indices and mean litter sizes). The reproductive NOEL is 1 ppm (0.08 to 0.16 mg/kg/day).**

**f. Mutagenicity Studies**

The purpose of mutagenicity tests is to assess the potential of the test substance to alter genetic material. The results of the mutagenicity studies with isofenphos were reviewed and summarized below.

**1) Gene Mutations: *Salmonella typhimurium* reverse gene mutation assay:** A gene mutation assay (Ames Assay) (MRID No. 41609912, HED Doc No.: 009748) was conducted using isofenphos (92.3%) at five dose levels ranging from 667 to 10,000 $\mu$g/plate. Isofenphos at doses of 3,333 $\mu$g/plate and higher with and without S9 precipitated. The results indicated that isofenphos was neither cytotoxic nor mutagenic in any strain either with or without S9 metabolic activation.

**2) Chromosomal Aberrations: *In vitro* Chinese hamster ovary (CHO) cell chromosome aberration assay**: An *in vitro* structural chromosomal aberration study (MRID No.: 41008801, HED Doc No.: 007192) with Chinese Hamster Ovary (CHO) cells was conducted using isofenphos (91%). Isofenphos was assayed with or without S9 metabolic activation at dose levels of 0.02 to 0.16 $\mu$g/mL. The results of the assay indicated that isofenphos was cytotoxic, but was not clastogenic.

**3) Other Mutagenic Mechanisms: Unscheduled DNA synthesis (UDS) in primary rat hepatocytes**: An unscheduled DNA synthesis assay (MRID No.: 41008802, HED Doc No.: 007192) with rat hepatocytes was conducted with isofenphos (91%) at five dose levels ranging from 0.001 to 0.03 $\mu$g/mL (limit of solubility was 0.03 $\mu$g/mL). Isofenphos did not induce significant increases in mean net nuclear grain counts. Under the conditions of this assay, there was no evidence of a genotoxic effect.

**4) Summary for mutagenicity studies:** Findings of the mutagenicity studies indicated that isofenphos was not mutagenic in bacteria and not mutagenic and clastogenic in cultured mammalian cells.



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**g. Metabolism**

The purpose of general metabolism testing is to obtain information on the absorption, distribution, biotransformation, and excretion of the test substance as a function of dose.

In a metabolism study (MRID No.: 42282101, HED Doc No.: 009739) [phenyl-(UL) $^{14}$C]-labeled isofenphos (>96%, 23.5 mCi/mmole) was studied in male and female Wistar rats (5/sex/group). Two groups were treated with a single oral dose of labeled test compound at either 1 mg/kg or 10 mg/kg; a third group of animals was treated daily, for 14 days, with unlabeled isofenphos at 1 mg/kg/day, followed on the 15th day by $^{14}$C-labeled isofenphos at 1 mg/kg.

The distribution of labeled residues in the tissues was determined at terminal sacrifice. In general, the tissue levels of labeled residues were higher in the females, with the highest concentration (0.605 ppm) present in the fat of the high dose females; this value was approximately ten-times higher than that of the males (0.062 ppm). In both the low and repeat dose groups, the accumulation of labeled residues in the kidneys was approximately three-times higher in females than in males.

Essentially all of the administered isofenphos was eliminated within the first 48 hours. Urinary elimination accounted for 80 to 94% of the administered dose, while less (5 to 18%) was present in the feces. Essentially all (> 96%) of the administered radioactivity was accounted for in the excreta, cage wash and total body.

Identification of $^{14}$C-labeled metabolites was carried out using pooled (0-48 hour) urinary and fecal samples. Of the total radioactivity recovered, 64 to 74% of the urinary metabolites and 1 to 12% of the fecal metabolites were identified. Four major urinary metabolites (% of administered dose) were isolated and identified as 1,2-isoproxycarbonyl-phenly sulfate (32 to 54%); 2-hydroxy-hippuric acid (1.5 to 12%); 2,5-dihydroxy-isoproxycarbonyl-phenyl glucuronide (5 to 11%); and 2-isoproxycarbonyl-phenyl glucuronide (8.2 to 18%). Of the two fecal metabolites isolated, one was identified as isopropyl-salicylate (0.7 to 1.5%) and the other as unmetabolized parent compound (0 to 11%). Unidentified urinary metabolites accounted for 18 to 20% of the total, while unidentified fecal metabolites accounted for approximately 2 to 6%. The unidentified percentage consisted of many metabolites, none of which exceeded 10% of the total radioactivity recovered.

Compared to the other metabolites, the sulfate metabolite, 2-isopropoxy-carbonylphenyl sulfate, was present in the highest percentages. Sulfation appears to be more active in males than in both the single low-dose (41% in males and 32% in

females) and repeat low-dose (54% in males and 39% in females). Animals in the high dose group, the percentage of sulfated residues were comparable in both males (49%) and females (45%), suggesting that the arylsulfotransferase reaction was saturated.

The proposed pathway for the metabolic degradation shows that isofenphos is first metabolized to isopropyl salicylate, which then undergoes secondary metabolism to sulfate, glucuronide and glycine conjugates. Another metabolite, 2-hydroxyhippuric acid, formed by the conjugation of glycine with isopropyl salicylate, was present in low amounts.

**h. Neurotoxicity Studies**

Neurotoxicity studies are designed to identify acute, subchronic and/or delayed neurotoxic effects. While all chemicals are evaluated for major neurobehavioral and neuropathological effects in the acute and subchronic neurotoxicity screening batteries in rats; organophosphates are also evaluated for delayed neurotoxicity in adult hens.

**1) Acute Neurotoxicity Study in the Rat:** In an acute neurotoxicity study in the rat (MRID No.: 44285601, HED Doc No.: 012306), male and female Wistar rats (12/sex/dose, main study; 6/sex/dose, ChE substudy) were fasted overnight and then orally gavaged once with isofenphos (92.5%) at nominal doses of 0 (vehicle), 2, 8, or 15 mg/kg (analytically confirmed doses: 0, 2.6, 7.9 or 13.8 mg/kg, respectively). Main study animals were evaluated for neurobehavioral effects [functional observational battery (FOB) and motor activity] on day 0, at the peak time-of-effect [1 hr 50 min (minimum) in males and 5 hr (minimum) in females] and days 7 and 14. Movement in the activity chambers was measured as motor activity (rearings, head movements, etc) and locomotor activity (walking within the chamber). Neuropathological evaluations were carried out on day 14 on six animals/sex/dose; animals were perfusion-fixed *in situ*. The ChE substudy group was used for determination of plasma, erythrocyte and brain ChE activities at the peak time-of-effect on day 0.

Clinical signs and FOB evaluations were consistent with acute cholinergic toxicity. At the mid-dose level, gait abnormalities and involuntary motor movements were observed in males and females. In high-dose males and females, a higher incidence of these findings was observed along with uncoordinated righting reflex, decreased number of rearings, decreased forelimb and hindlimb grip strength and decreased body temperature. No reaction to the approach response was noted in 4/12 high-dose males. In general, the onset of clinical signs was sooner in males (4 hr) than in females (8 hrs), but did not last as long (day 6 in males and day 7 in females).



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Mean body weighs and body weight gains were decreased in high-dose males and females. At day 7, the body weights of high-dose males and females were 11% and 7% lower, respectively, than the concurrent control values. By day 14, males regained some, but not all, of the decrement in body weight; the mean body weight was, however, still significantly lower than the concurrent control value. At the end of the study, the mean body weight of high-dose females was comparable to the control value. For high-dose animals, body weight gains for days 0 to 7 was 38% lower in males and 37%, in females. Overall body weight gain (day 0 to 14) for high-dose males was 18% lower, while that of high-dose females was comparable to the control value.

At the peak time-of-effect, high-dose animals had decreased motor activity (58% in males and 64% in females) and locomotor activity (79% in males and 85% in females). The day 7 evaluation of high-dose animals showed a decrease in motor activity of 28% (not significant) in females and decreased locomotor activity of 29% (not significant) in males and 34% ($p \leq 0.05$) in females.

Plasma, erythrocyte and brain ChE were all statistically significantly ($p \leq 0.01$) decreased in low- mid- and high-dose males and females at the peak time-of-effect on day 0. At the low-dose level, plasma, erythrocyte and brain ChE activities were decreased 59, 18 and 10%, respectively, in males and 89, 55 and 21%, respectively, in females; at the mid-dose level, 85, 68, and 51%, respectively, in males and 97, 89, and 69%, respectively, in females; and at the high-dose level, 94, 95, and 83%, respectively, in males and 98, 98, and 85%, respectively, in females.

At terminal sacrifice, gross and neuropathological findings of treated animals were comparable to control animals.

**Based on the results of this study [inhibition of plasma, erythrocyte and brain ChE with clinical signs (muscle fasciculations) in females], the LOEL was established at 2 mg/kg; the NOEL was not established.**

**2) Subchronic Neurotoxicity Study in the Rat:** In a subchronic neurotoxicity study (MRID No.: 44236601, HED Doc No: 012306), male and female Wistar rats (12/sex/dose) were fed diets containing isofenphos (91.6%) at 0 (basal diet ), 1, 25, or 125 ppm (mg/kg/day equivalents: 0, 0.06, 1.62, or 8.45 in males and 0, 0.09, 2.07, or 11.54 in females) for at least 13 weeks. Neurobehavioral evaluations, consisting of FOB and motor activity measurements, were performed at prestudy and after 4, 8 and 13 weeks of treatment. Gross pathology (all animals) and neuropathological (6/sex/dose) examinations were carried out at terminal sacrifice. Six animals/sex/dose were selected for determination of plasma and erythrocyte ChE activities at week 4 and plasma, erythrocyte and brain ChE activities at week 14.

Treatment-related, clinical signs, consistent with cholinergic toxicity, were observed in high-dose males and females. High incidences of saltatory spasms and non-specific behavioral disturbances (females only) were observed during the entire study; additionally, males and females showed piloerection and tremors during the first two to four weeks of treatment. Ophthalmological examination at week 13 also revealed a slow pupillary reflex in five high-dose females. No treatment-related clinical signs were observed in the low and mid-dose groups. All animals survived to terminal sacrifice.

Body weights and body weight gains were adversely affected in high-dose males and females. During the first six to seven weeks of treatment, mean body weights were decreased 9 to 14% in males and 8 to 15% in females. By the end of the study, however, the mean body weights of treated animals were comparable to control values. Treatment-related decreases in body weight gains were also observed. During the first week of treatment, statistically significant deceases in body weight gain was observed in males (51%) and females (0%, no weight gain). The decreased body weight gains appear to be a result of decreased food consumption (19% in males and 35% in females). Excluding the body weight data for the first week of the study, the body weight gains for weeks 1 to 13 were comparable to the control values in males and 11% greater than control value in females.

Neurobehavioral evaluations revealed treatment-related effects in high-dose males and females, with females being more affected than males. Treatment-related FOB effects consisted in part, of muscle fasciculations in both sexes and abnormal gait and decreased grip strength in females. Motor and locomotor activities were significantly decreased in high-dose females.

The incidences of gross and neuropathological finding of treated animals were comparable to controls.

Plasma, erythrocyte and brain ChE activities of mid- and high-dose animals were all significantly decreased. The evaluations at week 4 for mid-dose animals showed significant decreases in plasma (54% in males and 84% in females) and erythrocyte (64% in males and 81% in females) ChE activities. At week 14, mid-dose animals had decreases in plasma, erythrocyte and brain ChE activities of 54, 63 and 32% in males and respectively, and 88, 66 and 60% in females, respectively. At week 4, high-dose animals had decreases in plasma and erythrocyte ChE activities of 85 and 98%, in males, respectively and 97 and 100% (complete inhibition) in females, respectively. At week 14, plasma, erythrocyte and brain ChE activities of high-dose animals were decreased 84, 96, and 75% in males, respectively and 97, 97, and 89% in females, respectively.

**Based on the results of this study (inhibition of plasma, erythrocyte and brain ChE), the LOEL was established at 25 ppm (1.62 mg/kg/day in males, 2.07 mg/kg/day in females); the NOEL was established at 1 ppm (0.06 mg/kg/day in males, 0.09 mg/kg/day in females).**

**3) Subchronic Delayed Neurotoxicity Study in the Hen**: In a subchronic delayed neurotoxicity study (MRID Nos.: 00146887, 40459701, 41074101, HED Doc Nos: 005435, 006808, 007612), hens (10/group) were assigned to control groups [vehicle-treated and naive, untreated], isofenphos (92.5%) treatment groups, 0.25, 1.00 and 2.00 mg a.i./kg/day, or a positive control group [TOCP (tri-o-tolyl phosphate (TOCP) at 5 mg/kg/day]. Hens were treated daily by oral gavage for 90 days.

Mean body weights were significantly decreased at 2.0 mg/kg/day from week 1 through 13; non-significant decreases were observed in the positive control hens.

At day 26, plasma ChE activity was significantly decreased by 53% at 1 mg/kg/day and 65% at 2 mg/kg/day. At 2 mg/kg/day, erythrocyte ChE activity was significantly decreased by 24% on day 26. On day 55, whole blood ChE activity was decreased by 25% at 1 mg/kg/day and 36% at 2 mg/kg/day.

Compared to the vehicle control hens, isofenphos at 2 mg/kg/day did not produce any appreciable neuropathological effects in hens. There were no indications of delayed neurotoxicity due to isofenphos treatment. TOCP treatment produced the expected neural degeneration indicative of its delayed neurotoxicity in both the peripheral and central neurons.

**i. Dermal Absorption**

No study available

**j. Other Toxicological Considerations: Non FIFRA, Open Literature Publications**

**1) Human accidental exposure incident:** In a publication by Catz *et al.* (J. Neurology, Neurosurgery, and Psychiatry 51: 1338-1340, 1988), late onset neuropathy was described in an agricultural worker following the accidental ingestion of few milliliters of a mixture of isofenphos (0.75 mg/ml) and Maneb (2.0 mg/ml). The worker was treated by a physician with atropine and taken to a local hospital. Since there were no clinical signs of cholinergic toxicity and the serum ChE value was within the normal range, the worker was discharged. Cholinergic signs of toxicity (weakness, dyspnea, vomiting) developed within several hours of the exposure with recovery by 16 hours.

The worker developed pain in the calves and gait impairment two weeks after the exposure and was readmitted to the hospital after three weeks. Clinical evaluation over the next few weeks revealed abnormal electromylographs and nerve conduction tests. These findings were described at distal, mainly axonal, motor neuropathy.

Although the toxicity was attributed to isofenphos, the worker was exposed to mixture of pesticides, making identification of the causative agent unclear. Additionally, prior-exposure to pesticides and medical history of the worker were not given in the publication.

**2) *In vitro* and *in vivo* studies with isofenphos and selected metabolites:** Chow *et al.* (Toxicol. Appl. Pharmacol. 83: 178-183 (1986) evaluated isofenphos and some of its metabolites for their ability to inhibit neurotoxic esterase (NTE) *in vitro*. This study showed that metabolic activation of isofenphos was necessary for the formation of NTE-inhibiting substance(s). Without metabolic activation, isofenphos and the oxon metabolite (an unexpected finding) were essentially inactive and inhibited NTE by 0.0% and 1.3%, respectively. Another metabolite, des-N-isopropyl isofenphos inhibited NTE by 16%, while des-N-isopropyl isofenphos oxon inhibited NTE by 99%. With microsomal activation, NTE was inhibited by 20%, 80%, and 73% for isofenphos, isofenphos oxon, des-N-isopropyl isofenphos, respectively (des-N-isopropyl isofenphos oxon was not assayed).

Isofenphos metabolites were further studied *in vivo* for their ability to cause delayed neurotoxicity in chickens. Chickens were dosed subcutaneously with a single dose with isofenphos oxon at 10, 25, 50, or 75/100 mg/kg or des-N-isopropyl isofenphos at 10, 25, or 50 mg/kg. Four weeks post-dosing, isofenphos oxon produced slight ataxia at 50 mg/kg and paralysis at 75/100 mg/kg. Des-N-isopropyl isofenphos produced ataxia at 25 mg/kg and paralysis at 50 mg/kg. Based on the results of these studies, des-N-isopropyl isofenphos oxon was proposed as the possible neurotoxic metabolite of isofenphos.

**3) Delayed neurotoxicity study in the hen:** In another publication, Francis *et al.* (J. Environ. Sci. Health B20(1): 73-95, 1985; also reviewed by EPA: Accession No.: 258240, HED Doc No.: 005428), hens were evaluated for neurotoxicity toxicity after repeated dermal dosing with isofenphos at 4.7, 4.9 or 5.2 mg/kg/day (1 hen/dose). Isofenphos was extracted from commercial sample of Amaze® granular insecticide (purity of final product not given) and formulated in xylene and 2% Triton X-100. Hens were unprotected by atropine and 2-PAM during the study. During treatment, hens were scored for the development of ataxia, ranging from irregular gait (T-1), ataxia (T-2), severely ataxic (T-3) to paraplegia (T-4). Dosing was discontinued when a hen became severely ataxic (T-3), and not started again until the hen recovered.

Hens were treated for 18 to 52 days, with ataxia occurring either during treatment or shortly after treatment was stopped. The hens progressed to paraplegia after 20 to 59 days, with death occurring one to two days later. Only one hen survived long enough after cession of dosing to experience a gradation in neurotoxic responses from T-3 to T-4. Ataxia seen in hens was a result of cumulative toxicity, and probably not due to delayed neurotoxicity. No histopathology or determination of NTE activity were performed in this study.

Deficiencies noted in the EPA review included: 1) too few hens were used (4 for oral study, 3 for dermal), 2) neurohistopathological evaluations were not performed, 3) hens were too young (6-7 months vs 8-14 months). This study was not submitted to satisfy regulatory requirements.

**4) Evaluation of the neuropathic potential of isofenphos in hens:** In another publication (Wilson *et al.* (Bull. Environ. Contam. Toxicol. 33: 386-394, 1984) the neuropathic potential of isofenphos was evaluated in hens. Hens protected with atropine/2-PAM survived a lethal challenge of isofenphos at 100 mg/kg (15 to 20 times the $LD_{50}$); symptoms consistent with organophosphate-induced delayed neuropathy (OPIDN) were observed. Although the hens had regained their ability walk, 10 to 14 days after the isofenphos challenge, the condition of the hens progressed to symptoms of leg ataxia and paralysis. NTE activity in the brains of hens, challenged with 100 mg/kg isofenphos, was inhibited by 64% one day dosing and 85% after three days. Histopathologic evaluation of the most severely affected hens revealed lesions in the peripheral and central nervous systems; similar lesions were observed in TOCP-treated (positive control) hens.

Although isofenphos appears to induce delayed neuropathy in hens, it should be noted that the doses used in this study greatly exceed those recommended for Agency guideline delayed neurotoxicity studies. Although the results obtained from unconventional studies such as this are scientifically intriguing, isofenphos, when evaluated using Agency-approved protocols, did not induce delayed neuropathology in the subchronic hen study.

## 2. Dose/Response Assessment

On October 23 and 30, 1997 and December 10 and 17, 1997 (document dated January 13, 1997), the Health Effects Division Hazard Identification Assessment Review Committee evaluated the toxicology data base for isofenphos and selected doses and endpoints for acute dietary, chronic dietary (RfD) as well as occupational and residential exposure risk assessments [short-, intermediate and long-term exposure (dermal and inhalation)], assessed the carcinogenic potential and addressed the

sensitivity of children and infants from exposure to isofenphos as required by the Food Quality Protection Act (FQPA).

**a. Special Sensitivity to Infants and Children**

Under P.L. 104-170, FQPA was promulgated as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA). This directed the Agency to "ensure that there is a reasonable certainty that no harm will result to infants and children" from aggregate exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this reasonable certainty of no harm, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Pursuant to the language and intent of the FQPA directive regarding infants and children, the applicable toxicity database for isofenphos was evaluated by the Hazard Identification Assessment Review Committee. The following discussion represents the information that was considered and the conclusions that were drawn by the Committee:

**1) Adequacy of the data**: The data base for isofenphos included an acceptable two-generation reproduction studies in rats and prenatal development toxicity studies in rats and rabbits, meeting the FIFRA basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. Additionally, the Committee reviewed several open literature publications which suggested that isofenphos caused delayed neuropathy in the hen.

**2) Susceptibility issues:** In evaluating the susceptibility issues for isofenphos and the recommendation for a developmental neurotoxicity, the Hazard Identification Assessment Review Committee reviewed the toxicology database for studies submitted to the Agency and open literature publications dealing with the development of delayed neurotoxicity in a human exposure and three studies in the hen.

**(i) The Hazard Identification Assessment Review Committee evaluated the following evidence to support the recommendation for a developmental neurotoxicity study:**

- Administration of isofenphos, like most other organophosphate pesticides, to various species results in plasma, erythrocyte and brain ChE inhibition.

- Isofenphos is considered to be relatively acutely toxic, with oral $LD_{50}$ values ranging from 29 to 39 mg/kg in two rat studies and from 91 to 127 mg/kg in a mouse study. The dermal $LD_{50}$ ranged from 70 to 191 mg/kg in rats and 315 to 1172 mg/kg/day in rabbits. The $LC_{50}$ for inhalation exposure ranged from 0.14 to 0.53 mg/L over 5 separate studies.

- A report of delayed neuropathy in an agricultural worker [see section I.1) above] described clinical manifestations, electromylographs, and nerve conduction assays which suggested a pathology of a distal, mainly axonal, motor neuropathy following accidental isofenphos ingestion.

- In a non-guideline open literature publication, isofenphos was shown to inhibit NTE at very high concentrations in an *in vitro* chicken brain assay [section I.2), above]. This group also demonstrated that oxon and des-N-isopropyl metabolites of isofenphos, at very high doses, produced symptoms of delayed neurotoxicity in hens.

**(ii) The Hazard Identification Assessment Review Committee evaluated the following evidence which were insufficient to support the recommendation for a developmental neurotoxicity study:**

- In two guideline developmental toxicity studies in the rat and rabbit, no evidence that isofenphos produced developmental abnormalities in the fetal nervous system at maternally toxic oral doses (4.0 mg/kg/day in the rat and 7.5 mg/kg/day in the rabbit).

- In the developmental toxicity study in the rat, evaluation of fetal brain ChE at gestation day 20 was not different from the control value, although in maternal, erythrocyte and brain cholinesterase were significantly inhibited at that time point.

- In guideline acute and subchronic neurotoxicity studies in the rat, there was no evidence that isofenphos produced alterations in either brain weight or the incidence of neuropathological lesions.

- In a guideline subchronic delayed neurotoxicity study in the hen, there was no evidence for the development of OPIDN.

**3) Uncertainty factor (UF)**: The Committee determined that for isofenphos the 10-fold uncertainty factor for the protection of infants and children would be retained because of the lack of a developmental neurotoxicity study in rats.

**4) Recommendation for a developmental neurotoxicity study**: Based on the evaluation of the toxicology database, the Hazard Identification Assessment Review Committee determined that a developmental neurotoxicity study in rats is required for isofenphos in order to assess functional development following prenatal exposure. This is considered a data gap for the assessment of the effects of isofenphos following *in utero* and/or early postnatal exposure.

**b. Reference Dose (RfD)**

$$RfD = \frac{0.08 mg/kg/day (NOEL)}{1000 (UF)} = 0.00008 mg/kg/day$$

**Critical Study:** 2-Generation Reproductive Toxicity Study in Rats (83-4), MRID 41609902 [see section B.1.e, above].

**Endpoint and Dose Selected for Use in Risk Assessment**

The NOEL for parental animals was established at 1 ppm (0.08 to 0.16 mg/kg/day); the LOEL was established at 5 ppm (0.44 to 0.69 mg/kg/day) based on inhibition of plasma and erythrocyte ChE in both sexes and brain ChE in males.

Further, the reproductive NOEL is 1 ppm (0.08-0.16 mg/kg/day), based on clinical signs of toxicity (small to very small and emaciated pups) and increased pup mortality (reductions in the lactation indices and mean litter sizes) observed at 5 ppm (0.44-0.69 mg/kg/day).

**Uncertainty Factor (UF)**: A UF of 1000 was applied; this includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability. An additional UF of 10 was recommended because of FQPA considerations.

**Comments and Rationale**: The NOEL and the effects observed in this study are supported by similar findings (ChE inhibition) in the chronic dog study (MRID No. 92085016, 43198001).

**Chronic Dietary Risk Assessment:** There is potential for chronic dietary exposure to isofenphos from drinking water sources. A screening level chronic dietary risk assessment for isofenphos in drinking waster sources is required. A chronic dietary (food source) risk assessment is not required for isofenphos because currently there are no isofenphos end-use products registered for food/feed uses; thus, there is no potential for chronic dietary exposure to isofenphos from food sources at this time.

**c. Acceptable Daily Intake (FAO/WHO)**

Isofenphos was evaluated for acceptable daily intake (ADI) in 1986 (87 JMPR 1986). The estimate of the ADI for humans was established at 0 to 0.001 mg/kg. The ADI was based on a no effect level for plasma ChE inhibition of 1 ppm (equivalent to 0.05 mg/kg/day) in both the rat and dog and an uncertainty factor of 50.

**d. Carcinogenicity Classification and Risk Quantification:** At an October 30, 1997 meeting, the Hazard Identification Assessment Review Committee, based on the toxicology data available, determined that isofenphos did not alter the spontaneous tumor profile in the mouse under the testing conditions. Therefore, it was recommended that isofenphos be classified as a **"Group E"**, indicating evidence of non-carcinogenicity for humans; i.e., the chemical is characterized as **"Not Likely"** to be carcinogenic in humans via relevant routes of exposure.

This weight of the evidence judgement was largely based on the absence of significant tumor increases in an adequate carcinogenicity study in mice [see section B.1.c.2), above]. This classification was also supported by the lack of mutagenic activity in several mutagenicity assays [see sections B.1.f.1), 2), and 3), above].

It should be noted, however, that designation of an agent as being in **"Group E"** or **"Not Likely"** was based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

**e. Dermal Absorption**: There were no dermal absorption studies appropriate for use for the purpose of risk assessment. Therefore, the default value of 100% will be used for the dermal absorption rate.

**f. Other Toxicological Endpoints for Use in Human Risk Assessment**

**1) Acute Dietary Exposure (one day)**

**Critical Study**: Acute Oral Neurotoxicity Study in Rats (81-8), MRID No. 44285601 [see section B.2.h.1), above].

**Endpoint and Dose Level Selected for Use in Risk Assessment**: The NOEL was not established in this study. The LOEL is 2.0 mg/kg/day based on inhibition of plasma, erythrocyte and brain ChE with clinical signs (muscle fasciculation) in females.

**Uncertainty Factor (UF)**: The Committee determined that the 10X factor to account for enhanced sensitivity to infants and children (as required by FQPA) should be retained. For acute dietary risk assessment, a MOE of 3000 is required. This MOE is based on a UF of 100 to account for both interspecies extrapolation and intraspecies variability, an additional UF of 3 to account for the lack of a NOEL, and a UF of 10 for FQPA considerations.

**Comments:** The effect of concern is the acute inhibition of ChE, which this study demonstrates, and the length of the study (acute exposure) is appropriate for the exposure scenario.

**Acute Dietary Risk Assessment**: There is a potential for acute dietary exposure to isofenphos from drinking water sources. An acute dietary (food source) risk assessment in not required for isofenphos because currently there are no isofenphos end-use products registered for food/feed uses; thus, there is no potential for acute dietary exposure from food sources at this time. However,.a screening level acute dietary risk assessment for isofenphos in drinking water is required.

**2) Short Term Occupational or Residential Exposure (1-7 days)**

**Critical Study**: Acute oral neurotoxicity study (81-8), MRID No. 44285601 [see section B.1.h.1), above].

**Endpoint and Dose Level Selected for Use in Risk Assessment**: The NOEL was not established in this study. The LOEL is 2.0 mg/kg/day based on inhibition of plasma, erythrocyte and brain ChE inhibition in both sexes with clinical signs (muscle fasciculation) in females.

**Uncertainty Factor (UF)**: A UF of 3000 was applied; this includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability, an additional UF of 3 to account for the lack of a NOEL, and an additional UF of 10 for FQPA considerations.

**Comments**: Although two 21-day and a 90-day dermal toxicity studies were available on isofenphos, and although these studies cover the time points of 1-7 days, the Committee recommended the use of an oral study for this purpose. This conclusion was based on the fact that the 21-day dermal toxicity studies were conducted with isofenphos formulations not with the technical material (in the rabbit), and the 90-day dermal toxicity study, though conducted with the technical material, was also performed in the rabbit. The rabbit is considered inappropriate to conduct dermal studies with organophosphorus compound requiring metabolic activation, i.e., thiophosphates, phosphorothioates, and phosphorodithioates which are normally activated to the corresponding phosphates by the hepatic microsomal enzymes. (Robert Zendzian, HED memo dated March 31, 1997).

Because of the lack of a dermal absorption study and because of the similarity of toxic effects via the oral and dermal routes as evidenced in several acute oral and dermal toxicity studies, the Committee recommended the use of a dermal absorption rate of 100%. The Committee recommended that the dermal absorption rate may be changed with the submission and favorable review of either a 21-day dermal study with technical isofenphos in the rat or a dermal penetration study in the rat.

**Short- and Intermediate-Term Occupational and Residential Risk Assessment**: Based on the currently registered use pattern, short-term occupational and residential risk assessment is required.

**3) Intermediate Term Occupational or Residential Exposure (one week to several months)**

**Critical Study**: Subchronic Neurotoxicity Screening Study in Wistar Rats (82-7), MRID No.: 44236601 [see section B.1.h.2), above].

**Endpoint and Dose Level Selected for Use in Risk Assessment**: The NOEL of 1 ppm (0.06 mg/kg/day, males; 0.09 mg/kg/day, females), based on inhibition of plasma, erythrocyte and brain ChE observed at the next higher dose level of 25 ppm (1.62 mg/kg/day, males; 2.07 mg/kg/day, females).

**Uncertainty Factor (UF)**: A UF of 1000 was applied. This includes a UF of 100X to account for both interspecies extrapolation and intraspecies variability and 10X to account for enhanced sensitivity of infants and children (as required by FQPA) was retained.

**Comments and Rationale**: See comments and rationale for Section 2.f.2), above, for the explanation of why an oral toxicity was used for dermal risk assessment although dermal studies were available covering the range of 1-90 days, and what is the dermal absorption rate to be used for the derivation of the dermal equivalent dose in this case and why.

**4) Chronic Occupational and Residential Exposure (Non-cancer)**

**RfD = 0.00008 mg/kg/day**

**Critical Study**: 2-Generation Reproductive Toxicity Study in Rats (83-4), MRID 41609902 [see section B.1.e, above]

**Endpoint and Dose Selected for Use in Risk Assessment**

For parental animals, the ChE NOEL was established at 1 ppm (0.08 to 0.16 mg/kg/day); the LOEL was established at 5 ppm (0.44 to 0.69 mg/kg/day) based on inhibition of plasma and erythrocyte ChE in both sexes and brain ChE in males.

Further, the reproductive NOEL is 1 ppm (0.08-0.16 mg/kg/day), based on clinical signs of toxicity (small to very small and emaciated pups) and increased pup mortality (reductions in the lactation indices and mean litter sizes) observed at 5 ppm (0.44-0.69 mg/kg/day).

**Uncertainty Factor (UF)**: A UF of 1000 was applied; this includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability. A UF of 10X to account for enhanced sensitivity of infants and children (as required by FQPA) was retained.

**Comments and Rationale:** The NOEL and the effects observed in this study (ChE inhibition) are supported by similar findings in the chronic dog study [see Section B.1.c.1 above for details].

**Chronic Occupational and Residential (non-cancer) Risk Assessment:** Based on the currently registered use pattern, chronic dermal exposure in not anticipated and thus the long term dermal risk assessment is not required.

**5) Inhalation Exposure (variable duration)**

For the purpose of inhalation risk assessment of short and intermediate duration, the Committee recommended that the inhalation exposure be converted from mg/L to

the equivalent mg/kg/day dose assuming an inhalation absorption rate of 100%. This dose should be compared to the oral LOEL of 2 mg/kg/day from the acute neurotoxicity study [see section B.1.h.1), above], in the case of short term and compared to the oral NOEL of 0.06 mg/kg/day from the subchronic neurotoxicity study [see section B.1.h.2), above] in the case of the intermediate-term risk assessment. Based on the use pattern and exposure profile, the Committee determined that the long-term inhalation risk assessment would not be required.

A UF of 3000 was recommended for the short-term exposure. This includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability, an additional UF of 3 to account for the lack of a NOEL, and the 10X factor for enhanced sensitivity of infants and children (as required by FQPA) was retained.

An UF of 1000 was recommended for the intermediate-term exposure. This includes an UF of 100 to account for both interspecies extrapolation and intraspecies variability, and the 10x factor for enhanced sensitivity of infants and children (as required by FQPA) be retained.

**Comments and Rationale**: Since there was no appropriate subchronic inhalation study, but there was concern about potential inhalation exposure, the inhalation exposure was converted to an equivalent oral dose assuming 100% lung absorption. This was added to the dermal exposure (after assuming 100% dermal absorption) and compared to the oral neurotoxicity endpoint of either 2 or 0.06 mg/kg/day depending on the exposure duration.

**6) Aggregate Risk**

Because of the similarity of the endpoints identified both in the dermal and inhalation exposure, i.e. ChE inhibition, the following equation is appropriate in expressing the aggregate risk for isofenphos.

$$\textit{Combined Dermal and Inhalation Risk} = \frac{1}{\frac{1}{MOE_{dermal}} + \frac{1}{MOE_{Inhalation}}}$$

**SUMMARY of TOXICOLOGICAL ENDPOINTS for Isofenphos**

| Exposure Duration | Exposure Route | Endpoint and Toxicological Effect | MOE |
|---|---|---|---|
| Acute | Dietary | NOEL = not established, LOEL = 2 mg/kg<br><br>Uncertainty Factors10x = Interspecies<br>10x = Intraspecies<br>10x = FQPA<br>3x = Lack of NOEL (FIFRA)<br><br>Based on inhibition of plasma, erythrocyte and brain ChE activity in an acute neurotoxicity study in the rat | 3000 |
| Short-Term (1-7 Days) Occupational/Residential | Dermal and Inhalation | NOEL = not established, LOEL = 2 mg/kg<br><br>Uncertainty Factor 10x = Interspecies<br>10x = Intraspecies<br>10x = FQPA<br>3x = Lack of NOEL (FIFRA)<br><br>Based on inhibition of plasma, erythrocyte and brain ChE activity in an acute neurotoxicity study in the rat. Assume 100% dermal and inhalation absorption. | 3000 |
| Intermediate-Term (7-90 days) Occupational/Residential | Dermal and Inhalation | NOEL = 0.06 mg/kg/day, males; 0.09 mg/kg/day, females<br><br>Uncertainty Factor 10x = Interspecies<br>10x = Intraspecies<br>10x = FQPA<br><br>Based on inhibition of plasma, erythrocyte and brain ChE activity in a subchronic neurotoxicity study in the rat. Assume 100% dermal and inhalation absorption. | 1000 |

## 3. Dietary Exposure and Risk Assessment/Characterization

### a. Dietary Exposure (Food Sources)

Isofenphos is an organophosphate insecticide used for control of insects in turf and ornamental plants. Isofenphos is sold in the U.S. under the trade name Oftanol®. There are no products registered for food/feed use. No residue chemistry data have been submitted and no residue data are required in support of the reregistration of isofenphos provided no food/feed uses are proposed.

1) Tolerance Reassessment Summary Table

The tolerances listed in 40 CFR §180.387 are expressed in terms of isofenphos and its cholinesterase-inhibiting benzoate metabolites. There are currently no registered food/feed uses of isofenphos; therefore, the established tolerances on corn (fresh, grain, forage, and fodder), meat, milk, poultry, and eggs should be revoked. A summary of isofenphos tolerance reassessments is presented in Table A.

Table A. Tolerance Reassessment Summary for Isofenphos.

| Commodity | Current Tolerance (ppm) | Tolerance Reassessment | Comment |
|---|---|---|---|
| **Tolerances Listed Under 40 CFR §180.387:** | | | |
| Corn, forage and fodder | 1.0 | Revoke | No registered or proposed food/feed uses of isofenphos. |
| Corn, fresh including sweet (K+CWHR) | 0.1 | Revoke | |
| Corn, grain | 0.1 | Revoke | |
| Eggs | 0.02 | Revoke | |
| Meat, fat, and meat byproducts of cattle, goats, hogs, horses, sheep, and poultry | 0.1 | Revoke | |
| Milk | 0.02 | Revoke | |

2) Codex Harmonization

Codex MRLs have been established for isofenphos; however, there will be no issues of compatibility once the U.S. tolerances have been revoked.

3) Dietary Exposure Assessment

Currently there are no isofenphos end-use products registered for food/feed uses; thus, there is no potential for dietary exposure to isofenphos from food sources at this time.

**b. Dietary Exposure (Drinking Water Source)**

1) Ground Water

**Monitoring Data:** Ground-water monitoring data for isofenphos are limited. EPA's Pesticides in Ground Water Database reports isofenphos detections in 2 of 19 well samples in Massachusetts and 0 of 78 wells sampled in New York. The concentrations in the two detections in Massachusetts were 1.17 and 2.12 ug/L. The quality of this data is uncertain since nothing is known about specific locations, uses or rates, or type of well or sample. STORET shows no detections of isofenphos (limits of detection ranging from 0.04 to 0.5 ug/L) in 1,040 ground-water monitoring samples taken between August 1989 and September 1996 in Florida. No sample depths (depth to ground water) were reported. No specific link was established between the well samples and specific isofenphos use areas.

**Modeled Data:** A preliminary ground water assessment was made using SCI-GROW (Screening Concentrations In GROund Water) to estimate concentrations of pesticides in ground water under highly vulnerable conditions. SCI-GROW uses fate properties of the pesticide (aerobic soil half-life and sorption coefficients), the maximum application rate, and the existing body of data from small-scale ground-water monitoring studies. The model assumes the pesticide is applied at its maximum rate in areas where the ground water is particularly vulnerable to contamination. The highly-vulnerable ground water upon which the SCI-GROW estimates is believed to represent only a small percentage of drinking water in the pesticide use area. Because SCI-GROW is a regression model, it does not account for site-specific hydrology, soil properties, climatic conditions, or agronomic practices. Overestimates are particularly likely for foliarly-applied pesticides that are susceptible to photolysis or for volatile pesticides. As such, SCI-GROW is likely to provide high-end estimates of acute or chronic exposure and should be used only for screening purposes.

2) Surface Water

**Monitoring Data:** The STORET database reported no detections of isofenphos in a limited number of sediment and surface water samples taken in Florida, Illinois, and New York. In Florida, isofenphos was not detected (limits of detection ranging from 1.2 to 36 mg/kg, dry weight) in 68 sediment samples taken from lakes,

estuaries, streams and outflows. No concentration was reported for one stream sample in Illinois. Isofenphos was not found above the limit of detection/quantification (0.03 to 0.5 ug/L) in 237 New York water samples (231 stream, 4 canal, and 2 lake samples). The utility of this data is uncertain because of the wide range in limits of detection and because no specific link was established between the water/sediment samples and specific isofenphos use areas.

**Modeled Data:** Preliminary (Tier 1) Estimated Environmental Concentrations (EECs) are estimated using GENEEC, a screening model that provides an upper-bound estimate of EECs on a high exposure site. GENEEC uses basic environmental fate values (adsorption to soil, degradation in soil before runoff and in water) and pesticide label information (rates, intervals, incorporation, method of application) to estimate the EECs in a one-hectare, two-meter deep pond following the treatment of a 10 hectare field. The runoff event occurs two days after the last application. The model accounts for direct deposition of spray drift onto the water body (assuming 1 percent for ground spray applications).

3) Drinking Water Data for use in Risk Assessment

Insufficient monitoring data is available to provide estimates of isofenphos concentrations in ground and surface water sources of drinking water. Thus, both acute and chronic drinking water estimated concentrations from ground-water sources are based on the screening model SCI-GROW. The only modeling data available for predicting estimated environmental concentrations of isofenphos in surface water comes from the preliminary screening model GENEEC. Given the use patterns, the turf scenario is best applicable to modeling for drinking water assessments.

Estimated concentrations of isofenphos in drinking water (DWEC) were based on maximum single application rate of 2 lb ai/acre, applied twice at a minimum 30 day interval for a maximum seasonal rate of 4 lb ai/acre. Tier 1 modeling was used for both surface- and ground-water sources of drinking water due to inadequate monitoring data. Because isofenphos oxon is structurally similar and is likely to be at least as toxic as the parent, both models were run for the combined isofenphos plus oxon residues. A reliable Tier 2 scenario for use on golf courses and residential lawns is not available for surface water. No Tier 2 ground water models have been developed at this time. The following DWECs should be used solely for screening purposes:

- Ground water: 0.8 ug/L for both acute and chronic risk. For the combined isofenphos and isofenphos oxon residues, the acute and chronic DWEC is 22.8 ug/L.

- Surface water: 52 ug/L for acute risk and 37 ug/L for chronic risk. For the combined isofenphos and oxon residues, the acute DWEC is 122 ug/L and the chronic DWEC is 95 ug/L.

### c. Dietary Risk Assessment and Characterization

#### 1) Chronic Risk (TMRC, ARC)

A chronic dietary (food source) risk assessment is not required for isofenphos. There are no isofenphos end-use products registered for food/feed uses and the established tolerances listed under 40 CFR §180.387 for corn (fresh, grain, forage, and fodder), meat, milk, poultry, and eggs should be revoked.

#### 2) Carcinogenic Risk (TMRC, ARC)

Based on the toxicology data available, the Hazard Identification Committee determined that isofenphos did not alter the spontaneous tumor profile in rats or mice under the testing conditions. Therefore, it was recommended that isofenphos be classified as a **"Group E"**, indicating evidence of non-carcinogenicity for humans; i.e., the chemical is characterized as **"Not Likely"** to be carcinogenic in humans via relevant routes of exposure. There are no isofenphos end-use products registered for food/feed uses and the established tolerances listed under 40 CFR §180.387 for corn (fresh, grain, forage, and fodder), meat, milk, poultry, and eggs should be revoked.

#### 3) Acute Dietary Risk (tiered assessment)

An acute dietary (food source) risk assessment is not required for isofenphos. There are no isofenphos end-use products registered for food/feed uses and the established tolerances listed under 40 CFR §180.387 for corn (fresh, grain, forage, and fodder), meat, milk, poultry, and eggs should be revoked.

#### 4) Drinking Water Risk (Acute and Chronic)

EPA does not have sufficient data to perform a quantitative drinking water exposure and risk assessment. EFED (Nelson Thurman 2/13/98) has conducted both a Tier 1 screening assessment and a qualitative evaluation of the potential impact of the use of isofenphos on drinking water resources. The initial screening assessment provides likely upper bound estimates of the concentration of isofenphos that might be found in ground- and surface-water sources of drinking water (DWECs). Surface water sources of drinking water are most likely to be impacted by the use of isofenphos.

To calculate drinking water levels of concern (DWLOCs) for acute and chronic exposure to isofenphos in drinking water, HED used GENEEC Tier 1 upper-bound estimates of concentrations in surface water (acute $DWEC_{sw}$ of 52 ug/L; chronic $DWEC_{sw}$ of 37 ug/L). Since there is no acute or chronic exposure to isofenphos from food sources, the acceptable chronic exposure to isofenphos in drinking water would be the RfD of 0.0008 mg/kg/day. The acceptable acute exposure to isofenphos in drinking water would be the ratio of the NOEL for acute dietary risk assessment to the acceptable MOE (2:3000 = 0.00067 mg/kg/day). Using default body weights and consumption values of 2L/70 kg (adult male), 2L/60 kg (adult female), and 1L/10kg (child), the calculated chronic and acute DWLOCs exceed OPP's levels of concern.

Since the Tier 1 models serve only as a screening tool, exceedances using these model predictions mean a refined assessment is needed (refined modeling or monitoring data). Currently, OPP does not have Tier 2 screening models that adequately model runoff from golf courses or residential lawns; existing surface water monitoring data is very limited and not of much use in assessing the extent of isofenphos occurrences in water. However, OPP believes the overall impact of isofenphos on drinking water resources is likely to be less than what would be estimated in the Tier 1 screens due to its apparent susceptibility to enhanced degradation by soil microorganisms; its limited uses (primarily lawns and golf courses) and limited acreage, and label recommendations which would minimize off-target movement to surface water. The impact of these factors cannot be sufficiently quantified to generate a refined $DWEC_{sw}$.

OPP has considered the registered uses and published literature indicating enhanced degradation of isofenphos. OPP has determined through a qualitative risk assessment that the limited use associated with isofenphos (no more than two applications per season to lawns and golf courses where only about 132,000 acres are treated nationally) is not expected to impact water resources through labeled uses. In light of this finding, OPP believes that isofenphos use will not impact ground water or surface water resources, and therefore is not expected to lead to exposure to humans through drinking water. If new uses are added in the future, OPP will reassess the potential impacts of isofenphos on drinking water as part of the aggregate risk assessment process.

**d. Statement of the adequacy of the dietary exposure data base to assess infants' and children's exposure**

The dietary (food and water) exposure database for isofenphos is adequate to assess infants' and children's exposure.

**4. Occupational and Residential Exposure and Risk Assessment/Characterization**

## a. Occupational and Residential Exposure

### 1) Summary of Use Patterns and Formulations: Occupational and Residential

Isofenphos is an organophosphate insecticide used in commercial and residential settings. Isofenphos is used on turf and ornamental plants. Currently there are no isofenphos end-use products registered for food/feed uses as they have been voluntarily canceled by the registrant. Use on buildings and utility poles (for termite control) has been voluntarily canceled by the registrant. Isofenphos is formulated as a technical-grade manufacturing product (91.7 percent active ingredient), granules (ranging from 0.5 to 5 percent active ingredient), and emulsifiable concentrate (22 percent active ingredient).

Isofenphos can be applied with a groundboom, rights-of-way sprayer, chemigation, handgun (turf), tractor-drawn spreader, backpack sprayer, low-pressure handwand, belly grinder, and a lawn drop spreader at a rate of 2.0 pounds per acre. It can also be applied by hand and shaker can to fire ant mounds at a rate of 0.057 pounds per 1,000 square feet; and mixed with potting soil at a rate of 0.020 pounds per cubic yard. Application frequency varys from "as needed" (for fire ant mounds) to "up to 2 times per season" on turf with a 30 day minimum interval between applications.

**Occupational-use Products and Homeowner Use Products**: At this time, products containing isofenphos are intended for occupational and homeowner uses. The emulsifiable concentrate formulation (Reg. No. 3125-342), and the granular formulations (Reg Nos. 538-162, 3125-330, and others) containing 2 to 5 percent active ingredient, are intended for occupational use only. Several other granular formulation products, with concentrations ranging from 0.66 to 1.5 percent active ingredient, can be used by the homeowner. Termiticide use has been canceled.

### 2) Epidemiological Information

A Review of Isofenphos Incident Reports by Jerome Blondell and Monica Spann dated 3/4/98 is attached.

### 3) Handler Exposures and Assumptions

**Occupational Handler Exposures**: Based on the use patterns, EPA has identified thirteen major isofenphos exposure scenarios for occupational handlers: (1) mixing/loading liquids for groundboom, rights-of-way sprayer, chemigation, and handgun application; (2) loading granules for tractor-drawn/mechanical spreader

application; (3) applying sprays with a groundboom sprayer; (4) applying sprays to rights-of-way; (5) applying sprays with a handgun sprayer; (6) applying granules with a tractor-drawn spreader; (7) loading/applying granules by hand to fire ant mounds; (8) mixing/loading/applying liquids with a backpack sprayer; (9) mixing/loading/ applying liquids with a low pressure handwand; (10) loading/applying granules to potting soil by hand; (11) loading/applying granules with a shaker can to fire ant mounds (12) loading/applying granules with a belly grinder; and (13) loading/applying granules with a push-type lawn drop spreader.

Dermal and inhalation exposures (developed using PHED Version 1.1 surrogate data) are presented in Table 1. Table 2 presents the risk assessment for short- and intermediate-term dermal and inhalation exposures at baseline attire. Table 3 presents the risk assessment for short- and intermediate-term dermal and inhalation exposures with additional personal protective equipment. Table 4 presents the risk assessment for short- and intermediate-term dermal and inhalation exposures with engineering controls. Table 5 summarizes the caveats and parameters specific to each exposure scenario and corresponding risk assessment.

The following assumptions are made in the exposure calculations:

- Average body weight of an adult handler is 70 kg.
- Average workday interval represents an 8-hour workday (e.g., the acres treated in a typical day).
- Calculations of handler exposures are completed using the application rates recommended by the available isofenphos labels and LUIS report.
- Due to a lack of scenario-specific data, HED calculated unit exposure values using generic data from the Pesticide Handler Exposure Database (PHED). When generic data were not available to represent various risk mitigation options (i.e., the use of PPE and engineering controls) for a particular scenario, protection factors were applied. The details for each scenario are discussed in Table 5.
- Area treated in each scenario: 80 acres for groundboom and tractor-drawn spreader application; 40 acres for rights-of-way sprayer and chemigation application; 2 acres for handgun, belly grinder, and push-type lawn drop spreader application; 5,000 square feet for application by backpack sprayer and low pressure handwand; 1 one-pound can for application by hand and shaker can; and 2 cubic yards for application by hand to potting soil.

**Residential Handler Exposures:** Based on the use patterns, EPA has identified five major isofenphos exposure scenarios for residential handlers: (1) loading/applying granules by hand to fire ant mounds; (2) loading/applying granules to potting soil by hand; (3) loading/applying granules with a shaker can to fire ant mounds (4) loading/applying granules with a belly grinder; and (5) loading/applying granules with a push-type lawn drop spreader.

Short-term dermal and inhalation exposures (developed using PHED Version 1.1 surrogate data and chemical-specific data) are presented in Table 6. Table 7 presents the risk assessment for short-term dermal and inhalation exposures. Table 8 summarizes the caveats and parameters specific to each exposure scenario and corresponding risk assessment.

The following assumptions were made in the exposure calculations:

- Average body weight of an adult handler is 70 kg.
- The amount handled is based on 1,000 square feet for application by hand and shaker can; 0.25 cubic yard for application by hand to potting soil; and 0.5 acre for application with a belly grinder and push-type lawn drop spreader.
- Due to a lack of scenario-specific data, HED calculated unit exposure values using generic data from the Pesticide Handler Exposure Database (PHED). The details for each scenario are discussed in Table 8.
- Generally, the use of PPE and engineering controls are not considered acceptable options for products sold for use by homeowners because they are not available and/or are inappropriate for the exposure scenario.



CALCULATIONS: Potential inhalation and dermal daily exposures for both occupational and residential handlers were calculated using the following formulas (100 percent dermal and inhalation absorption were assumed):

$$\text{aily Inhalation Exposure}\left(\frac{mg\ ai}{day}\right) =$$

$$\text{nit Exposure}\left(\frac{\mu g\ ai}{lb\ ai}\right) \times \text{Conversion Factor}\left(\frac{1mg}{1{,}000\ \mu g}\right) \times \text{Use Rate}\left(\frac{lb\ ai}{A}\right) \times \text{Daily Acres Treated}\left(\frac{A}{day}\right.$$

$$\text{ily Dermal Exposure}\left(\frac{mg\ ai}{day}\right) = \text{Unit Exposure}\left(\frac{mg\ ai}{lb\ ai}\right) \times \text{Use Rate}\left(\frac{lb\ ai}{A}\right) \times \text{Daily Acres Treated}\left(\frac{A}{day}\right.$$

The inhalation and dermal daily doses were calculated using the following formulas:

$$\text{Daily Inhalation Dose}\left(\frac{mg\ ai}{kg/day}\right) = \text{Daily Inhalation Exposure}\left(\frac{mg\ ai}{day}\right) \times \left(\frac{1}{\text{Body Weight (kg)}}\right)$$

$$\text{Daily Dermal Dose}\left(\frac{mg\ ai}{kg/Day}\right) = \text{Daily Dermal Exposure}\left(\frac{mg\ ai}{Day}\right) \times \left(\frac{1}{\text{Body Weight (kg)}}\right)$$

The inhalation and dermal MOEs were calculated using the following formulas:

$$\text{Dermal MOE} = \frac{\text{NOEL}\left(\frac{mg}{kg/day}\right)}{\text{Dermal Daily Dose}\left(\frac{mg}{kg/day}\right)}$$

$$\text{Inhalation MOE} = \frac{\text{NOEL}\left(\frac{mg}{kg/day}\right)}{\text{Inhalation Daily Dose}\left(\frac{mg}{kg/day}\right)}$$

The total MOE was calculated using the following formula:

$$Total\ MOE = \frac{1}{\left(\frac{1}{MOE_{dermal}}\right) + \left(\frac{1}{MOE_{inhalation}}\right)}$$

For isofenphos, the LOEL for short-term dermal and inhalation toxicity is 2 mg/kg/day, and the intermediate-term dermal and inhalation NOEL is 0.06 mg/kg/day.

## 4) Post Application Exposures and Assumptions

Except for termiticide (a use which has been voluntarily canceled) studies, chemical-specific postapplication exposure data have not yet been submitted by the registrant in support of reregistration of isofenphos. In lieu of these data, a surrogate rangefinder postapplication exposure assessment was conducted to determine potential risks for two representative scenarios. The surrogate assessment presented in Table 9 is based on the application rate recommended for turf in isofenphos labels, and activities that bracket the reentry exposure levels anticipated from isofenphos use on turf. The two scenarios addressed by the calculations are described below:

- Low Exposure Reentry Activity (golf course mowing): transfer coefficient (Tc) = 500 $cm^2$/hour, and
- High Exposure Reentry Activity (turf farm harvesting): Tc = 10,000 $cm^2$/hour.

The DFR is derived from the application rate for turf, using an estimated 20 percent of the rate applied as initial dislodgeable residues, and an estimated 10 percent dissipation rate per day. This estimate may be a lower bound as environmental fate data suggest that isofenphos has an aerobic soil metabolism half-life of 352 days. The equation used for the calculations in Table 9 are presented below:

$$DFR\left(\frac{\mu g}{cm^2}\right) = AR\left(\frac{lb\ ai}{A}\right) \times CF\left(\frac{\mu g/cm^2}{lb\ ai/A}\right) \times F \times (1 - DR)^t$$

Where:
AR = Application rate is 2.0 lb ai/A
CF = Conversion factor is 11.2 ~~lb~~ µg per $cm^2$/lb per A
F = Fraction retained on foliage is 20 percent
DR = Daily dissipation rate (10 percent/day)
t = Days after treatment

$$Dose\ (mg/kg/d) = \frac{(DFR\ (\mu g/cm^2) \times Tc\ (cm^2/hr) \times CF\left(\frac{1\ mg}{1{,}000\ \mu g}\right) \times Abs \times ED\ (hrs/day))}{BW}$$

Where:
DFR = Initial DFR or daily DFR
Tc = Transfer coefficient; 500 $cm^2/hr$ or 10,000 $cm^2/hr$
CF = Conversion factor
Abs = Dermal absorption (assume 100 percent)
ED = Exposure duration; 8 hours worked per day
BW = Body weight (70 kg)

$$MOE = \frac{NOEL\ (mg/kg/d)}{Dose\ (mg/kg/d)}$$

Where:
NOEL = 0.06 mg/kg/day
Dose = Calculated dose

The resulting surrogate postapplication assessment indicates that:

- MOEs equal or exceed 1,000 for activities with a dermal transfer of 500 $cm^2/hr$ (low exposure reentry activity) at the 80th day following applications at a rate of 2.0 pounds active ingredient per acre to turf.

- MOEs equal or exceed 1,000 for activities with a dermal transfer of 10,000 $cm^2/hr$ (high exposure reentry activity) at the 108th day following applications at a rate of 2.0 pounds active ingredient per acre to turf.

Based on the findings of the surrogate agricultural assessment, occupational postapplication risks are of concern, and should be investigated further.

## 5) Residential Post-Application Exposures and Assumptions

EPA has determined that there are potential post-application exposures to residents entering treated lawns. The scenarios likely to result in post-application exposures are listed in Table 10 and are as follows:

- Dermal exposure from residue on turf (adult and child);
- Incidental nondietary ingestion of residue on lawn from hand-to-mouth transfer (toddler);
- Ingestion of treated turfgrass (toddler); and
- Incidental ingestion of soil from treated areas (toddler).

The equations and assumptions used for each of the scenarios were taken from the Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments guidance document, and are given below. The following general assumptions were made for all scenarios:

- On the day of application, it was assumed that 20 percent of the application rate are available from the turfgrass as dislodgeable residue.

- Postapplication was assessed on the same day the pesticide is applied because it was assumed that the homeowner could be exposed to turfgrass immediately after application. Therefore, postapplication exposures were based on day 0.

- Adults were assumed to weigh 70. Toddlers (3 years old), used to represent the 1 to 6 year old age group, were assumed to weigh 15 kg.

**Dermal exposure:**

$$ADD = (DFR_t * CF1 * Tc * ET) / BW$$

Where:

| | | |
|---|---|---|
| ADD | = | average daily dose (mg/kg/day) |
| $DFR_t$ | = | dislodgeable foliar residue on day "t" ($\mu g/cm^2$) |
| CF1 | = | weight unit conversion factor to convert $\mu g$ units in the DFR value to mg for the daily dose (0.001 mg/$\mu g$) |
| Tc | = | transfer coefficient ($cm^2/hr$) |
| ET | = | exposure time (hr/day) |
| BW | = | body weight (kg) |

and

$$DFR_t = AR * F * (1-D)^t * CF2 * CF3$$

Where:

AR = application rate (lb ai/acre)
F = fraction of ai retained on foliage (0.20, unitless)
D = fraction of residue that dissipates daily (0.10, unitless)
t = postapplication day on which exposure is being assessed (day 0)
CF2 = weight unit conversion factor to convert the lbs ai in the application rate to $\mu$g for the DFR value (4.54E8 $\mu$g/lb)
CF3 = area unit conversion factor to convert the surface area units ($ft^2$) in the application rate to $cm^2$ for the DFR value (2.47E-8 acre/$cm^2$ if the application rate is per acre)

- The mean dermal transfer coefficient was assumed to be 43,000 $cm^2$/hr for adults and 8,700 $cm^2$/hr for toddlers.

- The duration of exposure for toddlers and adults was assumed to be 2 hours per day.

**Hand-to-mouth:**

$$ADD = (DFR_t * SA * FQ * ET * CF1) / BW$$

where:

ADD = average daily dose (mg/kg/day)
$DFR_t$ = dislodgeable foliar residue on day "t" ($\mu$g/$cm^2$ turf)
SA = surface area of the hands ($cm^2$/event)
FQ = frequency of hand-to-mouth activity (events/hr)
ET = exposure time (hr/day)
CF1 = weight unit conversion factor to convert $\mu$g units in the DFR value to mg for the daily exposure (0.001 mg/$\mu$g)
BW = body weight (kg)

- The median surface area of both hands was assumed to be 350 $cm^2$ for a toddler (age 3 years).

- Replenishment of the hands with pesticide residues was assumed to be an implicit factor in this assessment.

- It was assumed that there is a one-to-one relationship between the dislodgeable residues on the turf and on the surface area of the skin after contact (i.e., if the dislodgeable residue on the turf is 1 mg/cm$^2$, then the residue on the human skin is also 1 mg/cm$^2$ after contacting the turf).

- The mean rate of hand-to-mouth activity is 0.026 events/minute (i.e., 1.56 events/hr) for toddlers (3 to 5 years old).

- The duration of exposure for toddlers was assumed to be 2 hours per day.

**Turfgrass ingestion:**

$$ADD = (GR_t * IgR * CF1) / BW$$

where:

| | | |
|---|---|---|
| ADD | = | average daily dose (mg/kg/day) |
| $GR_t$ | = | grass (and plant matter) residue on day "t" ($\mu$g/cm$^2$) |
| IgR | = | ingestion rate of grass (cm$^2$/day) |
| CF1 | = | weight unit conversion factor to convert the $\mu$g of residues on the grass to mg to provide units of mg/day (1E-3 mg/$\mu$g) |
| BW | = | body weight (kg) |

and

$$GR_t = AR * F * (1-D)^t * CF2 * CF3$$

where:

| | | |
|---|---|---|
| AR | = | application rate (lb ai/acre) |
| F | = | fraction of ai available on the grass (unitless) |
| D | = | fraction of residue that dissipates daily (unitless) |
| t | = | postapplication day on which exposure is being assessed |
| CF2 | = | weight unit conversion factor to convert the lbs ai in the application rate to $\mu$g for the grass residue value (4.54E8 $\mu$g/lb) |
| CF3 | = | area unit conversion factor to convert the surface area units (ft$^2$) in the application rate to cm$^2$ for the grass residue value (2.47E-8 acre/cm$^2$ if the application rate is per acre) |

- The assumed ingestion rate for grass for toddlers (age 3 years) was 25 cm$^2$/day (i.e., 2 x 2 inches or 4 in$^2$). This value was intended to represent the approximate area from which a child may grasp a handful of grass.

**Incidental Soil Ingestion:**

$$ADD = (SR_t * IgR * CF1) / BW$$

where:

| | | |
|---|---|---|
| ADD | = | average daily dose (mg/kg/day) |
| $SR_t$ | = | soil residue on day "t" ($\mu$g/g) |
| IgR | = | ingestion rate of soil (mg/day) |
| CF1 | = | weight unit conversion factor to convert the $\mu$g of residues on the soil to grams to provide units of mg/day (1E-6 g/$\mu$g) |
| BW | = | body weight (kg) |

and

$$SR_t = AR * F * (1-D)^t * CF2 * CF3 * CF4$$

where:

| | | |
|---|---|---|
| AR | = | application rate (lb ai/acre) |
| F | = | fraction of ai available in uppermost cm of soil (fraction/cm) |
| D | = | fraction of residue that dissipates daily (unitless) |
| t | = | postapplication day on which exposure is being assessed |
| CF2 | = | weight unit conversion factor to convert the lbs ai in the application rate to $\mu$g for the soil residue value (4.54E8 $\mu$g/lb) |
| CF3 | = | area unit conversion factor to convert the surface area units ($ft^2$) in the application rate to $cm^2$ for the SR value (2.47E-8 acre/$cm^2$ if the application rate is per acre) |
| CF4 | = | volume to weight unit conversion factor to convert the volume units ($cm^3$) to weight units for the SR value (U.S. EPA, 1992) (0.67 $cm^3$/g soil) |

- On the day of application, it was assumed that 100 percent of the application rate are located within the soil's uppermost 1 cm.

- The assumed soil ingestion rate for children (ages 1-6 years) was assumed to be 100 mg/day.

## b. Risk Calculations

Intermediate-term and short-term MOEs were calculated as follows:

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

## C. Summary of Combined Dermal and Inhalation Risk from Handler Exposures

### 1) Occupational

**Short-Term**: Dermal and inhalation MOEs were combined and risk was calculated using the short-term dermal LOEL of 2.0 mg/kg/day. The acceptable MOE was assumed to be 3,000.

- The calculations based on combined dermal and inhalation risks indicate that the MOEs are not more than 3,000 at **baseline** for any scenarios.

- The calculations based on combined dermal and inhalation risks indicate that the MOEs are not more than 3,000 at **additional personal protective equipment** (double layer body protection and chemical-resistant gloves) for any scenarios.

- The calculations based on combined dermal and inhalation risks indicate that the MOEs are not more than 3,000 at **engineering controls** for all scenarios except scenario (2) loading granules for tractor-drawn/mechanical spreader application.

**Intermediate-Term**: Dermal and inhalation MOEs were combined and risk was calculated using the intermediate-term dermal NOEL of 0.06 mg/kg/d. The acceptable MOE was assumed to be 1,000.

- The calculations based on combined dermal and inhalation risks indicate that the MOEs are not more than 1,000 at **baseline** for any scenarios.

- The calculations based on combined dermal and inhalation risks indicate that the MOEs are not more than 1,000 at **additional personal protective equipment** (double layer body protection and chemical-resistant gloves) for any scenarios.

- The calculations based on combined dermal and inhalation risks indicate that the MOEs are not more than 1,000 at **engineering controls** for any scenarios.

**2) Residential**

**Short-Term**: Dermal and inhalation MOEs were combined and risk was calculated using the short-term dermal LOEL of 2.0 mg/kg/day. The acceptable MOE was assumed to be 3,000.

- The calculations based on combined dermal and inhalation risks indicate that the MOEs are not more than 3,000 at **baseline** for any scenarios.

In summary, the calculations of risk are not over the MOE for any of the short-term and intermediate-term scenarios except occupational scenario (2), which exceeds the short-term MOE with the use of engineering controls for risk mitigation.

**d) Summary of Combined Dermal and Inhalation Risk from Postapplication Exposures**

Dermal and inhalation MOEs were combined and risk was calculated using the intermediate-term dermal NOEL of 0.06 mg/kg/day for both occupational and residential scenarios. The acceptable MOE was assumed to be 1,000.

**Occupational**

- MOEs equal or exceed 1,000 for activities (e.g., mowing golf course) with a dermal transfer of 500 $cm^2$/hr at the 80th day following application.
- MOEs equal or exceed 1,000 for activities (e.g., harvesting at a turf farm) with a dermal transfer of 10,000 $cm^2$/hr at the 108th day following application.

**Residential**

- The calculation of risks indicate that the MOEs are not more than 1,000 for any scenarios except for incidental soil ingestion by a toddler where the MOE is 3000.

**e. Additional Occupational/Residential Exposure Studies**

**1) Handler Studies**

Two studies were performed in 1988 to monitor mixer / loader / applicator exposure to isofenphos during typical use as a termiticide (MRID 419904-01, 419904-02) by Mobay Corporation to satisfy the requirements of Subdivision U of the Pesticide Assessment Guidelines. A total of 17 replicates were included in four distinct types of homes. Each replicate consisted of treating a single building in or around the Kansas City metropolitan area. Exposure levels were estimated using passive dosimetry (dermal and inhalation) as well as biological monitoring techniques.

Neither study met the requirements of Subdivision U because of many issues, including the following: inadequate number of replicates performed per home type, lack of adequate description of application equipment, test subjects wearing rubber gloves (not required by label), lack of laboratory recovery samples generated and analyzed with the field samples, insufficient information concerning storage stability, and no description of the field spike preparation procedures. It should be noted that the acceptability of these studies is moot because the use of isofenphos as a termiticide has been voluntarily canceled by the registrant.

Notwithstanding the Subdivision U guideline issues described above, the data from these studies form the complete basis for the termiticide mixer/ loader / applicator scenario unit exposure estimates in the Pesticide Handlers Exposure Database (PHED). Based on these data, the dermal unit exposure is 0.36 mg / lb ai handled and the inhalation unit exposure is 2.2 µg / lb ai handled. These values should not be considered worst case in comparison with that from other exposure scenarios, as they are well within the observed range for both inhalation and dermal unit exposures from PHED.

**2) Postapplication Studies**

One dislodgeable residue from turf study (MRID 00159625) was submitted. This study was conducted in 1980, prior to the issuance of guidelines for conducting dislodgeable residue studies. In this study, the isofenphos formulation was diluted with water and applied to bluegrass turf at the rate of two lbs ai per acre using a tractor-mounted boom. Triplicate samples of grass

clippings were taken at 0, 1, 3, and 7 days post-treatment from two treatment plots and one control plot. Immediately after sampling, residues were dislodged from a 10 gram aliquot of grass clippings and analyzed for both isofenphosl and its oxygen analog. Results showed that over the 7 day sampling period, dislodgeable isofenphos residues declined from approximately 280 ppm on day 0 to about 3-4 ppm on day 7. Isofenphos oxygen analog levels were constant over time at less than 12 ppm.

Under current guidelines this study is not considered acceptable. The technical registrant, Bayer, is a member of the Outdoor Residential Exposure Task Force (ORETF) and plans to submit dislodgeable residue data for isofenphos under this task force.

Two indoor air monitoring studies were submitted. One study (MRID 410075-01) measured the indoor air concentration of isofenphos in nine residential homes in and around Kansas City treated with Pryfon 6 termiticide during application and up to one year after application. The other study (MRID 419013-02) measured indoor air concentrations of isofenphos in eight residential homes in eastern Massachusetts treated with Pryfon 6 Termiticide. These studies were not formally reviewed because the registrant has voluntarily canceled termiticide uses for isofenphos and does not plan to support this or any other indoor use of this chemical.

**f. Statement of the adequacy of the residential exposure data base to assess infants' and children's exposures**

The residential exposure data base is adequate to assess infants' and children's exposure to isofenphos.

Table 1: Occupational Handler Short- and Intermediate-term Dermal and Inhalation Exposures to Isofenphos

| Exposure Scenario (Scenario #) | Baseline Dermal Unit Exposure (mg/lb ai)[a] | Baseline Inhalation Unit Exposure (µg/lb ai)[b] | Range of Application Rates (lb ai/acre)[c] | Daily Acres Treated[d] | Daily Dermal Exposure (mg/day)[e] | Daily Inhalation Exposure (mg/day)[f] |
|---|---|---|---|---|---|---|
| **Mixer/Loader Exposure** | | | | | | |
| Mixing/loading liquids for groundboom application (1a) | 2.9 | 1.2 | 2.0 lb ai/A | 80 acres | 460 | 0.19 |
| Mixing/loading liquids for rights-of-way sprayer (1b) | | | | 40 acres | 230 | 0.096 |
| Mixing/loading liquids for chemigation application (1c) | | | | 40 acres | 230 | 0.096 |
| Mixing/loading liquids for handgun application (1d) | | | | 5 acres | 29 | 0.012 |
| Loading granules for tractor drawn/mechanical spreader application (2) | 0.0084 | 1.7 | 2.0 lb ai/A | 80 acres | 1.3 | 0.27 |
| **Applicator Exposure** | | | | | | |
| Applying sprays with a groundboom sprayer (3) | 0.014 | 0.74 | 2.0 lb ai/A | 80 acres | 2.2 | 0.12 |
| Applying sprays to rights-of-way (4) | 1.3 | 3.9 | 2.0 lb ai/A | 40 acres | 100 | 0.31 |
| Applying sprays with a handgun sprayer (5) | 0.34 (gloves) | 1.4 | 2.0 lb ai/A | 5 acres | 3.4 | 0.014 |
| Applying granules with tractor-drawn sprayer (6) | 0.0099 | 1.2 | 2.0 lb ai/A | 80 acres | 1.6 | 0.19 |
| **Mixer/Loader/Applicator Exposure** | | | | | | |
| Loading/applying granules by hand to fire ant mounds (7) | 71 (gloves) | 470 | 0.015 lb ai/can | 1 lb can | 1.1 | 0.007 |
| Mixing/loading/applying liquids with a backpack sprayer (8) | 2.5 | 30 | 2.0 lb ai/A | 5000 $ft^2$ | 0.57 | 0.0069 |
| Mixing/loading/applying liquids with a low pressure handwand (9) | 100 | 30 | 2.0 lb ai/A | 5000 $ft^2$ | 23 | 0.0069 |
| Loading/applying granules to potting soil by hand (10)[g] | 71 (gloves) | 470 | 0.020 lb ai/$yd^3$ | 2 $yd^3$ | 2.8 | 0.019 |
| Loading/applying granules with a shaker can to fire ant mounds (11)[g] | 71 (gloves) | 470 | 0.015 lb ai/can | 1 lb can | 1.1 | 0.007 |
| Loading/applying granules with a belly grinder (12) | 10 | 62 | 2.0 lb ai/A | 2 acres | 40 | 0.25 |

| Exposure Scenario (Scenario #) | Baseline Dermal Unit Exposure (mg/lb ai)[a] | Baseline Inhalation Unit Exposure (µg/lb ai)[b] | Range of Application Rates (lb ai/acre)[c] | Daily Acres Treated[d] | Daily Dermal Exposure (mg/day)[e] | Daily Inhalation Exposure (mg/day)[f] |
|---|---|---|---|---|---|---|
| Loading/applying granules with a push type lawn drop spreader (13) | 2.9 | 6.3 | 2.0 lb ai/A | 2 acres | 11.6 | 0.025 |

[a] Baseline dermal unit exposure represents long pants, long sleeved shirt, no gloves, open mixing/loading, open cab tractor. The exceptions are scenarios 5 (applying sprays with a handgun), 7 (loading/applying granules by hand), 10 (loading/applying granules to potting soil by hand), and 11 (loading/applying granules with a shaker can), for which the PHED unit exposure value includes the use of protective gloves.

[b] Baseline inhalation exposure represents no respirator.

[c] Application rates are maximum rate values found on isofenphos labels.

[d] Daily acres treated values are from the EPA HED estimates of acreage, square footage, or cubic yardage that could be treated in a single day for each exposure scenario of concern.

[e] Daily dermal exposure (mg/day) = Unit Exposure (mg/lb ai) * Appl. rate (lb ai/acre) * Acres treated (acres/day).

[f] Daily inhalation exposure (mg/day) = Unit Exposure (µg/lb ai) * (1mg/1000 µg) Conversion * Application Rate (lb ai/A) * Acres treated (acres/day).

[g] Unit exposure data from PHED for application of granules by hand were used as surrogate values for these scenarios.

Table 2: Occupational Handler Short-term and Intermediate-term Risks from Isofenphos at Baseline

| Exposure Scenario (Scenario #) | Baseline Dermal | | | Baseline Inhalation | | | Baseline Total | |
|---|---|---|---|---|---|---|---|---|
| | Daily Dose (mg/kg/day)[a] | Short-term MOE[b] | Int.-term MOE[c] | Daily Dose (mg/kg/day)[d] | Short-term MOE[e] | Int.-term MOE[f] | Short-term MOE[g] | Int.-term MOE[h] |
| **Mixer/Loader Exposure** | | | | | | | | |
| Mixing/loading liquids for groundboom application (1a) | 6.6 | 0.30 | 0.0091 | 0.0027 | 740 | 22 | 0.30 | 0.0091 |
| Mixing/loading liquids for rights-of-way sprayer (1b) | 3.3 | 0.61 | 0.018 | 0.0014 | 1,400 | 43 | 0.61 | 0.018 |
| Mixing/loading liquids for chemigation application (1c) | 3.3 | 0.61 | 0.018 | 0.0014 | 1,400 | 43 | 0.61 | 0.018 |
| Mixing/loading liquids for handgun application (1d) | 0.41 | 4.9 | 0.15 | 0.00017 | 12,000 | 350 | 4.9 | 0.15 |
| Loading granules for tractor drawn/mechanical spreader application (2) | 0.019 | 110 | 3.2 | 0.0039 | 510 | 15 | 90 | 2.6 |
| **Applicator Exposure** | | | | | | | | |
| Applying sprays with a groundboom sprayer (3) | 0.030 | 67 | 2.0 | 0.0017 | 1,200 | 35 | 63 | 1.9 |
| Applying sprays to rights-of-way (4) | 1.4 | 1.4 | 0.043 | 0.0044 | 460 | 14 | 1.4 | 0.043 |
| Applying sprays with a handgun sprayer (5) | 0.049 | 41 | 1.2 | 0.00020 | 10,000 | 300 | 41 | 1.2 |
| Applying granules with tractor-drawn sprayer (6) | 0.023 | 87 | 2.6 | 0.0027 | 740 | 22 | 78 | 2.3 |
| **Mixer/Loader/Applicator Exposure** | | | | | | | | |
| Loading/applying granules by hand to fire ant mounds (7) | 0.016 | 130 | 3.8 | 0.0001 | 20,000 | 600 | 130 | 3.8 |
| Mixing/loading/applying liquids with a backpack sprayer (8) | 0.0081 | 250 | 7.4 | 0.000099 | 20,000 | 600 | 250 | 7.4 |
| Mixing/loading/applying liquids with a low pressure handwand (9) | 0.33 | 6 | 0.18 | 0.000099 | 20,000 | 600 | 6 | 0.18 |
| Loading/applying granules to potting soil by hand (10) | 0.040 | 50 | 1.5 | 0.00027 | 7,400 | 220 | 50 | 1.5 |
| Loading/applying granules with a shaker can to fire ant mounds (11) | 0.016 | 130 | 3.8 | 0.0001 | 20,000 | 600 | 130 | 3.8 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Loading/applying granules with a belly grinder (12) | 0.57 | 3.5 | 0.11 | 0.0036 | 560 | 17 | 3.5 | 0.11 |



| Exposure Scenario (Scenario #) | Baseline Dermal | | | Baseline Inhalation | | | Baseline Total | |
|---|---|---|---|---|---|---|---|---|
| | Daily Dose (mg/kg/day)[a] | Short-term MOE[b] | Int.-term MOE[c] | Daily Dose (mg/kg/day)[d] | Short-term MOE[e] | Int.-term MOE[f] | Short-term MOE[g] | Int.-term MOE[h] |
| Loading/applying granules with a push type lawn drop spreader (13) | 0.17 | 12 | 0.35 | 0.00036 | 5,600 | 170 | 12 | 0.35 |

[a] Daily Dermal Dose (mg/kg/day) = Daily Dermal Exposure (mg/day)/ Body weight (70 kg).
[b] Short-term Dermal MOE = LOEL (2 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).
[c] Intermediate-term Dermal MOE = NOEL (0.06 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).
[d] Daily Inhalation Dose (mg/kg/day) = Daily Inhalation Exposure (mg/day)/ Body weight (70 kg).
[e] Short-term Inhalation MOE = LOEL (2 mg/kg/day)/ Daily Inhalation Dose (mg/kg/day).
[f] Intermediate-term Inhalation MOE = NOEL (0.06 mg/kg/day)/ Daily Inhalation Dose (mg/kg/day).
[g] Total Short-term MOE = 1/ ((1/ Short-term Dermal MOE) + (1/ Short-term Inhalation MOE)).
[h] Total Intermediate-term MOE = 1/ ((1/ Intermediate-term Dermal MOE) + (1/ Intermediate-term Inhalation MOE)).

Table 3: Occupational Handler Short-term and Intermediate-term Risks from Isofenphos with Additional PPE

| Exposure Scenario (Scenario #) | Dermal - Additional PPE | | | | Inhalation - Additional PPE | | | | Total - Additional PPE | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Unit Exposure (mg/lb ai)[a] | Daily Dose (mg/kg/day)[b] | Short-term MOE[c] | Int.-term MOE[d] | Unit Exposure (µg/lb ai)[a] | Daily Dose (mg/kg/day)[e] | Short-term MOE[f] | Int.-term MOE[g] | Short-term MOE[h] | Int.-term MOE[i] |
| **Mixer/Loader Exposure** | | | | | | | | | | |
| Mixing/loading liquids for groundboom application (1a) | 0.017 | 0.039 | 51 | 1.5 | 0.24 | 0.00055 | 3,600 | 110 | 50 | 1.5 |
| Mixing/loading liquids for rights-of-way sprayer (1b) | | 0.019 | 110 | 3.2 | | 0.00027 | 7,400 | 220 | 110 | 3.2 |
| Mixing/loading liquids for chemigation application (1c) | | 0.019 | 110 | 3.2 | | 0.00027 | 7,400 | 220 | 110 | 3.2 |
| Mixing/loading liquids for handgun application (1d) | | 0.0024 | 830 | 25 | | 0.000034 | 59,000 | 1,800 | 820 | 25 |
| Loading granules for tractor drawn/ mechanical spreader application (2) | 0.0034 | 0.0078 | 260 | 7.7 | 0.34 | 0.00078 | 2,600 | 77 | 240 | 7.0 |
| **Applicator Exposure** | | | | | | | | | | |
| Applying sprays with a groundboom sprayer (3) | 0.014 | 0.032 | 63 | 1.9 | 0.15 | 0.00034 | 5,900 | 180 | 62 | 1.9 |
| Applying sprays to rights-of-way (4) | 0.29 | 0.33 | 6.1 | 0.18 | 0.78 | 0.00089 | 2,200 | 67 | 6.1 | 0.18 |
| Applying sprays with a handgun sprayer (5) | 0.19 | 0.027 | 74 | 2.2 | 0.28 | 0.000040 | 50,000 | 1,500 | 74 | 2.2 |
| Applying granules with tractor-drawn sprayer (6) | 0.0042 | 0.010 | 200 | 6.0 | 0.24 | 0.00055 | 3,600 | 110 | 190 | 5.7 |
| **Mixer/Loader/Applicator Exposure** | | | | | | | | | | |
| Loading/applying granules by hand to fire ant mounds (7) | 40 | 0.0086 | 230 | 7.0 | 94 | 0.00002 | 100,000 | 3000 | 230 | 7.0 |
| Mixing/loading/applying liquids with a backpack sprayer (8) | 1.6 | 0.0052 | 3.8 | 12 | 6 | 0.00002 | 100,000 | 3000 | 380 | 12 |

| Exposure Scenario (Scenario #) | Dermal - Additional PPE | | | | Inhalation - Additional PPE | | | | Total - Additional PPE | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Unit Exposure (mg/lb ai)[a] | Daily Dose (mg/kg/day)[b] | Short-term MOE[c] | Int.-term MOE[d] | Unit Exposure (µg/lb ai)[a] | Daily Dose (mg/kg/day)[e] | Short-term MOE[f] | Int.-term MOE[g] | Short-term MOE[h] | Int.-term MOE[i] |
| Mixing/loading/applying liquids with a low pressure handwand (9) | 0.37 | 0.0012 | 1700 | 50 | 6 | 0.00002 | 100,000 | 3000 | 1700 | 50 |
| Loading/applying granules to potting soil by hand (10)[j] | 40 | 0.023 | 87 | 2.6 | 94 | 0.000054 | 37,000 | 1,100 | 87 | 2.6 |
| Loading/applying granules with a shaker can to fire ant mounds (11)[j] | 40 | 0.0086 | 233 | 7.0 | 94 | 0.00002 | 100,000 | 3000 | 233 | 7.0 |
| Loading/applying granules with a belly grinder (12) | 4.6 | 0.26 | 7.7 | 0.23 | 12 | 0.00069 | 2,900 | 87 | 7.7 | 0.23 |
| Loading/applying granules with a push type lawn drop spreader (13) | 0.73 | 0.042 | 48 | 1.4 | 1.3 | 0.000074 | 27,000 | 810 | 48 | 1.4 |

[a] Additional PPE for all scenarios includes double layer of clothing (50% PF for clothing, except scenario 2, for which double layer data were available), chemical resistant gloves (90% PF for gloves in scenarios 6, 12, and 13), and dust/mist respirator (5-fold PF).
[b] Daily Dermal Dose (mg/kg/day) = Daily Dermal Exposure (mg/day)/ Body weight (70 kg).
[c] Short-term Dermal MOE = LOEL (2 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).
[d] Intermediate-term Dermal MOE = NOEL (0.06 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).
[e] Daily Inhalation Dose (mg/kg/day) = Daily Inhalation Exposure (mg/day)/ Body weight (70 kg).
[f] Short-term Inhalation MOE = LOEL (2 mg/kg/day)/ Daily Inhalation Dose (mg/kg/day).
[g] Intermediate-term Inhalation MOE = NOEL (0.06 mg/kg/day)/ Daily Inhalation Dose (mg/kg/day).
[h] Total Short-term MOE = 1/ ((1/ Short-term Dermal MOE) + (1/ Short-term Inhalation MOE)).
[i] Total Intermediate-term MOE = 1/ ((1/ Intermediate-term Dermal MOE) + (1/ Intermediate-term Inhalation MOE)).
[j] Unit exposure data for application of granules by hand were used as surrogate values for these scenarios.

Table 4: Occupational Handler Short-term and Intermediate-term Risks from Isofenphos with Engineering Controls

| Exposure Scenario (Scenario #) | Dermal - Engineering Controls | | | | Inhalation - Engineering Controls | | | | Total - Eng. Controls | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Unit Exposure (mg/lb ai)[a] | Daily Dose (mg/kg/day)[b] | Short-term MOE[c] | Int.-term MOE[d] | Unit Exposure (µg/lb ai)[a] | Daily Dose (mg/kg/day)[e] | Short-term MOE[f] | Int.-term MOE[g] | Short-term MOE[h] | Int.-term MOE[i] |
| **Mixer/Loader Exposure** | | | | | | | | | | |
| Mixing/loading liquids for groundboom application (1a) | 0.0086 | 0.020 | 100 | 3.0 | 0.083 | 0.00019 | 11,000 | 320 | 99 | 3.0 |
| Mixing/loading liquids for rights-of-way sprayer (1b) | | 0.0098 | 200 | 6.1 | | 0.000095 | 21,000 | 630 | 200 | 5.9 |
| Mixing/loading liquids for chemigation application (1c) | | 0.0098 | 200 | 6.1 | | 0.000095 | 21,000 | 630 | 200 | 5.9 |
| Mixing/loading liquids for handgun application (1d) | | 0.0012 | 1,700 | 50 | | 0.000012 | 170,000 | 5,000 | 1,700 | 50 |
| Loading granules for tractor drawn/ mechanical spreader application (2) | 0.00017 | 0.00039 | 5,100 | 150 | 0.034 | 0.000078 | 26,000 | 770 | 4,300 | 130 |
| **Applicator Exposure** | | | | | | | | | | |
| Applying sprays with a groundboom sprayer (3) | 0.005 | 0.011 | 180 | 5.5 | 0.043 | 0.000098 | 20,000 | 600 | 180 | 5.5 |
| Applying sprays to rights-of-way (4) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |
| Applying sprays with a handgun sprayer (5) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |
| Applying granules with tractor-drawn sprayer (6) | 0.0021 | 0.0048 | 420 | 13 | 0.22 | 0.00050 | 4,000 | 120 | 380 | 12 |
| **Mixer/Loader/Applicator Exposure** | | | | | | | | | | |
| Loading/applying granules by hand to fire ant mounds (7) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |
| Mixing/loading/applying liquids with a backpack sprayer (8) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |

| Exposure Scenario (Scenario #) | Dermal - Engineering Controls | | | | Inhalation - Engineering Controls | | | | Total - Eng. Controls | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Unit Exposure (mg/lb ai)[a] | Daily Dose (mg/kg/day)[b] | Short-term MOE[c] | Int.-term MOE[d] | Unit Exposure (µg/lb ai)[a] | Daily Dose (mg/kg/day)[e] | Short-term MOE[f] | Int.-term MOE[g] | Short-term MOE[h] | Int.-term MOE[i] |
| Mixing/loading/applying liquids with a low pressure handwand (9) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |
| Loading/applying granules to potting soil by hand (10) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |
| Loading/applying granules with a shaker can to fire ant mounds (11) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |
| Loading/applying granules with a belly grinder (12) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |
| Loading/applying granules with a push type lawn drop spreader (13) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |

[a] Engineering Controls:
1a/1b/1c/1d: Closed mixing/loading, single layer clothing, chemical resistant gloves.
2: Lock n' load (98% PF), single layer clothing, no gloves.
3: Enclosed cab, single layer clothing, no gloves.
6: Enclosed cab, single layer clothing, no gloves.

[b] Daily Dermal Dose (mg/kg/day) = Daily Dermal Exposure (mg/day)/ Body weight (70 kg).

[c] Short-term Dermal MOE = LOEL (2 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).

[d] Intermediate-term Dermal MOE = NOEL (0.06 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).

[e] Daily Inhalation Dose (mg/kg/day) = Daily Inhalation Exposure (mg/day)/ Body weight (70 kg).

[f] Short-term Inhalation MOE = LOEL (2 mg/kg/day)/ Daily Inhalation Dose (mg/kg/day).

[g] Intermediate-term Inhalation MOE = NOEL (0.06 mg/kg/day)/ Daily Inhalation Dose (mg/kg/day).

[h] Total Short-term MOE = 1/ ((1/ Short-term Dermal MOE) + (1/ Short-term Inhalation MOE)).

[i] Total Intermediate-term MOE = 1/ ((1/ Intermediate-term Dermal MOE) + (1/ Intermediate-term Inhalation MOE)).

NF Not Feasible - the Agency does not consider engineering controls an effective approach for mitigating exposures during the use of certain types of equipment.

Table 5: Exposure Scenario Descriptions for the Use of Isofenphos

| Exposure Scenario (Number) | Data Source | Standard Assumptions[a] (8-hr work day) | Comments[b] |
|---|---|---|---|
| **Mixer/Loader Descriptors** | | | |
| Mixing/Loading Liquid Formulations (1a/1b/1c/1d) | PHED V1.1 | 80 acres for groundboom, 40 acres for rights-of-way sprayer and chemigation, and 5 acres for handgun | **Baseline:** Hand, dermal, and inhalation data are AB grades. Hand = 72 to 122 replicates; dermal = 53 replicates, and inhalation = 85 replicates. High confidence in hand/dermal and inhalation data. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively. Hand data are AB grades, with 59 replicates. High confidence in hand/dermal data.<br><br>**Engineering Controls:** Hand, dermal, and inhalation data are AB grades. Hand = 31 replicates; dermal = 16 to 22 replicates; inhalation = 27 replicates. High confidence in hand/dermal and inhalation data. |
| Loading granules for tractor drawn/mechanical spreader application (2) | PHED V1.1 | 80 acres | **Baseline:** Hand data are All grades, and dermal and inhalation are ABC grades. Hand = 10 replicates; dermal = 33 to 78 replicates; and inhalation = 58 replicates. Low confidence in hand/dermal data, and high confidence in inhalation data. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** Hand data are AB grades, and dermal data are ABC grades. The same inhalation data are used as for the baseline coupled with an 80% protection factor to account for the use of a dust/mist respirator. Hand = 45 replicates and dermal = 12 to 59 replicates. Low confidence in hand/dermal data.<br><br>**Engineering Controls:** Hand data are All grades; dermal are ABC grades; and inhalation are AB grades. Hand = 10 replicates; dermal =33 to 78 replicates; inhalation = 58 replicates. Low confidence in hand/dermal data and high confidence in inhalation data. |
| **Applicator Exposure** | | | |
| Applying sprays with a groundboom sprayer (3) | PHED V1.1 | 80 acres | **Baseline:** Hand, dermal, and inhalation data are AB grades. Hand = 29 replicates; dermal = 23 to 42 replicates; and inhalation = 22 replicates. High confidence in hand/dermal and inhalation data. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively. Hand data are ABC grades, with 21 replicates. Medium confidence in hand/dermal data.<br><br>**Engineering Controls:** Hand and dermal data are ABC grades, and inhalation are AB grades. Hand = 16 replicates; dermal =20 to 31 replicates; inhalation = 16 replicates. Medium confidence in hand/dermal data, and high confidence in inhalation data. |
| Applying sprays to rights-of-way (4) | PHED V1.1 | 40 acres | **Baseline:** Hand data are AB grades, dermal are ABC grades, and inhalation data are A grades. Hand = 16 replicates, dermal = 4 to 30 replicates; and inhalation = 16 replicates. Low confidence in hand/dermal data , and high confidence inhalation data. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively. Hand data are AB grades, with 4 replicates. Low confidence in hand/dermal data.<br><br>**Engineering Controls:** Not feasible for this scenario. |

| Exposure Scenario (Number) | Data Source | Standard Assumptions[a] (8-hr work day) | Comments[b] |
|---|---|---|---|
| Applying sprays with a handgun sprayer (5) | PHED V1.1 | 5 acres | Baseline: Hand and dermal data are C grades, and inhalation data are AB grades. Hand = 14 replicates; dermal = 0 to 14 replicates; and inhalation = 14 replicates. Low confidence in hand/dermal data, and low to medium confidence inhalation data. Baseline data includes chemical resistant gloves. No protection factor was needed to define the unit exposure value.<br><br>PPE: The same hand data are used as for the baseline, as chemical resistant glove data were used. The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively.<br><br>Engineering Controls: Not feasible for this scenario. |
| Applying granules with tractor-drawn sprayer (6) | PHED V1.1 | 80 acres | Baseline: Hand, dermal, and inhalation data are AB grades. Hand = 5 replicates; dermal = 1 to 5 replicates; and inhalation = 5 replicates. Low confidence in hand/dermal and inhalation data. No protection factor was needed to define the unit exposure value.<br><br>PPE: The same hand and dermal data are used as for the baseline coupled with a 90% protection factor to account for chemical resistant gloves, and a 50% protection factor to account for an additional layer of clothing, respectively. The same inhalation data are used as for the baseline coupled with an 80% protection factor to account for the use of a dust/mist respirator.<br><br>Engineering Controls: Hand, dermal, and inhalation data are AB grades. Hand = 24 replicates; dermal =27 to 30 replicates; inhalation = 37 replicates. High confidence in hand/dermal and inhalation data. |
| Mixer/Loader/Applicator Exposure | | | |
| Loading/applying granules by hand to fire ant mounds (7) | PHED V1.1 | One 1 lb can | Baseline: Hand, dermal, and inhalation data are ABC grades. Hand = 15 replicates; dermal = 16 replicates; and inhalation = 16 replicates. Medium confidence in hand/dermal and inhalation data. Baseline data includes chemical resistant gloves. No protection factor was needed to define the unit exposure value.<br><br>PPE: The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively. Hand data are ABC grades, with 15 replicates. Medium confidence in hand/dermal data.<br><br>Engineering Controls: Not feasible for this scenario. |
| Mixing/loading/applying liquids with a backpack sprayer (8) | PHED V1.1 | 5,000 $ft^2$ | Baseline: Hand data are C grade, dermal are AB grades, and inhalation data are A grades. Hand = 11 replicates; dermal = 9 to 11 replicates; and inhalation = 11 replicates. Low confidence in hand/dermal and inhalation data. A 90% protection factor was needed to "backcalculate" the no glove exposure value.<br><br>PPE: The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively. Hand data are C grade, with 11 replicates. Low confidence in hand/dermal data.<br><br>Engineering Controls: Not feasible for this scenario. |

| Exposure Scenario (Number) | Data Source | Standard Assumptions[a] (8-hr work day) | Comments[b] |
|---|---|---|---|
| Mixing/loading/applying liquids with a low pressure handwand (9) | PHED V1.1 | 5,000 ft$^2$ | **Baseline:** Hand data are All grades, dermal are ABC grades, and inhalation data are ABC grades. Hand = 70 replicates; dermal = 9 to 80 replicates; and inhalation = 80 replicates. Low confidence in hand/dermal data, and medium confidence in inhalation data. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively. Hand data are ABC grades, with 10 replicates. Low confidence in hand/dermal data.<br><br>**Engineering Controls:** Not feasible for this scenario. |
| Loading/applying granules to potting soil by hand (10)[c] | PHED V1.1 | 2 yd$^3$ | **Baseline:** Hand, dermal, and inhalation data are ABC grades. Hand = 15 replicates; dermal = 16 replicates; and inhalation = 16 replicates. Medium confidence in hand/dermal and inhalation data. Baseline data includes chemical resistant gloves. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively. Hand data are ABC grades, with 15 replicates. Medium confidence in hand/dermal data.<br><br>**Engineering Controls:** Not feasible for this scenario. |
| Loading/applying granules with a shaker can to fire ant mounds (11)[c] | PHED V1.1 | One 1-lb can<br>(assume that if more than 1 can is to be used, then different application equipment would be used). | **Baseline:** Hand, dermal, and inhalation data are ABC grades. Hand = 15 replicates; dermal = 16 replicates; and inhalation = 16 replicates. Medium confidence in hand/dermal and inhalation data. Baseline data includes chemical resistant gloves. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively. Hand data are ABC grades, with 15 replicates. Medium confidence in hand/dermal data.<br><br>**Engineering Controls:** Not feasible for this scenario. |
| Loading/applying granules with a belly grinder (12) | PHED V1.1 | 2 acres | **Baseline:** Hand and dermal data are ABC grades, and inhalation data are AB grades. Hand = 23 replicates; dermal = 29 to 45 replicates; and inhalation = 40 replicates. Medium confidence in hand/dermal data, and high confidence in inhalation data. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same hand and dermal data are used as for the baseline coupled with a 90% protection factor to account for chemical resistant gloves, and a 50% protection factor to account for an additional layer of clothing, respectively. The same inhalation data are used as for the baseline coupled with an 80% protection factor to account for the use of a dust/mist respirator.<br><br>**Engineering Controls:** Not feasible for this scenario. |
| Loading/applying granules with a push type lawn drop spreader (13) | PHED V1.1 | 2 acres | **Baseline:** Hand and dermal data are C grade, and inhalation data are B grade. Hand = 15 replicates; dermal = 0 to 15 replicates; and inhalation = 15 replicates. Low confidence in hand/dermal data, and high confidence in inhalation data. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same hand and dermal data are used as for the baseline coupled with a 90% protection factor to account for chemical resistant gloves, and a 50% protection factor to account for an additional layer of clothing, respectively. The same inhalation data are used as for the baseline coupled with an 80% protection factor to account for the use of a dust/mist respirator.<br><br>**Engineering Controls:** Not feasible for this scenario. |

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

[b] All handler exposure assessments in this document are based on the "Best Available" data as defined by OREB SOP for meeting Subdivision U Guidelines. Best available grades are assigned to data as follows: matrices with grades A and B data and a minimum of 15 replicates; if not available, then grades A, B and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality (i.e., All Grade Data) and number of replicates. High quality data with a protection factor take precedence over low quality data with no protection factor. Generic data confidence categories are assigned as follows:

High = grades A and B and 15 or more replicates per body part
Medium = grades A, B, and C and 15 or more replicates per body part
Low = grades A, B, C, D and E or any combination of grades with less than 15 replicates

[c] Unit exposure data for application of granules by hand were used as surrogate values for these scenarios.

Table 6: Residential Handler Short-term Dermal and Inhalation Exposures to Isofenphos

| Exposure Scenario (Scenario #) | Baseline Dermal Unit Exposure (mg/lb ai)[a] | Baseline Inhalation Unit Exposure (µg/lb ai)[b] | Range of Application Rates (lb ai/ft$^2$ or yd$^3$)[c] | Daily Acres Treated[d] | Daily Dermal Exposure (mg/day)[e] | Daily Inhalation Exposure (mg/day)[f] |
|---|---|---|---|---|---|---|
| Mixer/Loader/Applicator Exposure | | | | | | |
| Loading/applying granules by hand to fire ant mounds (1) | 430 | 470 | 0.015 lb ai / can | 1 can | 6.5 | 0.0071 |
| Loading/applying granules to potting soil by hand (2)[g] | 430 | 470 | 0.019 lb ai/yd$^3$ | 0.25 yd$^3$ | 2.0 | 0.0022 |
| Loading/applying granules with a shaker can to fire ant mounds (3)[g] | 430 | 470 | 0.015 lb ai / can | 1 can | 6.5 | 0.0071 |
| Loading/applying granules with a belly grinder (4) | 110 | 62 | 2.0 lb ai/A | 0.5 acre | 110 | 0.062 |
| Loading/applying granules with a push type lawn drop spreader (5) | 3 | 6.3 | 2.0 lb ai/A | 0.5 acre | 3.0 | 0.0063 |

[a] Baseline dermal unit exposure represents short pants, short sleeved shirt, no gloves, and open mixing/loading.
[b] Baseline inhalation exposure represents no respirator.
[c] Application rates are maximum rate values found on isofenphos labels.
[d] Daily acres treated values are from the EPA HED estimates of acreage, square footage, or cubic yardage that could be treated in a single day for each exposure scenario of concern.
[e] Daily dermal exposure (mg/day) = Unit Exposure (mg/lb ai) * Appl. rate (lb ai/acre) * Acres treated (acres/day).
[f] Daily inhalation exposure (mg/day) = Unit Exposure (µg/lb ai) * (1mg/1000 µg) Conversion * Application Rate (lb ai/A) * Acres treated (acres/day).
[g] Unit exposure data for application of granules by hand were used as surrogate values for these scenarios.

Table 7: Residential Handler Short-term Risks from Isofenphos

| Exposure Scenario (Scenario #) | Baseline Dermal | | Baseline Inhalation | | Baseline Total |
|---|---|---|---|---|---|
| | Daily Dose (mg/kg/day)[a] | Short-term MOE[b] | Daily Dose (mg/kg/day)[c] | Short-term MOE[d] | Short-term MOE[e] |
| Mixer/Loader/Applicator Exposure | | | | | |
| Loading/applying granules by hand to fire ant mounds (1) | 0.093 | 21 | 0.0001 | 20,000 | 21 |
| Loading/applying granules to potting soil by hand (2) | 0.029 | 68 | 0.000031 | 65,000 | 68 |
| Loading/applying granules with a shaker can to fire ant mounds (3) | 0.093 | 21 | 0.0001 | 20,000 | 21 |
| Loading/applying granules with a belly grinder (4) | 1.6 | 1.3 | 0.00089 | 2,200 | 1.3 |
| Loading/applying granules with a push type lawn drop spreader (5) | 0.043 | 47 | 0.000090 | 22,000 | 47 |

[a] Daily Dermal Dose (mg/kg/day) = Daily Dermal Exposure (mg/day)/ Body weight (70 kg).
[b] Short-term Dermal MOE = LOEL (2 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).
[c] Daily Inhalation Dose (mg/kg/day) = Daily Inhalation Exposure (mg/day)/ Body weight (70 kg).
[d] Short-term Inhalation MOE = LOEL (2 mg/kg/day)/ Daily Inhalation Dose (mg/kg/day).
[e] Total Short-term MOE = 1/ ((1/ Short-term Dermal MOE) + (1/ Short-term Inhalation MOE)).

Table 8: Residential Exposure Scenario Descriptions for the Use of Isofenphos

| Exposure Scenario (Number) | Data Source | Standard Assumptions[a] | Comments[b] |
|---|---|---|---|
| Mixer/Loader/Applicator Exposure | | | |
| Loading/applying granules by hand to fire ant mounds (1) | PHED V1.1 | One 1-lb can | **Baseline:** Hand, dermal, and inhalation data are ABC grades. Hand = 16 replicates; dermal = 16 replicates; and inhalation = 16 replicates. Medium confidence in hand/dermal and inhalation data. A 90% protection factor was needed to "backcalculate" a no glove unit exposure value from all non-detects<br><br>**PPE:** Not feasible for this scenario.<br><br>**Engineering Controls:** Not feasible for this scenario. |
| Loading/applying granules to potting soil by hand (2)[c] | PHED V1.1 | 0.25 yd[3] | **Baseline:** Hand, dermal, and inhalation data are ABC grades. Hand = 16 replicates; dermal = 16 replicates; and inhalation = 16 replicates. Medium confidence in hand/dermal and inhalation data. A 90% protection factor was needed to "backcalculate" a no glove unit exposure value from all non-detects<br><br>**PPE:** Not feasible for this scenario.<br><br>**Engineering Controls:** Not feasible for this scenario. |
| Loading/applying granules with a shaker can to fire ant mounds (3)[c] | PHED V1.1 | One 1-lb can | **Baseline:** Hand, dermal, and inhalation data are ABC grades. Hand = 16 replicates; dermal = 16 replicates; and inhalation = 16 replicates. Medium confidence in hand/dermal and inhalation data. A 90% protection factor was needed to "backcalculate" a no glove unit exposure value from all non-detects<br><br>**PPE:** Not feasible for this scenario.<br><br>**Engineering Controls:** Not feasible for this scenario. |
| Loading/applying granules with a belly grinder (4) | PHED V1.1 | 0.5 acres | **Baseline:** Hand and dermal data are ABC grades, and inhalation data are AB grades. Hand = 23 replicates; dermal 20 to 45 replicates; and inhalation = 40 replicates. Medium confidence in hand/dermal data, and high confidence in inhalation data. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** Not feasible for this scenario.<br><br>**Engineering Controls:** Not feasible for this scenario. |
| Loading/applying granules with a push type lawn drop spreader (5) | PHED V1.1 | 0.5 acres | **Baseline:** Hand and dermal data are C grade, and inhalation data are B grade. Hand = 15 replicates; dermal = 0 to 15 replicates; and inhalation = 15 replicates. Low confidence in hand/dermal data, and high confidence in inhalation data. A 50% protection factor was needed to "backcalculate" unit exposure value that reflects a short sleeved shirt.<br><br>**PPE:** Not feasible for this scenario.<br><br>**Engineering Controls:** Not feasible for this scenario. |

[a] Standard Assumptions based on granular use as estimated by OREB. BEAD data were not available.

[b] All handler exposure assessments in this document are based on the "Best Available" data as defined by OREB SOP for meeting Subdivision U Guidelines. Best available grades are assigned to data as follows: matrices with grades A and B data and a minimum of 15 replicates; if not available, then grades A, B and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality (i.e., All Grade Data) and number of replicates. High quality data with a protection factor take precedence over low quality data with no protection factor. Generic data confidence categories are assigned as follows:

High grades A and B and 15 or more replicates per body part

Medium = grades A, B, and C and 15 or more replicates per body part
Low = grades A, B, C, D and E or any combination of grades with less than 15 replicates

[c] Unit exposure data for application of granules by hand were used as surrogate values for these scenarios.

Table 9. Isofenphos Intermediate-Term Surrogate Occupational Postapplication Assessment (Range Finder).

| DAT[a] | DFR ($\mu g/cm^2$)[b] | Dermal Dose (mg/kg/day)[c] | | MOE[d] | |
|---|---|---|---|---|---|
| | | Low | High | Low | High |
| 0 | 4.5 | 0.26 | 5.1 | 0.23 | 0.012 |
| 50 | 0.023 | 0.0013 | 0.026 | 46 | 2.3 |
| 80 | 9.8E-4 | 5.6E-5 | 0.0011 | 1,100 | 55 |
| 100 | 1.2E-4 | NA | 1.4E-4 | NA | 430 |
| 108 | 5.1E-5 | NA | 5.9E-5 | NA | 1,000 |

a DAT is "days after treatment"

b Initial DFR= Application rate (2.0 lb ai/A) x Conversion factor (1 lb ai/acre= 11.209 ug/cm2) x fraction of initial ai retained on foliage

$$DFR\left(\frac{\mu g}{cm^2}\right) = AR\left(\frac{lb\ ai}{A}\right) \times CF\left(\frac{\mu g/cm^2}{lb\ ai/A}\right) \times F \times (1 - DR)^t$$

Where : Assumed percent DFR after initial treatment is 20%, and each day after the percent dissipation per day is 10%.

c Dose = DFR (ug/cm2) x Transfer coefficient (low is 500, high is 10,000 $cm^2$/hr ) x Conversion Factor (1mg/1000 ug) x Dermal Absorption (1) x Hrs w day (8hrs)/ Body weight (70 kg)

d MOE = NOEL ( mg/kg/day)/ Dermal Dose (mg/kg/day). Where: intermediate-term NOEL is 0.06 mg/kg/day.

Table 10. Isofenphos Residential Post-application Scenarios and Estimated Risks.

| Scenario | Receptor | Application Rate Per Treatment (AR) (lbs ai/A) | DFR ($ug/cm^2$)[a] | GRt ($ug/cm^2$)[b] | SRt (ug/g)[c] | Transfer Coefficient (Tc) ($cm^2/hr$) | Exposure Time (ET) (hrs/day) | Dermal Abs. (%) | Surface Area (SA) ($cm^2$/ event) | Freq. (FQ) (events/ hr) | IgR ($cm^2$/day) or (mg/day)[d] | BW (kg ) | ADD (mg/kg/day)[e] | MOE[f] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dermal exposure | Adult | 2.0 | 4.5 | - | - | 43,000 | 2 | 100 | - | - | - | 70 | 5.5 | 0.011 |
| | Toddler | | | | | 8,700 | | | | | | 15 | 5.2 | 0.012 |
| Hand-to-Mouth | Toddler | 2.0 | 4.5 | - | - | - | 2 | - | 350 | 1.56 | - | 15 | 0.33 | 0.18 |
| Turfgrass ingestion | Toddler | 2.0 | - | 4.5 | - | - | - | - | - | - | 25 | 15 | 0.0075 | 8.0 |
| Incidental soil ingestion | Toddler | 2.0 | - | - | 3 | - | - | - | - | - | 100 | 15 | 0.00002 | 3000 |

[a] Dislodgeable foliar residue ($ug/cm^2$) = [AR (lbs ai/A) * fraction ai retained on foliage (20%) * 4.54E+8 ug/lb * 2.47E-8 $A/cm^2$]

[b] Grass residue ($ug/cm^2$) = [AR (lbs ai/A) * fraction ai retained on foliage (20%) * 4.54E+8 ug/lb * 2.47E-8 $A/cm^2$]

[c] Soil residue (ug/g) = [AR (lbs ai/A) * fraction ai retained on soil (20%/cm) * 4.54E+8 ug/lb * 2.47E-8 $A/cm^2$ * 0.67 $cm^3/g$ soil]

[d] Ingestion rate: $cm^2$/day for grass ingestion, and mg/day for incidental soil ingestion.

[e] Average daily dose (ADD) (mg/kg/day)

Dermal exposure: = [DFR ($ug/cm^2$) * Tc ($cm^2/hr$) * mg/1,000 ug * ET ( hrs/day) * absorption factor (1.0)] / [BW (kg)];
Hand-to-mouth: = [DFR ($ug/cm^2$) * SA ($cm^2$/event) * FQ (events/hr) * mg/1,000 ug * ET (2 hrs/day)] / [BW (kg)];
Turfgrass ingestion: = [GRt ($ug/cm^2$) * IgR ($cm^2$/day) * mg/1,000 ug] / [BW (kg)]; and
Incidental soil ingestion: = [SRt (ug/g) * IgR (mg/day) * g/1,000,000 ug] / [BW (kg)].

[f] MOE = NOEL (0.06 mg/kg/day) / ADD.

## 5. Aggregate Exposure and Risk Assessment/Characterization

Based on the toxic effects of cholinesterase inhibition seen for oral, dermal, and inhalation routes of exposure, an aggregate risk assessment for isofenphos is appropriate. However, since, isofenphos is not registered for use on food/feed crops, the only potential for exposure to isofenphos would be in drinking water and from residential applications.

### a. Acute Aggregate Exposure and Risk

An exposure and risk assessment for combined acute risks from dietary consumption of isofenphos in food and water is not required because currently there are no isofenphos end-use products registered for food/feed uses. Although, EPA does not have sufficient data to perform quantitative drinking water exposure and risk assessment, EPA believes that, on a qualitative basis, any risk to drinking water resources from isofenphos use would be highly localized in space and time. On a national basis, isofenphos is not expected to be a concern for drinking water resources.

### b. Chronic Aggregate Exposure and Risk

Chronic residential exposure is not expected for use of isofenphos on lawns. An exposure and risk assessment for combined chronic risks from dietary consumption of isofenphos in food and water is not required because currently there are no isofenphos end-use products registered for food/feed uses. Although, EPA does not have sufficient data to perform quantitative drinking water exposure and risk assessment, EPA believes that, on a qualitative basis, any risk to drinking water resources from isofenphos use would be highly localized in space and time. On a national basis, isofenphos is not expected to be a concern for drinking water resources.

### c. Short- and Intermediate- Term Aggregate Exposure and Risk

A short- and intermediate- term aggregate risk assessment was not conducted because there are no registered uses of isofenphos on food/feed and exposure to isofenphos in drinking water cannot be adequately quantified. Furthermore, exposure to isofenphos from residential applications alone result in risks of concern to adults, infants, and children.

## 6. Other Food Quality Protection Act Considerations

### a. Cumulative Risk

Isofenphos is structurally similar to other organophosphorous pesticides. Further, other pesticides may have common toxicity endpoints with isofenphos. Since the primary molecular mechanism of action of the organophosphorous pesticides is inhibition of acetylcholinesterase, EPA will be conducting a cumulative risk assessment which will include isofenphos and all other registered organophosphorus pesticides. However

cumulative risk assessment considering risks from other pesticides having a common mechanism of toxicity is not addressed in this document.

**b. Endocrine disruption**

EPA is required to 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.....". The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end-use products for endocrine disrupter effects.

**c. Determination of Safety (U.S. Population, Infants, and Children)**

The residential MOEs for adult handlers (male and female) range from 1.3 to 68. The residential MOEs for post-application exposure of adults and toddlers are 0.011 and 0.012, respectively. These MOE calculations were based on inhibition of plasma, erythrocyte and brain ChE activity in an acute neurotoxicity study in the rat.

HED cannot conclude with reasonable certainty that no harm will result to infants and children from residential exposure to isofenphos from playing on treated lawns or from incidental nondietary ingestion of isofenphos from hand-to-mouth transfer, or from ingestion of isofenphos-treated turfgrass.

**7. Data requirements**

a. Toxicology

Based on a weight of the evidence determination a developmental neurotoxicity study is required for isofenphos.

It is recomended that the registrant conduct a 21-day dermal toxicity or dermal absorption absorption study in the rat.

b. Occupational and Residential Exposure

No additional data are required at this time.

# APPENDIX 1

Case No. 2345
Chemical No. 109401

Case Name: Isofenphos
Registrant: Bayer Corporation
Product(s): 91.7% T (EPA Reg. No. 3125-326)

## PRODUCT CHEMISTRY DATA SUMMARY

| Guideline Number | Requirement | Are Data Requirements Fulfilled? [1] | MRID Number [2] |
|---|---|---|---|
| 830.1550 | Product Identity and Disclosure of Ingredients | Y | 41901301 [3] |
| 830.1600<br>830.1620<br>830.1650 | Starting Materials and Manufacturing Process | Y | 41901301 [3], 43220001 [4] |
| 830.1670 | Discussion of Formation of Impurities | Y | 41901301 [3] |
| 830.1700 | Preliminary Analysis | Y | 00149918 |
| 830.1750 | Certification of Ingredient Limits | Y | 41901301 [3], 43220001 [4], Letter 6/12/96 [5] |
| 830.1800 | Analytical Methods to Verify the Certified Limits | N [6] | 00149918 |
| 830.6302 | Color | Y | 00149918 |
| 830.6303 | Physical State | Y | 00149918 |
| 830.6304 | Odor | Y | 00149918 |
| 830.6313 | Stability | N [7] | 00149918, 41609906 |
| 830.7000 | pH | Y | 41609906 |
| 830.7050 [7] | UV/Visible Absorption | N [8] | |
| 830.7200 | Melting Point/Melting Range | N/A [9] | |
| 830.7220 | Boiling Point/Boiling Range | Y | 00149918 |
| 830.7300 | Density/Relative Density/Bulk Density | Y | 41609906 |
| 830.7370 | Dissociation Constant in Water | N/A [10] | |
| 830.7550<br>830.7560<br>830.7570 | Partition Coefficient (Octanol/Water) | Y | 41609906 |
| 830.7840<br>830.7860 | Solubility | Y | 41609906, 42319801 [11] |
| 830.7950 | Vapor Pressure | Y | 41609906 |

Y = Yes; N = No; N/A = Not Applicable.

References were reviewed under D234560, 4/11/97, C. Eiden unless otherwise noted.

CBRS No. 8338, D166893, 9/7/93, P. Deschamp.

CBRS No. 14017, D205447, 1/3/96, C. Eiden.

CBRS No. 17432, D228024, 8/20/96, K. Dockter.

[6] Validation data are required for the methods used to determine isofenphos and its impurities present at ≥0.1% or of toxicological concern.

[7] Data demonstrating the stability of the TGAI when exposed to metals and metal ions are required.

[8] The OPPTS Series 830, Product Properties Test Guidelines require data pertaining to UV/visible absorption for the PAI.

[9] Data are not required because the T/TGAI is a liquid at room temperature.

[10] Data are not required because the T/TGAI is not dispersible in water.

[11] CBRS No. 10223, D180664, 8/13/92, K. Dockter.

ATTACHMENT 2: HED HAZID Report. George Z. Ghali (01/13/98)

Paula

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

012450
15PP

JAN 13 1998

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: **Isofenphos** [1-Methylethyl 2-{[ethoxy[(1-methylethyl)amino] phosphinothioyl] oxy] benzoate}: Hazard Identification Committee Report.

CASRN: 25311-71-1
PC Code: 109401
Caswell: 447AB

FROM: George Z. Ghali, PhD. G.Z.Ghali 12.22.97
Executive Secretary, Hazard Identification Committee
Health Effects Division (7509C)

Thru: Clark Swentzel
Chairman, Hazard Identification Committee
Health Effects Division (7509C)
Memorandum for C. Swentzel 12/23/97

To: Tina Levine, PM 04
Insecticide-Rodenticide Branch
Registration Division (7505C)

The Health Effects Division-Hazard Identification Committee met on October 23, and 30 and on December 10 and 17, 1997 to evaluate the existing and/or recently submitted toxicology data in support of isofenphos re-registration, identify toxicological endpoints and dose levels of concern appropriate for use in risk assessments for different exposure routes and duration, and assess/reassess the reference dose for this chemical.

Material available for review consisted of data evaluation records (DERs) for an acute dermal toxicity study in rats **(81-2)**, an acute inhalation toxicity study in rats **(81-3)**, acute neurotoxicity study in rats **(81-8)**, a subchronic dermal toxicity study in rabbits **(82-3)**, a subchronic neurotoxicity study in rats **(82-7)**, a two-year feeding study in dogs **(83-1b)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)**, a two-generation reproductive toxicity study in rats **(83-4)**, a subchronic delayed neurotoxicity study in hens **(82-5)**, a metabolism study in rats **(85-1)** and a battery of mutagenicity studies **(84-2)**.



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## INDIVIDUALS IN ATTENDANCE

Hazard Identification Committee members present, in at least one of the four meetings, were Karle Baetcke (Senior Science Advisor, HED), William Burnam (Chief, SAB, HED), George Ghali (Executive Secretary, Hazard Identification Committee, HED), Susan Makris, Nancy McCarroll, Melba Morrow, Kathleen Raffaele, John Redden, Jess Rowland, and Clark Swentzel (Chief TB II, Chairman, Hazard Identification Committee, HED). Hazard Identification Committee member(s) in absentia: David Anderson.

In attendance also were Stephen Dapson, Sanjivani Diwan, Pauline Wagner, Nicole Paguette, and Jonathan Becker, HED, as observers.

Scientific reviewer(s) (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report and concurrence with the hazard identification assessment review unless otherwise stated.

Robert Fricke Robert F. Fricke Jan 6, 1998

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## I. TOXICOLOGY PROFILE:

### A. Carcinogenicity:

The carcinogenicity issue has not been discussed by the Hazard Identification Committee in the meeting of October 23, 1997 since the rat carcinogenicity study was not submitted to the Committee at that time. Subsequently, on October 30, 1997, based on the toxicology data available, the Hazard Identification Committee determined that isofenphos did not alter the spontaneous tumor profile in rats or mice under the testing conditions. Therefore, it was recommended that isofenphos be classified as a **"Group E"**, indicating evidence of non-carcinogenicity for humans; i.e., the chemical is characterized as **"Not Likely"** to be carcinogenic in humans via relevant routes of exposure.

This weight of the evidence judgement is largely based on the absence of significant tumor increases in adequate carcinogenicity studies in rats (MRID No. 000000) and mice (MRID No. 000000). This classification is also supported by the lack of mutagenic activity in several mutagenicity assays (MRID Nos. 41609912, 41008801, 41008802).

It should be noted, however, that designation of an agent as being in **"Group E"** or **"Not Likely"** is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

### B. Neurotoxicity:

In an acute neurotoxicity study (MRID 44285601; Doc. No. 012306), isofenphos (92.5% Purity) was administered by a single gavage dose to fasted Wistar rats at nominal doses of 2, 8, or 15 mg/kg. The NOEL for neurotoxicity was not established. The LOEL of 2 mg/kg was based on inhibition of plasma, RBC, and brain cholinesterase, clinical signs (muscle fasciculation) in females. In addition, at 8 mg/kg, gait abnormalities and involuntary muscle movements were observed. At 15 mg/kg, there was a higher incidence of those findings along with uncoordinated righting reflex, decreased number of rearings, decreased forelimb and hindlimb grip strength, decreased body temperature, and decreased motor and locomotor activities on days 0 and 7 posttreatment. There were no effects on brain weight or indications of neuropathology at any treatment level.

In a 90-day neurotoxicity study in rats (MRID 44236601; Doc. No. 012306), isofenphos (91.6%) was administered to male and female Wistar rats at dietary levels of 1, 25, or 125 ppm (0.06, 1.62, or 8.45 mg/kg/day in males and 0.09, 2.07, or 11.54 mg/kg/day in females). The NOEL was 1 ppm (0.06 mg/kg/day in males and 0.09 mg/kg/day in females). The LOEL was 25 ppm (1.62/2.07 mg/kg/day in M/F), based on inhibition of plasma, RBC, and brain cholinesterase.

In addition, at 125 ppm, the HDT, clinical signs (piloerection, tremors, palmus, and nonspecific behavioral disturbances), decreased body weight gain and food consumption in the first week of study, FOB effects (muscle fasciculation in both sexes and abnormal gait and decreased grip strength in females), and a slow pupillary reflex in five males.

Several acute delayed neurotoxicity studies in hens described in the "toxicology one-liners" did not elicit neurotoxic effects at doses up to 100 mg/kg by gavage.

In a subchronic delayed neurotoxicity study (MRID 00146887, 41074101; Doc. No. 005435, 006808, 007612), hens were administered 92.5% isofenphos once daily by gavage to the crop at doses of 0.25, 1.00, or 2.00 mg/kg/day for 90 days. The study was negative for delayed neurotoxicity at a dose of 2.00 mg/kg/day. The study NOEL was 0.25 mg/kg/day, based on decreased plasma and/or RBC cholinesterase at the LOEL of 1.00 mg/kg/day. Additionally, at 2.00 mg/kg/day, mean body weight was depressed.

A neurotoxic esterase assay submitted to the Agency was declared invalid. The literature, however, indicates that isofenphos inhibits NTE in hens at high doses in vivo (Chow et al., 1986, as cited by Cherniack, 1988). A report of delayed neuropathy in an agricultural worker in the published literature described clinical manifestations, EMG, and nerve conduction assays compatible with a pathology of a distal, mainly axonal, motor neuropathy following accidental ingestion isofenphos.

There were no indications of effects on brain weight, and following processing of tissues without perfusion, no effects on the histopathology of the brain or peripheral nervous system were observed in the 2-year chronic dog study and 90-day rabbit dermal study. No other subchronic or chronic study DERs were provided for Committee review, but the one-liners did not describe findings of this nature.

C. **Reproductive and Developmental Toxicity:**

The following evaluation of the chemical isofenphos is provided to address FQPA considerations on the sensitivity of infants and children.

1. Reproductive Toxicity:

In a two-generation reproduction study in Wistar rats (MRID 41509902; Doc. No. 012311), isofenphos (92.9%) was administered at dietary concentrations of 1, 5, or 25 ppm (0.08-0.16, 0.44-0.69, or 2.21-3.92 mg/kg/day). The parental systemic NOEL was 1 ppm (0.08-0.16 mg/kg/day), based on plasma, RBC, and/or brain cholinesterase inhibition at 5 ppm (0.44-0.69 mg/kg/day), the parental systemic LOEL. In addition, at 25 ppm (2.21-3.92 mg/kg/day), treatment-

related increases in mortality and increases in absolute ovarian weights were observed. The offspring NOEL was 1 ppm (0.08-0.16 mg/kg/day) and the offspring LOEL was 5 ppm (0.44-0.69 mg/kg/day), based on clinical signs of toxicity (small to very small and emaciated pups) and increased pup mortality (observed as reductions in the lactation indices and mean litter sizes). Cholinesterase inhibition was apparently not measured in parental animals or pups.

2. Developmental Toxicity:

In a prenatal developmental toxicity study in Sprague-Dawley rats (MRID 42381201; Doc. No. 009740), 91.4% isofenphos was administered on gestation days 6-15 by gavage in carboxymethylcellulose and Tween 80 at dose levels of 0.05, 0.45, or 4.0 mg/kg/day. Cholinesterase activity was measured in dams (blood and brain) at days 16 and 20 and fetuses (brain only) at gestation day. The maternal NOEL was 0.05 mg/kg/day, and the maternal LOEL was 0.45 mg/kg/day, based on decreased plasma, RBC, and brain cholinesterase at gestation day 16. By gestation day 20, cholinesterase activity was recovered at 0.45 mg/kg/day and only RBC and brain cholinesterase activity was decreased at 4.0 mg/kg/day. No developmental toxicity was observed (developmental NOEL $\geq$4.0 mg/kg/day. Fetal brain cholinesterase activity was not altered. This study was included in the review by Astroff et al, 1996.

In a prenatal developmental toxicity study conducted in New Zealand white rabbits (MRID 42382801; Doc. No. 009896), isofenphos (91.4%) was administered by gavage in carboxymethylcellulose and Tween 80 at doses of 0.25, 1.25, or 7.5 mg/kg/day on gestation days 6-18. Cholinesterase activity was measured in dams (blood and brain) at days 19 and 29; fetal cholinesterase values were apparently not measured. The maternal cholinesterase inhibition NOEL was 0.25 mg/kg/day, based upon plasma cholinesterase inhibition on gestation day 19, and RBC and brain cholinesterase inhibition on gestation day 19 and 29, at the maternal cholinesterase inhibition LOEL of 1.25 mg/kg/day. The maternal systemic NOEL was 1.25 mg/kg/day, and the maternal systemic LOEL was 7.5 mg/kg/day, based upon increased mortality, decreased body weight and body weight gain, and decreased food consumption, in addition to the decreased cholinesterase activity. No developmental effects were observed (developmental NOEL $\geq$7.5 mg/kg/day).

3. Developmental Neurotoxicity:

In developing a weight of evidence for the need for a developmental neurotoxicity study on isofenphos, primary consideration was given to the following:

On one hand, administration of isofenphos, like most other organophosphorus pesticides, to various species results in plasma,

erythrocytes, and brain cholinesterase inhibition. Isofenphos also inhibits NTE in hens at high doses in vivo (Chow et al., 1986, as cited by Cherniack, 1988).

A report of delayed neuropathy in an agricultural worker in the published literature (Catz et al., 1988) described clinical manifestations, EMG, and nerve conduction assays compatible with a pathology of a distal, mainly axonal, motor neuropathy following accidental isofenphos ingestion.

Isofenphos is considered to be relatively acutely toxic, with oral $LD_{50}$ values ranging from 28.8-38.7 mg/kg in 2 studies in the rat and from 91-127 mg/kg in the mouse. The dermal $LD_{50}$ ranged from 70 to 191 mg/kg in rats and 315-1172 in rabbits. The $LC_{50}$ ranged from 0.144 to 0.525 mg/L over 5 separate studies.

On the other hand, no evidence of abnormalities in the development of the fetal nervous system, were observed in the prenatal developmental toxicity studies in either rats or rabbits, at maternally toxic oral doses up to 4.0 or 7.5 mg/kg/day, respectively.

In the prenatal developmental toxicity study in rats, fetal brain cholinesterase was not different from control on gestation day 20, although maternal RBC and brain cholinesterase were inhibited at that time point.

Neither brain weight nor histopathology (nonperfused) of the nervous system were affected in the subchronic and chronic toxicity studies examined.

Acute and subchronic delayed neurotoxicity studies in hens were negative for OPIDN. Acute and subchronic neurotoxicity studies in rats did not indicate brain weight changes or neuropathological lesions.

The Committee determined that a developmental neurotoxicity study in rats should be conducted with isofenphos in order to assess functional development following prenatal exposure. The following information was considered in arriving at this decision.

D. **FQPA Considerations:**

Under the Food Quality Protection Act (FQPA), P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency was directed to "ensure that there is a reasonable certainty that no harm will result to infants and children" from aggregate exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this

reasonable certainty of no harm, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Pursuant to the language and intent of the FQPA directive regarding infants and children, the applicable toxicity database for isofenphos was evaluated by the Hazard Identification Committee. The following conclusions were made:

**Adequacy of data:** The data base included acceptable two-generation reproduction study in rats and prenatal developmental toxicity studies in rats and rabbits, meeting the FIFRA basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. However, the Committee recommend for a developmental neurotoxicity study in rats to assess functional development following prenatal exposure to isofenphos. This is considered a data gap for the assessment of the effects of isofenphos following *in utero* and/or early postnatal exposure.

**Susceptibility issues:** In the three-generation reproduction study in rats and the prenatal developmental toxicity studies in rats and rabbits, there was no indication of increased sensitivity of the young animals to pre-and/or postnatal exposure to isofenphos.

**Uncertainty factor:** The Committee determined that for isofenphos the 10-fold uncertainty factor for the protection of infants and children would be retained because of the lack of a developmental neurotoxicity study in rats to assess functional development following prenatal exposure to isofenphos. This is considered a data gap for the evaluation of hazard to infants and children (see weight of the evidence under developmental neurotoxicity, above).

**E. Mutagenicity:**

Three acceptable mutagenicity studies were available for review. The following are summaries of the these studies and the Committee's conclusions:

1. Gene Mutations:

Salmonella typhimurium reverse gene mutation assay (MRID No. 41609912, HED Doc. No. 009749): The test was negative in S. typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 up to

the highest dose tested (10,000 µg/plate +/-S9). Compound precipitation was seen at concentrations ≥3333 µg/plate +/-S9.

2. Chromosomal Aberrations:

In vitro Chinese hamster ovary (CHO) cell chromosome aberration assay (MRID No. 41008801, HED Doc. No. 007192): The test was negative up to cytotoxic concentrations (≥0.04 µL/mL -S9; ≥0.08 µL/mL +S9).

3. Other Mutagenic Mechanisms:

Unscheduled DNA synthesis (UDS) in cultured primary rat hepatocytes assay (MRID No. 41008802; Doc. No. 007192): The test was negative up to cytotoxic doses (≥0.03 µL/mL). Concentrations ≥1.0 µL/mL were insoluble.

4. Other Information:

Open literature information available indicated that isofenphos is not mutagenic in bacteria, clastogenic in vitro in mammalian cells, or genotoxic in cultured primary rat hepatocytes.

The submitted test battery satisfies the pre-1991 mutagenicity initial testing battery guidelines. No further testing is required at this time.

F. Dermal Absorption:

There were no dermal absorption studies appropriate for use for the purpose of risk assessment. The 21-day dermal toxicity study with formulations, and the 90-day dermal with the technical material, were conducted in rabbits. This species is inappropriate to conduct dermal studies with organophosphorus compound requiring activation, i.e, thiophosphates which are normally activated to phosphates. There were no dermal absorption studies conducted in rats, the most sensitive species in this case. Therefore, the default value of 100% will be used for the dermal absorption rate.



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## II. HAZARD IDENTIFICATION:

Based on comprehensive evaluation of the toxicology data available on isofenphos, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the hazard categories indicated below:

Dietary Hazard resulting from ingestion of residues of this particular pesticide when used on agricultural food commodities for pest control purposes or as a food additive and may include **acute and/or chronic exposure**,

Occupational/Residential Hazard resulting from **dermal and/or inhalation** exposure to the chemical and may include **short-, intermediate-, and/or long-term exposure.**

Issues related to the Food Quality Protection Act (FQPA), P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA) are also addressed.

Where no appropriate data have been identified for a particular duration or exposure scenario, or if a risk assessment is not warranted, this is noted. Levels of uncertainties associated with intraspecies variability, interspecies extrapolation, route to route conversion, or variable duration extrapolation are also addressed.

Based on the use pattern/exposure profile, the Committee determined that the risk assessments indicated below are required for isofenphos.

### Dietary Exposure

#### A. Acute Dietary Exposure (one day):

**Critical Study:** Acute Oral Neurotoxicity Study in Rats (81-8), MRID No. 44285601.

Male and female Wistar rats (12/sex/dose, main study; 6/sex/dose, satellite study) were fasted overnight and then orally dosed once with Isofenphos (92.5%) at nominal doses of 0 (vehicle), 2, 8, or 15 mg/kg (analytically confirmed doses: 0, 2.62, 7.86 or 13.82 mg/kg, respectively). Main study animals were evaluated for neurobehavioral effects (FOB and motor activity) on day 0, at the peak time-of-effect (1 hr 50 min (minimum), males; 5 hr (minimum), females) and days 7 and 14; neuropathological examination were carried out at terminal sacrifice (day 14) on 6 animals/sex/dose. The satellite group was used for determination of plasma, RBC and brain



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cholinesterase activities at the peak time-of-effect on day 0..

Clinical signs and FOB evaluations were consistent with acute cholinergic toxicity. At the mid-dose level, gait abnormalities and involuntary motor movements were observed in males and females. In high-dose males and females, a higher incidence of these findings was observed along with uncoordinated righting reflex, decreased number of rearings, decreased forelimb and hindlimb grip strength and decreased body temperature. No reaction to the approach response was noted in 4/12 high-dose males. In general, the onset of clinical signs started sooner in males (4 hr) than in females (8 hrs), but did not last as long (day 6, males; day 7, females).

Decreases in mean body weighs and body weight gains were observed in high-dose males and females. Following an overnight fast, high-dose males lost a significant ($p \leq 0.05$, 4%) amount of body weight. At day 7, the body weights of high-dose males and females were 11% and 7% lower, respectively, than the concurrent control values. By day 14, males regained some, but not all, of the lost body weight; the mean body weight was, however, still significantly lower than the concurrent control value. By day 14, the mean body weight of high-dose females was comparable to the control value. Body weight gain from day 0 to day 7 was 38% lower in males and 37% lower in females in the high-dose group. Overall body weight gain (day 0 to 14) for high-dose males was 18% lower for males, while that of high-dose females was comparable to the control value.

High-dose animals had significantly decreased motor (58%, males; 64% females) and locomotor (79%, males; 85%, females) activities on day 0 (peak time-of-effect). The day 7 evaluation of high-dose animals showed a decrease in motor activity of 28% (not significant) in females and decreased locomotor activity of 29% (not significant) in males and 34% ($p \leq 0.05$) in females.

Plasma, RBC and brain cholinesterase activity was statistically significantly ($p \leq 0.01$) decreased in low- mid- and high-dose males and females at the peak time-of-effect on day 0. At the low-dose level, plasma, RBC and brain cholinesterase activities were decreased 59 to 89%, 18 to 55%, and 10 to 21%, respectively. At the mid-dose level, plasma, RBC and brain Chew activities were significantly decreased 85 to 97%, 68 to 89%, and 51 to 69%, respectively. At the high-dose level plasma cholinesterase was inhibited 94 to 98%, RBC cholinesterase, 95 to 98%, and brain cholinesterase, 83 to 85%.

At terminal sacrifice, gross examination did not reveal any treatment-related effects. Terminal body weights of high-dose animals were significantly lower (10%, $p \leq 0.05$) than control values. The body weights of mid- and low dose animals and the absolute and relative brain weights of treated animals were



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comparable to controls. Neuropathological findings of treated animals were comparable to control animals.

Based on the results of this study [inhibition of plasma, RBC and brain cholinesterase with clinical signs (muscle fasciculation) in females], the LOEL was established at 2 mg/kg, the lowest dose level tested. The NOEL was not established.

**Endpoint and Dose Level Selected for Use in Risk Assessment:** The NOEL was not established in this study. The LOEL is 2.0 mg/kg/day based on inhibition of plasma, RBC and brain Chew with clinical signs (muscle fasciculation) in females.

**Uncertainty Factor (UF):** A UF of 3000 was applied; this includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability, an additional UF of 3 to account for the lack of a NOEL, and an additional UF of 10 for FQPA considerations.

**Comments:** The findings of this study are supported by the findings of an oral developmental toxicity study in the rat with a parental NOEL of 0.05 mg/kg/day based on cholinesterase inhibition observed at the next higher dose level of 0.45 mg/kg/day.

B. **Chronic Dietary Exposure-Reference Dose (RfD):**

**Reference Dose (RfD):** 0.00008 mg/kg/day

**Critical Study:** 2-Generation Reproductive Toxicity Study in Rats (83-4), MRID 41609902.

**Executive Summary:** In this study, SRA 12869 (92.9%) was administered to Bor strain:WISW (SPF Cpb) rats (25/sex/dose) at dietary levels of 0, 1, 5, or 25 ppm (achieved doses of 0, 0.08-0.16, 0.44-0.69, or 2.21-3.92 mg/kg/day). Exposure to $F_0$ animals began at 5 weeks of age and lasted for 13 weeks prior to mating the first time to produce $F_{1a}$ pups. $F_0$ animals were mated a second time to produce $F_{1b}$ pups. At 4 weeks of age, $F_{1b}$ pups were selected to become parents of the $F_{2a}$ and $F_{2b}$ generations and were given the same concentration of SPA 12869 in their diets as their dam. The $F_{1b}$ parental animals were given test diets for approximately 12 weeks prior to mating the first time to produce the $F_{2a}$ pups. Exposure of the test material to all animals was continuous in the diet throughout the study.

Parental toxicity was characterized at the mid-dose as reductions in cholinesterase activity in plasma (18.5-31.9%, $p \leq 0.01$, both sexes) and in erythrocytes (7.1%, $p \leq 0.05$, females only). At the high-dose, treatment-related reductions in cholinesterase activity in the brain (27.0%, males; 31.8%,

females; p≤0.01), plasma (16.5-26.4%, p≤0.01, both sexes), and RBC (53.7-80.7%, p≤0.01, both sexes) were noted. In addition at the high-dose, treatment-related increases in mortality (12%, $F_0$ females) and increases in absolute ovarian weights ($F_0$, 9%; $F_{1b}$, 12%; p≤0.05) were noted.

No treatment-related clinical findings or changes in body weights, body weight gains, food consumption, or reproductive indices were noted in either sex of either generation throughout the study.

The LOEL for systemic toxicity is 5 ppm (0.44-0.69 mg/kg/day) based on reductions in plasma and RBC cholinesterase activities. The systemic NOEL is 1 ppm (0.08-0.16 mg/kg/day).

Reproductive toxicity was demonstrated at 5 ppm as treatment-related increases in the number of litters with small to very small pups ($F_{1b}$) and emaciated pups ($F_{2b}$). For the $F_{1b}$ mid-dose litters, treatment-related reductions were noted in the lactation index (34.9% vs. 63.5% for controls, p≤0.01) and in mean litter sizes for days 14-28 (47%, p≤0.01). The lactation index was also decreased for the mid-dose $F_{2b}$ litters (71.2% vs. 89.6% in controls, p≤0.01).

At 25 ppm, treatment-related increases in the numbers of litters with small to very small pups ($F_{1a}$ and $F_{1b}$), cold pups ($F_{1b}$ and $F_{2b}$), and emaciated pups ($F_{2b}$) were observed. For the high-dose $F_{1a}$ and $F_{1b}$ litters, treatment-related increases were noted in the number of deaths between days 5-28 and related reductions were observed in mean litter sizes on days 14-28 ($F_{1a}$, 47%, p≤0.01) or 7-28 ($F_{1b}$, 34-60%, p≤0.01 or ≤0.05), number of pups alive by day 28, and lactational indices ($F_{1a}$: 47.1% vs. 88.1% for controls, p≤0.01; $F_{1b}$: 11.8% vs. 63.5% for controls, p≤0.01). In addition for the $F_{1b}$ litters, a treatment-related reduction in the viability index was noted (75.8% vs. 96.6% for controls, p≤0.01). For the high-dose $F_{2b}$ litters, treatment-related reductions in the viability index (91.5% vs. 99.1% for controls, p≤0.01) and lactation index (70.0% vs. 89.6%, p≤0.01) were observed. For both generations, the total number of pups born was reduced at the high-dose; this was because of increased mortality of the $F_0$ dams and their offspring (only 9 $F_{1b}$ females were available for mating) resulting in a smaller number of females which gave birth. A treatment-related reduction in pup body weights during lactation was also noted at the high-dose ($F_{1a}$, 11-19% p≤0.01 or 0.05; $F_{1b}$, 23-29%, p≤0.01).

The LOEL for reproductive toxicity is 5 ppm (0.44-0.69 mg/kg/day) based on clinical signs of toxicity (small to very small and emaciated pups) and increased pup mortality (reductions in the lactation indices and mean litter sizes). The reproductive NOEL is 1 ppm (0.08-0.16 mg/kg/day).



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**Endpoint and Dose selected for use in risk assessment:** The reproductive NOEL is 1 ppm (0.08-0.16 mg/kg/day), based on clinical signs of toxicity (small to very small and emaciated pups) and increased pup mortality (reductions in the lactation indices and mean litter sizes) observed at 5 ppm (0.44-0.69 mg/kg/day).

**Uncertainty Factor (UF):** An uncertainty factor of 1000 was applied; this includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability. An additional UF of 10 was recommended for FQPA considerations.

The use of a UF of 100 to account for interspecies extrapolation and intraspecies variability was justified based on the availability of two chronic toxicity studies (in rodent and non-rodent species) and the reproductive toxicity study in rats, in accordance with the rules established by the Agency-IRIS (Integration Risk Information System) Work Group.

**Comments and Rationale:** The NOEL and the effects observed in this study are supported by similar findings in the chronic dog study (MRID No. 92085016, 43198001).

C. **Short Term Occupational or Residential Exposure (1-7 days):**

2,00008

**Critical Study:** Acute Oral Neurotoxicity Study (81-8), MRID No. 44285601.

For more details about this study or the executive summary, see Section II-A, above.

**Endpoint and Dose Level selected for use in risk assessment:** There NOEL was not established in this study. The LOEL is 2.0 mg/kg/day based on inhibition of plasma, RBC and brain Cholinesterase inhibition with clinical signs (muscle fasciculation) in females.

**Uncertainty Factor (UF):** A UF of 3000 was applied; this includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability, an additional UF of 3 to account for the lack of a NOEL, and an additional UF of 10 for FQPA considerations.

**Comments:** Although two 21-day and a 90-day dermal toxicity studies were available on this chemical, and although these studies cover the time points of 1-7 days, the Committee recommended the use of an oral study for this purpose. This conclusion was based on the fact that the 21-say dermal toxicity studies were conducted with isofenphos formulations not with the technical material (in the rabbit), and the 90-day dermal toxicity study, though conducted with the technical material, was



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also performed in the rabbit. The rabbit is considered inappropriate to conduct dermal studies with organophosphorus compound requiring metabolic activation, i.e, thiophosphates, phosphorothioates, and phosphorodithioates which are normally activated to the corresponding phosphates by the hepatic microsomal enzymes. These particular organophosphorus compounds, when administered dermally to the rabbit, are metabolically deactivated and lose their anticholinesterase properties via hydrolytic cleavage of the ester bond by esterase enzymes normally present in the blood.

Because of the lack of a dermal absorption study and because of the similarity of toxicity via the oral and dermal routes as evidenced in several acute oral and dermal toxicity studies, the Committee recommended the use of a dermal absorption rate of 100%.

D. **Intermediate Term Occupational or Residential Exposure (one week to several months):**

**Critical Study:** Subchronic Neurotoxicity Screening Study in Wistar Rats (82-7), MRID No.: 44236601.

Male and female Wistar rats (12/sex/dose) were fed diets containing Isofenphos (91.6%) at 0 (basal diet ), 1, 25, or 125 ppm (mg/kg/day equivalents: 0, 0.06, 1.62, or 8.45, males; 0, 0.09, 2.07, or 11.54, females) for at least 13 weeks. Neurobehavioral evaluations, consisting of Functional Observational Battery and motor activity measurements, were performed at pretesting and after 4, 8 and 13 weeks of treatment. Gross pathology (all animals) and neuropathological (6/sex/dose) examinations were carried out at terminal sacrifice. Six animals/sex/dose were selected for determination of plasma and RBC cholinesterase activities at week 4 and plasma, RBC and brain cholinesterase activities at week 14.

Treatment-related, cholinergic signs were observed during the clinical evaluations of high-dose males and females. During the first two to four weeks of treatment, males and females showed piloerection and tremors; high incidences of palmus and non-specific behavioral disturbances (females only) were observed during the entire study. No treatment-related clinical signs were observed in the low and mid-dose groups. All animals survived to terminal sacrifice.

Mean body weights of high-dose males and females were statistically significantly lower than control values during the first six to seven weeks of the study. These decreases appear to be a result of decreased body weight gains of 51% in males and 100% (no weight gain) in females during the first week of the study. The decreased body weight gains appear to be a result of decreased food consumption (g/animals/day) of 19% in males and

35% in females. Excluding the body weight data for the first week of the study, the body weight gains for weeks 1 to 13 were the same as the control value in males and 11% greater than control value in females.

Plasma, RBC and brain cholinesterase activities of mid- and high-dose animals were all significantly decreased. The evaluations at week 4 for mid-dose animals showed significant decreases in plasma (54%, males; 84%, females) and RBC (64%, males; 81%, females) cholinesterase activities. At week 14, mid-dose animals had decreases in plasma, RBC and brain cholinesterase activities of 54%, 63% and 32% in males, respectively and 88%, 66% and 60% in females, respectively. At week 4, high-dose animals had decreases in plasma and RBC cholinesterase activities of 85% and 98%, in males, respectively and 97% and 100% in females, respectively. At week 14, plasma, RBC and brain cholinesterase activities of high-dose animals were decreased 84%, 96%, and 75% in males, respectively and 97%, 97%, and 89% in females, respectively.

Neurobehavioral evaluations revealed treatment-related effects in high-dose males and females, with females being more affected than males. Treatment-related FOB effects consisted in part, of muscle fasciculation in both sexes and abnormal gait and decreased grip strength in females. Motor and locomotor activities were significantly decreased in high-dose females.

Ophthalmological examination at week 13 revealed a slow pupillary reflex in five high-dose females, this is regarded as a treatment-related effect.

The incidences of gross and neuropathological finding of treated animals were comparable to controls.

Based on the results of this study (inhibition of plasma, RBC and brain cholinesterase, the LOEL was established at 25 ppm (1.62 mg/kg/day, males; 2.07 mg/kg/day, females); the NOEL was established at 1 ppm (0.06 mg/kg/day, males; 0.09 mg/kg/day, females).

**Endpoint and Dose Level Selected for Use in Risk Assessment:** The NOEL of 1 ppm (0.06 mg/kg/day, males; 0.09 mg/kg/day, females), based on inhibition of plasma, RBC and brain Chew observed at the next higher dose level of 25 ppm (1.62 mg/kg/day, males; 2.07 mg/kg/day, females).

**Uncertainty Factor:** An uncertainty factor of 1000 was applied; this includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability. An additional UF of 10 was recommended for FQPA considerations.

**Comments and Rationale:** See comments and rationale for Section

II-C, above, for the explanation of why an oral toxicity was used for dermal risk assessment although dermal studies were available covering the range of 1-90 days, and what is the dermal absorption rate to be used for the derivation of the dermal equivalent dose in this case and why.

F. **Inhalation Exposure (variable duration):**

For the purpose of inhalation risk assessment of short and intermediate duration, the Committee recommended that the inhalation exposure be converted from mg/L to the equivalent mg/kg/day dose assuming an inhalation absorption rate of 100%. This dose should be compared to the oral LOEL of 2 mg/kg/day (generated in the acute neurotoxicity study, MRID No. 44236601), in the case of short term and compared to the oral NOEL of 0.06 mg/kg/day (generated in the subchronic neurotoxicity study, MRID No. 44236601) in the case of the intermediate-term risk assessment. Based on the use pattern and exposure profile, the Committee determined that the long-term inhalation risk assessment would not be required.

An Uncertainty Factor of 3000 was recommended for the short-term exposure. This includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability, an additional UF of 3 to account for the lack of a NOEL, and an additional UF of 10 for FQPA considerations.

An Uncertainty Factor of 1000 was recommended for the intermediate-term exposure. This includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability. An additional UF of 10 was recommended for FQPA considerations.

**Comments and Rationale:** Since there were no appropriate subchronic inhalation studies, but there was concern about potential inhalation exposure, the inhalation exposure was converted to an equivalent oral dose assuming 100% lung absorption. This was added to the dermal exposure (after assuming 100% dermal absorption) and compared to the oral neurotoxicity endpoint of either 2 or 0.06 mg/kg/day depending on the exposure duration.

G. **Aggregate Risk:**

Because of the similarity of the endpoints identified both in the dermal and inhalation exposure, i.e. cholinesterase inhibition, the following equation might be appropriate in expressing the aggregate risk for this chemical.

Aggregate Risk = inverse $1/MOE_{(dermal)} + 1/MOE_{(inhalation)}$

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## III. References:


1. Astroff, B., G.K. Sangha, and J.H. Thyssen. (1996) The relationship between organophosphate-induced maternal cholinesterase inhibition and embryo/fetal effects in the Sprague-Dawley rat. *The Toxicologist* 30(1):191.

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3. Cherniack, M.G. (1988) Toxicological screening for organophosphorus-induced delayed neurotoxicity: complications in toxicity testing. *NeuroToxicology* 9(2):249-272.


cc: Stephanie Irene
Robert Fricke
Clark Swentzel
Michael Metzger
Paula Deschamp
Karen Whitby
Jess Rowland
Amal Mahfouz (OW)
Hazard ID file
Caswell File

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

26pp

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

**DATE:** **May 5, 1998**

**MEMORANDUM**

**SUBJECT:** **ISOFENPHOS** - Toxicology Chapter

**FROM:** Robert F. Fricke
Reregistration Branch II
Health Effects Division (7509C)

Robert F. Fricke 5 May 1998

Al Nielsen

**THROUGH:** Alan Nielsen, Branch Senior Scientist
Reregistration Branch II
Health Effects Division (7509C)

**TO:** Ruby Whiters
Reregistration Branch III
Special Review and Reregistration Division (7508W)

**PC Code: 109401**
**Case No: 2345**
**DP Barcode: D244542**

Attached is the Toxicology Chapter to support the reregistration of isofenphos.

cc HED Caswell File
Rick Whiting

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## III. Science Assessment: Isofenphos

## B. Human Risk Assessment

### 1. Hazard Assessment

The toxicological data base for isofenphos is adequate to support reregistration. Although the requirements for long-term chronic dietary, oncogenicity, subchronic (90-day) feeding studies have been waived based on the intended use patterns (terrestrial, non-food and residential outdoor) for isofenphos, available data from these studies are summarized in this hazard assessment.

All of the acute studies with isofenphos have been satisfied. Technical isofenphos was found to be acutely toxic when administered by oral, dermal or inhalation routes of exposure. Isofenphos produced moderate to slight irritation in the eye and dermal irritation studies, and did not induce dermal sensitization in guinea pigs. Additional acute toxicity studies were conducted with selected isofenphos metabolites. While oral toxicity of the oxon analog was similar to isofenphos, the des-isopropyl and des-isopropyl oxon analogs were slightly less toxic. The ester chloride is essentially non-toxic. It should be noted that none of the isofenphos metabolites were identified the in the rat metabolism study; they were in all likelihood present as intermediary metabolites.

The dermal toxicity in the rabbit was evaluated in two 21-day studies with formulated products [Oftanol 5G (5% granular preparation of isofenphos) and Oftanol 2 Insecticide (22% emulsion of isofenphos)] and in one subchronic, 90-day, study with technical isofenphos (92.1%). The LOEL was established by the inhibition of plasma cholinesterase (ChE) activity with the 21-day study with the granular preparation and inhibition of plasma, erythrocyte and brain ChE activities in both the 21-day study with the emulsion and 90-day study with technical isofenphos. In all three studies, there were no signs of dermal irritation.

The chronic toxicity of isofenphos was evaluated in a two-year feeding study in the dog and a combined chronic feeding/oncogenicity study in the mouse. In the dog study, clinical signs of cholinergic toxicity were observed. In the mouse study, no clinical signs, change in body weights or clinical pathology could be attributed to treatment; the tumor profiles of the treated animals were comparable to that of the control animals. In these studies, the LOEL was based on the inhibition of plasma and erythrocyte ChE in the dog and plasma ChE in the mouse.

Developmental and reproductive toxicity studies with isofenphos were carried out in the rabbit and rat. No maternal or fetal toxicity was observed in the rat developmental toxicity study. In the rabbit developmental study, maternal toxicity was limited to increased mortality, decreased body weight and body weight gain, and decreased food consumption. The reproductive toxicity study in the rat revealed clinical signs in parental animals and pup mortality. The LOELs for the developmental and reproductive toxicity studies in the rat were established by the inhibition of plasma, erythrocyte and



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brain ChE activities and for the rabbit developmental toxicity study by the inhibition of plasma and erythrocyte ChE activities.

Acute and subchronic neurotoxicity studies in the rat and acute and subchronic delayed neurotoxicity in the hen were also carried out. For the acute and subchronic neurotoxicity studies, clinical signs consistent with ChE inhibition were observed, but the LOEL was established by the inhibition of plasma, erythrocyte and brain ChE activity. In an acute delayed neurotoxicity study (graded as non-guideline by the Agency because of insufficient number of hens) and in a guideline subchronic delayed neurotoxicity, no evidence of delayed neurotoxicity was observed.

The metabolism of isofenphos in the rat revealed that essentially all of the administered dose was accounted for in the excreta, cage wash and total body. The major route of elimination was in the urine. Four major urinary metabolites were identified as 1,2-isoproxycarbonyl-phenly sulfate; 2-hydroxy-hippuric acid; 2,5-dihydroxy-isoproxycarbonyl-phenyl glucuronide; and 2-isoproxycarbonyl-phenyl glucuronide. Of the two fecal metabolites isolated, one was identified as isopropyl-salicylate and the other as unmetabolized parent compound.

In addition to studies submitted to the Agency, several open literature publications have been reviewed. A publication included a human exposure accident and four publications dealing with some of the *in vitro* and *in vivo* effects of isofenphos in the hen. These studies have been used, in part, to support the Hazard Identification Assessment Review Committee's recommendation for a developmental neurotoxicity study in the rat and retention of the 10X uncertainty factor as required by Food Quality Protection Act (FQPA).

**a. Acute Toxicity**

Acute toxicity studies provide information on the potential for health hazards that may arise as a result of short-term exposure. These data provide a basis for precautionary labeling, protective clothing requirements, and for calculation of agricultural reentry intervals. Sufficient data are available to evaluate the acute toxicity of isofenphos via oral, dermal or inhalation routes of administration. The acute toxicity data requirements 81-1 through 81-6 study in the rat are satisfied.

Results of acute toxicity studies, primary eye and dermal irritation studies and dermal sensitization study for isofenphos, technical, are summarized in the table below. The median lethal dose ($LD_{50}$) for acute oral toxicity in rats was approximately 39 to 45 mg/kg (mg isofenphos/kg body weight) in males and 28 to 32 mg/kg in females; these $LD_{50}$ values place isofenphos in Toxicity Category I for both males and females. Isofenphos was less toxic to mice, with oral $LD_{50}$ values of 127 mg/kg in males and 91.3 mg/kg in females (Toxicity Category II). A dermal toxicity study in the rat yielded $LD_{50}$ values of 191 mg/kg in the male and approximately 70 mg/kg in the female, both values resulted in Toxicity Category I for dermal exposure. Acute inhalation exposure to isofenphos resulted in a median lethal aerosol concentration of ( $LC_{50}$) of 0.21 to 0.525 mg/L in males and 0.144 to 0.273 mg/L in females, resulting in Toxicity Category II for



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both sexes. The primary eye irritation study in the rabbit showed slight conjunctival redness at 24 hours (Toxicity Category III), with complete clearing by 48 hours. Dermal application of isofenphos to rabbits produced very slight to well-defined erythema within 24 hours post-dosing, with complete recovery by 72 hours [primary dermal irritation score (PDIS = 0.42, Toxicity Category IV). Isofenphos did not induce dermal sensitization in guinea pigs.

**Acute Toxicity of Isofenphos, Technical**

| Study Type | Animal | Results | Tox Cat | MRID No |
|---|---|---|---|---|
| 81-1: Acute Oral | Rat | Male 38.7 (34.3-43.7) mg/kg<br>Female 28.0 (25.3-30.9) mg/kg | I | 96659 |
| | | Male 45 (39-53) mg/kg<br>Female 32 (28-36) mg/kg | I | 96657 |
| | Mice | Male 127 (113-143) mg/kg<br>Female 91.3 (84.9-98.2) mg/kg | II | 96659 |
| 81-2: Acute Dermal | Rat | Male 191 (143-256) mg/kg<br>Female 70 (estimated) mg/kg | I | 420300-01 |
| 81-3: Acute Inhalation | Rat | Male 0.525 mg/L (est)<br>Female 0.273 (0.199-0.374) mg/L | II | 416099-01 |
| | | Male 0.21 mg/L<br>Female 0.14 mg/L | II | 96659 |
| 81-4: Primary Eye Irritation | Rabbit | Slight conjunctival redness at 24 hrs | III | 416099-11 |
| 81-5: Primary Dermal Irritation | Rabbit | PDIS = 0.42 | IV | 416099-04 |
| | | PDIS = 0.69 | IV | 248241 |
| 81-6: Dermal Sensitization | Guinea Pig | Negative | N/A | 96657 |

Acute oral toxicity studies in the rat were also performed on selected isofenphos metabolites (table below). The acute oral $LD_{50}$ values of the oxygen metabolite (oxon) was 38 and 17 mg/kg for males and females, respectively, which were comparable to the $LD_{50}$ of the parent compound in males (38 to 45 mg/kg) but lower in females (28 to 32 mg/kg). Compared to the parent compound, the des-isopropyl oxon and des-isopropyl metabolites were both less toxic than the parent compound, with $LD_{50}$ values of 86 and 111 mg/kg, respectively, in males, and 50 and 194 mg/kg, respectively, in females. The chloride ester metabolite of isofenphos was non-toxic ($LD_{50}$ > 5000 mg/kg, Toxicity Category IV) in the male rat.



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**Acute Oral Toxicity of Isofenphos Metabolites in the Rat (MRID No.: 96657)**

| Metabolite | $LD_{50}$ (95% Conf Interval) | Tox Cat |
|---|---|---|
| Oxygen analog | Male 38 (31-48) mg/kg<br>Female 17 (14-22) mg/kg | I |
| Des-isopropyl | Male 111 (83-148) mg/kg<br>Female 194 (155-224) mg/kg | II |
| Des-isopropyl oxygen analog | Male 86 (69-108) mg/kg<br>Female 50 (44-56) mg/kg | Male: II<br>Female: I |
| Ester Cl | Male > 5000 mg/kg | IV |

**b. Subchronic Toxicity**

Subchronic toxicity testing is used to provide information on possible health hazards likely to arise from repeated exposures over a limited period of time (90-days). These studies are used to help identify target organs and can be used to select the dose levels for chronic studies.

Based on the use pattern for isofenphos, the data requirements for subchronic feeding studies in the rat [§82-1(a)] and dog [§82-1(b)] have been waived. However, acceptable 21-day dermal studies with isofenphos formulations (Oftanol 2 and Oftanol 5W) in the rabbit and a subchronic dermal toxicity study with technical isofenphos in the rabbit were available for review.

**21-Day Dermal Toxicity Studies in the Rabbit with End-Use Products**

In one 21-day dermal toxicity study (MRID No.: 40917101, HED Doc No: 007246), New Zealand White rabbits (5/sex/dose) were treated with Oftanol 2 Insecticide (22% a.i. in an emulsion) at dose levels of 0, 2.5, 10 or 40 mg/kg/day, six hours/day, five days/week, for 21 days. No treatment-related changes were noted in mean body weights or food consumption. No signs of dermal irritation were observed during the study. In high-dose females, plasma ChE activity measured at weeks 1, 2, and 3 was significantly ($p \leq 0.05$) inhibited by 21%, 24%, and 22%, respectively, while erythrocyte ChE was inhibited by 16% (not significant), 27% and 22%, respectively. At terminal sacrifice, brain ChE activity of high-dose females was significantly ($p \leq 0.05$) inhibited by 29%. Although ChE activity of high-dose males was inhibited, the value was not statistically significant.

**Based on the results of this study (inhibition of plasma, erythrocyte and brain ChE in females) the LOEL was established at 40 mg/kg/day; the NOEL was established at 10 mg/kg/day in females.**

In another 21-day dermal toxicity study (MRID No.: 40217401, HED Doc No: 006607), New Zealand White rabbits (5/sex/dose) were treated with Oftanol 5G (5% granular preparation) at dose levels of 0, 1000, 2250, or 5050 mg/kg/day (equivalent to



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0, 50, 113, or 253 mg a.i./kg/day) for 6 hours per day, 5 days/week for 3 weeks. Plasma and erythrocyte ChE activities were measured at the start of the study and after 1, 2, and 3 weeks of treatment; brain ChE was measured at terminal sacrifice. Body weights and food consumption were not affected by treatment. No signs of dermal irritation were observed during the study. After three weeks of treatment, plasma ChE of mid- and high-dose males were each inhibited by 19%, while mid- and high-dose females, by 16% and 18%, respectively. Erythrocyte ChE activity was significantly inhibited in mid- and high-dose females (20% and 16%, respectively) after two weeks of treatment. Brain ChE activity was not inhibited at any dose level.

**Based on the results of this study [inhibition of plasma (males and females) and erythrocyte (females only) ChE activity] the LOEL was established at 113 mg a.i./kg/day in both sexes; the NOEL was established at 50 mg a.i./kg/day.**

**Subchronic Dermal Toxicity**

In a subchronic dermal toxicity study (MRID No.: 42891702, HED Doc No.: 011204), male and females New Zealand white rabbits (10/dose/sex) were exposed to isofenphos (92.1%) at doses of 0, 2, 10 or 50 mg/kg/day, 6 hours/day, 5 days/week for 13 weeks. Plasma and erythrocyte ChE activities were measured on study days 28/29 (males/females); at terminal sacrifice (day 89) plasma, erythrocyte and brain ChE activities were measured.

All animals survived to terminal sacrifice without the appearance of any treatment-related clinical signs. Body weights and food consumption were also unaffected by treatment. Although statistically significant hematological and clinical chemistry changes were noted, none were outside of the historical control range, and therefore not considered to be biologically significant.

At the interim evaluation, plasma ChE activities were statistically significantly decreased, relative to the concurrent control values, in mid- and high-dose males (35% and 60%, respectively) and high-dose females (61%). Erythrocyte ChE activities were statistically lower than control values in high-dose males (46%) and mid- and high-dose females (44% and 74%, respectively). At terminal sacrifice, statistically significant decreases were noted in plasma ChE of mid- (37% in males and 21% in females) and high- (58%, males; 62% in females) dose animals, and, erythrocyte ChE of mid- (32% in males and 48% in females) and high- (71% in males and 77% in females) dose animals. Brain ChE activity was inhibited by 38 and 57% in mid- and high-dose males, respectively and by 63% in high-dose females.

At terminal sacrifice, gross pathological findings in the control, low-, mid- and high-dose animals included light red to yellow discoloration of the adipose tissue in 0/10, 1/10, 1/10 and 4/10 males, respectively, and 0/10, 3/10, 3/10, and 4/10 females, respectively. Histopathological examination, however, did not reveal any treatment-related changes in either the adipose tissue or any other tissue examined.

Statistically significant increases in absolute liver weights and the absolute and

relative adrenal weights were observed in high-dose males. The study author attributed the increases in adrenal weights to "incipient stress-related functional hypertrophy of the renal cortex as a reaction to marked inhibition of ChE activities in this dose group".

**Based on the results of the study, the NOEL for systemic toxicity was established at 50 mg/kg/day. The LOEL for systemic toxicity was not established.**

**Based on the results of the study (inhibition of plasma and erythrocyte ChE in males and females and brain ChE in males), the LOEL for ChE inhibition was established at 10 mg/kg/day. The NOEL for ChE inhibition was established at 2 mg/kg/day.**

**c. Chronic Toxicity/Carcinogenicity**

Chronic toxicity and carcinogenicity studies are used to assess the toxicity resulting from repeated exposure to a pesticide over a long period of time. These studies are designed to identify toxic and carcinogenic effects which are manifested only after a long latent period or are cumulative in nature. The results of these studies are designed to permit the determination of a no-observed-effect level, which may be used to characterize the potential risk of the pesticide to human health.

Sufficient toxicity data are available on isofenphos to assess the chronic toxicity and carcinogenic potential of isofenphos.

**1) Chronic (2-year feeding) Toxicity Study in the Dog:** In a 2-year study (MRID Nos.: 00083067, 92085010, 43198001, HED Doc Nos.: 009748, 012340), dogs (4/sex/dose) were fed diets containing isofenphos (89.3%) at dietary concentrations of 0 (basal diet), 3 ppm (males, weeks 1 to 83, females weeks 1 to 104), 2 ppm (males, weeks 84 to 104), 15 ppm (weeks 1 to 104), 75, ppm (weeks 1 to 53), 150 ppm (weeks 54 to 99), or 300 ppm (weeks 100 to 104) (equivalent to 0, 0.09, 0.45, or 4.24 mg/kg/day in males, 0, 0.1, 0.53, or 3.43 mg/kg/day in females). During the study, the high-dose level was progressively increased until clear clinical signs of toxicity were observed.

Compound-related clinical signs were observed in high-dose males and females. These animals exhibited vomiting, loose feces and signs of weakness, with males being more severely affected than females. At week 28, one high-dose male showed signs of anorexia, which persisted through the end of the study, while in another signs of anorexia appeared during the final weeks of the study. At week 88, hind limb weakness was observed in one of the affected males; by week 98, this animal became unsteady and showed additional clinical signs (drowsiness, salivation and immobility). The other high-dose male also exhibited weakness and gait abnormalities at week 100; at the end of week 100, this dog exhibited paresis of the hind limbs, trembling, sticky fur coat, salivation and protruding tongue. The clinical condition of the two high-dose males deteriorated following the increase in dose to 300 ppm at week 100. One of these high-dose males died during study week 104 and the other was sacrificed in moribund condition just prior to terminal sacrifice. These deaths were attributed to severe



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inhibition of ChE.

During the first 78 weeks of the study, body weight gains of the treated animals were comparable of control values. Overall (weeks 0 to 104) body weight gains by high-dose males, relative to concurrent control values, were decreased by 56%. Body weight gains by low- and mid-dose males and all treated females were comparable to control values.

Clinical pathological evaluations during the study included hematology, clinical chemistry and urinalysis. For high-dose animals, mean alkaline phosphatase activity was significantly increased by 166% in males and 70% in females after 66 weeks of treatment, and, 266% in males and 104% in females after 92 weeks of treatment. No treatment-related changes were noted in any of the urinalysis parameters. Slight decreases were noted in the erythrocyte counts, hematocrits and hemoglobin concentration of high-dose males. The values were, however, all within the historical control ranges for these parameters, and therefore, not considered to be biologically relevant.

Plasma and erythrocyte ChE activities were measured at the start of the study and after 14, 39, 79 and 104 weeks of treatment. At terminal sacrifice (week 104), brain ChE was also measured. After 39 weeks treatment at 75 ppm, plasma and erythrocyte ChE activities were markedly inhibited in males (74% and 60%, respectively) and females (46% and 34%, respectively). Increasing the dietary concentration of isofenphos in the high-dose diet to 150 ppm, resulted in further inhibition of plasma ChE (93% in males and 76% in females) and erythrocyte ChE (72% in males and 37% in females) activities. With the increase in the concentration of isofenphos in the high-dose diet to 300 ppm at the end of the study, severe inhibition of plasma ChE (89% in males and 87% in females), erythrocyte ChE (89% in males and 85% in females) and brain ChE (67% in both males and females) activities were observed. Treatment at 15 ppm resulted in significant inhibition of plasma ChE activities by 18 to 48% in males and 31% to 45% in females. Erythrocyte ChE activity was decreased in males (9% to 19%, not significant), while activity in females was unaffected by treatment.

**Based on the results of this study (decreased body weight gains in males and clinical signs in males and females), the LOEL for systemic toxicity was established at 75/150/300 ppm (4.24 mg/kg/day in males and 3.43 mg/kg/day in females); the NOEL was established at 15 ppm (0.45 mg/kg/day in males and 0.53 mg/kg/day) in females.**

**Based on the results of this study (plasma and erythrocyte ChE inhibition at week 39) the LOEL for ChE inhibition was established at 15 ppm in males (0.45 mg/kg/day) and females (3.43 mg/kg/day); the NOEL was established at 3 ppm (0.09 mg/kg/day in males and 0.1 mg/kg/day) in females.**

**2) Chronic Feeding and Oncogenicity Study in Mice:** Although the data requirement for carcinogenicity studies has been waived because of the intended use pattern for isofenphos, the Hazard Identification Assessment Review Committee



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reviewed a chronic feeding/carcinogenicity study in the mouse. In this study (MRID No.: 000000, HED Doc. No.: 002490), male and SPF female mice (40/sex/dose) were fed diets containing isofenphos (89.3%) at 0 (basal diet), 1, 10, or 100 ppm.

No treatment-related effects were noted in clinical signs, mortality, body weights, food consumption or routine clinical pathology. Plasma ChE activity was decreased at 10 ppm (74% in males and 78% in females) and 100 ppm (89% in males and 92% in females). Erythrocyte ChE activities were unaffected by treatment, while brain ChE activities were decreased by 46% in males and 31% in females.

Isofenphos was not carcinogenic under the conditions of this study. The tumor profiles of the treated animals were comparable to control values.

**Based on the results of this study (plasma ChE inhibition in males and females), the LOEL for ChE inhibition was established at 10 ppm (1.5 mg/kg/day, estimated). The NOEL was established at 1 ppm (0.15 mg/kg/day, estimated).**

**The LOEL for systemic toxicity and carcinogenicity was not established, while the NOEL was established at 100 ppm (15 mg/kg/day, estimated).**

**d. Developmental Toxicity Studies**

Developmental studies are designed to identify potential adverse effects in developing organisms resulting from the mother's exposure to the test material during pre-natal development. Acceptable data from rat and rabbit developmental studies satisfy the data requirements for guideline 83-3(a) and (b), respectively.

**1) Developmental Toxicity Study in the Rat**: In a developmental toxicity study (MRID No.: 42381201, HED Doc No.: 009740), pregnant CD Br rats (40/dose) were gavaged with isofenphos (91.4%) at doses of 0, 0.05, 0.45 and 4.0 mg/kg/day from gestation days (GDs) 6 to 15.

At the high-dose level, clinical signs of ChE inhibition (consisting of tremors and ear twitching) were observed in one animal on GD 13 and two other animals on GD 14. No other abnormal clinical signs were observed.

Of the parameters measured to assess developmental toxicity, mean pre-implantation losses of 4.5% and 3.1% were observed at the 0.5 and 4.0 mg/kg/day dose levels, respectively. Since these effects were lower than the control value of 21%, they were not considered to be toxicologically significant.

Fetal observations (viability indices, body weight or incidences of external, visceral and skeletal abnormalities) were not affected by treatment.

On GDs 16 (1 day postdosing) and 20 (5 days postdosing), maternal plasma, erythrocyte and brain ChE activities were evaluated; fetal brain ChE activity was measured on GD 20. On GD 16, plasma, erythrocyte and brain ChE activities were



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inhibited by 32, 20 and 16%, respectively, in mid-dose animals and 62, 73 and 71%, respectively, in high-dose animals. On the day 20 evaluations, maternal brain ChE activity was still significantly inhibited by 9.6% and 39% in mid- and high-dose animals respectively; erythrocyte ChE was significantly inhibited by 59% in high-dose animals. Fetal brain ChE activity was not affected by treatment.

**Based on the results of this study (clinical signs of ChE inhibition), the LOEL for systemic toxicity in maternal animals was established at 4.0 mg/kg/day; the NOEL was established at 0.45 mg/kg/day.**

**Based on the results of this study (plasma, erythrocyte and brain ChE inhibition), the LOEL for ChE inhibition in maternal animals was established at 0.45 mg/kg/day; the maternal NOEL was established at 0.05 mg/kg/day.**

**The LOEL for fetal toxicity was not established (> 4.0 mg/kg/day); the fetal NOEL was established at 4.0 mg/kg/day.**

**2) Developmental Toxicity Study in the Rabbit:** In another developmental toxicity study (MRID No.: 42382801& 42499601, HED Doc No.: 009896) study, New Zealand White rabbits (20/dose) were orally gavaged with isofenphos (91.4%) at dosages of 0, 0.25, 1.25, and 7.5 mg/kg/day, throughout the organogenesis period [gestation days (GDs) 6 to 18].

Clinical observations during the study revealed treatment-related effects at the high-dose level. Three does in the 7.5 mg/kg/day group died during the study, one on day 18 and two others on day 19. Two of the three animals had soft stools, diminished stool output and perianal soiling observed during the clinical evaluations.

At 7.5 mg/kg/day, statistically significant decreases in mean maternal body weights were observed on gestation days 19 (6.2%), 21 (7.1%) and 29 (6.0%). The mean body weight gain of these animals for gestation days 6 through 19 was only 0.02%, compared to the control value of 0.19% (an 89% decrease).

Necropsies were performed on animals which died during the study and all surviving animals on day 29. Incidental findings were limited to the high-dose group and included stomach erosions in two animals that died during the study and another at scheduled sacrifice. No statistically significant differences in caesarean section data were observed.

Fetal observations consisted of evaluation of body weight, viability indices, and incidences of external or visceral and skeletal abnormalities; fetal ChE activity was not measured. The mean fetal body weights of the treated animals were comparable to control values. Statistically significant observations were limited to an increase in the incidence of abnormal hyoid body or arch in the in high-dose fetuses (91%) compared to controls (76%). The litter incidence this skeletal abnormality, however, was not significantly different from the control group.

No developmental toxicity was present at the highest dose tested (7.5 mg/kg/day).

Plasma, erythrocyte and brain ChE activities were measure in maternal animals; fetal ChE activities was not determined. Plasma and erythrocyte cholinesterase activities were measured before treatment and on gestation days 19 (1 day post-treatment) and day 29 (11 days post-treatment); brain cholinesterase activity was measured on day 29. On gestation day 19, plasma and erythrocyte ChE activities were inhibited by 31% and 55%, respectively, in mid-dose animals and 69% and 88%, respectively, in high-dose animals. On day 29, plasma ChE activities were comparable to control values, while erythrocyte and brain ChE activities were both significantly inhibited in mid- (25% and 11%, respectively) and high- (48% and 22%, respectively) dose animals.

**Based on the results of this study (increased incidence of mortality, decreased body weight and body weight gain, and decreased food consumption), the LOEL for systemic toxicity in maternal animals was established at 7.5 mg/kg/day, and the NOEL, at 1.25 mg/kg/day.**

**Based on the results of this study (inhibition of plasma, erythrocyte, and brain ChE activities), the LOEL for ChE inhibition was established at 1.25 mg/kg/day; the NOEL was established 0.25 mg/kg/day:**

**Based on the results of this study, the LOEL for developmental toxicity was not established (> 7.5 mg/kg/day), the NOEL was established at 7.5 mg/kg/day.**

**e. Reproductive Toxicity**

The objective of multigeneration reproduction studies is to determine the general effects of a test material on overall reproductive capability of parental animals and the growth and development of the offspring.

In a two-generation, two litter reproduction study (MRID 41609902, HED Doc. No.: 012311) isofenphos (92.9%) was administered to Bor strain:WISW (SPF Cpb) rats (25/sex/dose) at dietary levels of 0, 1, 5, or 25 ppm (achieved doses of 0, 0.08 to 0.16, 0.44 to 0.69, or 2.21 to 3.92 mg/kg/day).

Evaluation body weights, body weight gains, food consumption, and reproductive indices did not reveal any treatment-related effects in either sex of either generation throughout the study. However, females in the high-dose group had increased mortality (12%, $F_0$ females) and increased absolute ovarian weights ($F_0$, 9%; $F_{1b}$, 12%; $p \leq 0.05$).

Reproductive toxicity was demonstrated at 5 ppm as treatment-related increases in the number of litters with small to very small pups ($F_{1b}$) and emaciated pups ($F_{2b}$). For the $F_{1b}$ mid-dose litters, treatment-related reductions were noted in the lactation index (35% vs. 64% for controls, $p \leq 0.01$) and in mean litter sizes were decreased at days 14 (3.1 vs. 5.8 for control, $p \leq 0.01$), 21 (3.0 vs 5.7 for controls, $p \leq 0.01$), and 28 (3.1 vs. 5.7 for controls, $p \leq 0.01$) . The lactation index was also decreased for the mid-dose $F_{2b}$

litters (71% vs. 90% in controls, $p \leq 0.01$).

At 25 ppm, treatment-related increases in the numbers of litters with small to very small pups ($F_{1a}$ and $F_{1b}$), cold pups ($F_{1b}$ and $F_{2b}$), and emaciated pups ($F_{2b}$) were observed. For the high-dose $F_{1a}$ and $F_{1b}$ litters, treatment-related increases were noted in the number of deaths between days 5 and 28, with related reductions in the mean litter sizes on days 14 to 28 ($F_{1a}$, 47%, $p \leq 0.01$) and 7 to 28 ($F_{1b}$, 34 to 60%, $p \leq 0.01$ or $\leq 0.05$), number of pups alive on day 28, and lactational indices ($F_{1a}$: 47% vs. 88% for controls, $p \leq 0.01$; $F_{1b}$: 12% vs. 64% for controls, $p \leq 0.01$). In addition for the $F_{1b}$ litters, a treatment-related reduction in the viability index was noted (76% vs. 97% for controls, $p \leq 0.01$). For the high-dose $F_{2b}$ litters, treatment-related reductions in the viability index (92% vs. 99% for controls, $p \leq 0.01$) and lactation index (70% vs. 90%, $p \leq 0.01$) were observed. For both generations, the total number of pups born was reduced at the high-dose; this was because of increased mortality of the $F_0$ dams and their offspring (only nine $F_{1b}$ females were available for mating) resulting in a smaller number of females which gave birth. A treatment-related reduction in pup body weights during lactation was also noted at the high-dose ($F_{1a}$, 11 to 19% $p \leq 0.01$ or 0.05; $F_{1b}$, 23 to 29%, $p \leq 0.01$).

Plasma, erythrocyte and brain ChE activities were determined on male and females $F_{1b}$ rats after the second mating (males) or after the $F_{2b}$ pups had been weaned (females). Inhibition of plasma (19% in males and 27% in females), erythrocyte (7% females only) and brain (27% in males only) ChE activities were observed in mid-dose animals. At the high-dose level, plasma, erythrocyte and brain ChE activities were inhibited by 54%, 16% and 27%, respectively, in males, and 80%, 26%, and 32%, respectively, in females.

**Based on the results of this study (inhibition of plasma and erythrocyte ChE in both sexes and brain ChE in males), the LOEL for ChE inhibition was established at 5 ppm (0.44 to 0.69 mg/kg/day), and the NOEL, at 1 ppm (0.08 to 0.16 mg/kg/day).**

**The LOEL for reproductive toxicity was established at 5 ppm (0.44 to 0.69 mg/kg/day) based on clinical signs of toxicity (small to very small and emaciated pups) and increased pup mortality (reductions in the lactation indices and mean litter sizes). The reproductive NOEL is 1 ppm (0.08 to 0.16 mg/kg/day).**

**f. Mutagenicity Studies**

The purpose of mutagenicity tests is to assess the potential of the test substance to alter genetic material. The results of the mutagenicity studies with isofenphos were reviewed and summarized below.

**1) Gene Mutations: *Salmonella typhimurium* reverse gene mutation assay:** A gene mutation assay (Ames Assay) (MRID No. 41609912, HED Doc No.: 009748) was conducted using isofenphos (92.3%) at five dose levels ranging from 667 to 10,000 $\mu$g/plate. Isofenphos at doses of 3,333 $\mu$g/plate and higher with and without S9

precipitated. The results indicated that isofenphos was neither cytotoxic nor mutagenic in any strain either with or without S9 metabolic activation.

**2) Chromosomal Aberrations: *In vitro* Chinese hamster ovary (CHO) cell chromosome aberration assay**: An *in vitro* structural chromosomal aberration study (MRID No.: 41008801, HED Doc No.: 007192) with Chinese Hamster Ovary (CHO) cells was conducted using isofenphos (91%). Isofenphos was assayed with or without S9 metabolic activation at dose levels of 0.02 to 0.16 $\mu$g/mL. The results of the assay indicated that isofenphos was cytotoxic, but was not clastogenic.

**3) Other Mutagenic Mechanisms: Unscheduled DNA synthesis (UDS) in primary rat hepatocytes**: An unscheduled DNA synthesis assay (MRID No.: 41008802, HED Doc No.: 007192) with rat hepatocytes was conducted with isofenphos (91%) at five dose levels ranging from 0.001 to 0.03 $\mu$g/mL (limit of solubility was 0.03 $\mu$g/mL). Isofenphos did not induce significant increases in mean net nuclear grain counts. Under the conditions of this assay, there was no evidence of a genotoxic effect.

**4) Summary for mutagenicity studies:** Findings of the mutagenicity studies indicated that isofenphos was not mutagenic in bacteria and not mutagenic and clastogenic in cultured mammalian cells.

**g. Metabolism**

The purpose of general metabolism testing is to obtain information on the absorption, distribution, biotransformation, and excretion of the test substance as a function of dose.

In a metabolism study (MRID No.: 42282101, HED Doc No.: 009739) [phenyl-(UL) $^{14}$C]-labeled isofenphos (>96%, 23.5 mCi/mmole) was studied in male and female Wistar rats (5/sex/group). Two groups were treated with a single oral dose of labeled test compound at either 1 mg/kg or 10 mg/kg; a third group of animals was treated daily, for 14 days, with unlabeled isofenphos at 1 mg/kg/day, followed on the 15th day by $^{14}$C-labeled isofenphos at 1 mg/kg.

The distribution of labeled residues in the tissues was determined at terminal sacrifice. In general, the tissue levels of labeled residues were higher in the females, with the highest concentration (0.605 ppm) present in the fat of the high dose females; this value was approximately ten-times higher than that of the males (0.062 ppm). In both the low and repeat dose groups, the accumulation of labeled residues in the kidneys was approximately three-times higher in females than in males.

Essentially all of the administered isofenphos was eliminated within the first 48 hours. Urinary elimination accounted for 80 to 94% of the administered dose, while less (5 to 18%) was present in the feces. Essentially all (> 96%) of the administered radioactivity was accounted for in the excreta, cage wash and total body.

Identification of $^{14}C$-labeled metabolites was carried out using pooled (0-48 hour) urinary and fecal samples. Of the total radioactivity recovered, 64 to 74% of the urinary metabolites and 1 to 12% of the fecal metabolites were identified. Four major urinary metabolites (% of administered dose) were isolated and identified as 1,2-isoproxycarbonyl-phenly sulfate (32 to 54%); 2-hydroxy-hippuric acid (1.5 to 12%); 2,5-dihydroxy-isoproxycarbonyl-phenyl glucuronide (5 to 11%); and 2-isoproxycarbonyl-phenyl glucuronide (8.2 to 18%). Of the two fecal metabolites isolated, one was identified as isopropyl-salicylate (0.7 to 1.5%) and the other as unmetabolized parent compound (0 to 11%). Unidentified urinary metabolites accounted for 18 to 20% of the total, while unidentified fecal metabolites accounted for approximately 2 to 6%. The unidentified percentage consisted of many metabolites, none of which exceeded 10% of the total radioactivity recovered.

Compared to the other metabolites, the sulfate metabolite, 2-isopropoxy-carbonylphenyl sulfate, was present in the highest percentages. Sulfation appears to be more active in males than in both the single low-dose (41% in males and 32% in females) and repeat low-dose (54% in males and 39% in females). Animals in the high dose group, the percentage of sulfated residues were comparable in both males (49%) and females (45%), suggesting that the arylsulfotransferase reaction was saturated.

The proposed pathway for the metabolic degradation shows that isofenphos is first metabolized to isopropyl salicylate, which then undergoes secondary metabolism to sulfate, glucuronide and glycine conjugates. Another metabolite, 2-hydroxyhippuric acid, formed by the conjugation of glycine with isopropyl salicylate, was present in low amounts.

**h. Neurotoxicity Studies**

Neurotoxicity studies are designed to identify acute, subchronic and/or delayed neurotoxic effects. While all chemicals are evaluated for major neurobehavioral and neuropathological effects in the acute and subchronic neurotoxicity screening batteries in rats; organophosphates are also evaluated for delayed neurotoxicity in adult hens.

**1) Acute Neurotoxicity Study in the Rat:** In an acute neurotoxicity study in the rat (MRID No.: 44285601, HED Doc No.: 012306), male and female Wistar rats (12/sex/dose, main study; 6/sex/dose, ChE substudy) were fasted overnight and then orally gavaged once with isofenphos (92.5%) at nominal doses of 0 (vehicle), 2, 8, or 15 mg/kg (analytically confirmed doses: 0, 2.6, 7.9 or 13.8 mg/kg, respectively). Main study animals were evaluated for neurobehavioral effects [functional observational battery (FOB) and motor activity] on day 0, at the peak time-of-effect [1 hr.50 min (minimum) in males and 5 hr (minimum) in females] and days 7 and 14. Movement in the activity chambers was measured as motor activity (rearings, head movements, etc) and locomotor activity (walking within the chamber). Neuropathological evaluations were carried out on day 14 on six animals/sex/dose; animals were perfusion-fixed *in situ*. The ChE substudy group was used for determination of plasma, erythrocyte and brain ChE activities at the peak time-of-effect on day 0.

Clinical signs and FOB evaluations were consistent with acute cholinergic toxicity. At the mid-dose level, gait abnormalities and involuntary motor movements were observed in males and females. In high-dose males and females, a higher incidence of these findings was observed along with uncoordinated righting reflex, decreased number of rearings, decreased forelimb and hindlimb grip strength and decreased body temperature. No reaction to the approach response was noted in 4/12 high-dose males. In general, the onset of clinical signs was sooner in males (4 hr) than in females (8 hrs), but did not last as long (day 6 in males and day 7 in females).

Mean body weighs and body weight gains were decreased in high-dose males and females. At day 7, the body weights of high-dose males and females were 11% and 7% lower, respectively, than the concurrent control values. By day 14, males regained some, but not all, of the decrement in body weight; the mean body weight was, however, still significantly lower than the concurrent control value. At the end of the study, the mean body weight of high-dose females was comparable to the control value. For high-dose animals, body weight gains for days 0 to 7 was 38% lower in males and 37%, in females. Overall body weight gain (day 0 to 14) for high-dose males was 18% lower, while that of high-dose females was comparable to the control value.

At the peak time-of-effect, high-dose animals had decreased motor activity (58% in males and 64% in females) and locomotor activity (79% in males and 85% in females). The day 7 evaluation of high-dose animals showed a decrease in motor activity of 28% (not significant) in females and decreased locomotor activity of 29% (not significant) in males and 34% ($p \leq 0.05$) in females.

Plasma, erythrocyte and brain ChE were all statistically significantly ($p \leq 0.01$) decreased in low- mid- and high-dose males and females at the peak time-of-effect on day 0. At the low-dose level, plasma, erythrocyte and brain ChE activities were decreased 59, 18 and 10%, respectively, in males and 89, 55 and 21%, respectively, in females; at the mid-dose level, 85, 68, and 51%, respectively, in males and 97, 89, and 69%, respectively, in females; and at the high-dose level, 94, 95, and 83%, respectively, in males and 98, 98, and 85%, respectively, in females.

At terminal sacrifice, gross and neuropathological findings of treated animals were comparable to control animals.

**Based on the results of this study [inhibition of plasma, erythrocyte and brain ChE with clinical signs (muscle fasciculations) in females], the LOEL was established at 2 mg/kg; the NOEL was not established.**

**2) Subchronic Neurotoxicity Study in the Rat:** In a subchronic neurotoxicity study (MRID No.: 44236601, HED Doc No: 012306), male and female Wistar rats (12/sex/dose) were fed diets containing isofenphos (91.6%) at 0 (basal diet ), 1, 25, or 125 ppm (mg/kg/day equivalents: 0, 0.06, 1.62, or 8.45 in males and 0, 0.09, 2.07, or 11.54 in females) for at least 13 weeks. Neurobehavioral evaluations, consisting of FOB and motor activity measurements, were performed at prestudy and after 4, 8 and 13 weeks of treatment. Gross pathology (all animals) and neuropathological



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(6/sex/dose) examinations were carried out at terminal sacrifice. Six animals/sex/dose were selected for determination of plasma and erythrocyte ChE activities at week 4 and plasma, erythrocyte and brain ChE activities at week 14.

Treatment-related, clinical signs, consistent with cholinergic toxicity, were observed in high-dose males and females. High incidences of saltatory spasms and non-specific behavioral disturbances (females only) were observed during the entire study; additionally, males and females showed piloerection and tremors during the first two to four weeks of treatment. Ophthalmological examination at week 13 also revealed a slow pupillary reflex in five high-dose females. No treatment-related clinical signs were observed in the low and mid-dose groups. All animals survived to terminal sacrifice.

Body weights and body weight gains were adversely affected in high-dose males and females. During the first six to seven weeks of treatment, mean body weights were decreased 9 to 14% in males and 8 to 15% in females. By the end of the study, however, the mean body weights of treated animals were comparable to control values. Treatment-related decreases in body weight gains were also observed. During the first week of treatment, statistically significant deceases in body weight gain was observed in males (51%) and females (0%, no weight gain). The decreased body weight gains appear to be a result of decreased food consumption (19% in males and 35% in females). Excluding the body weight data for the first week of the study, the body weight gains for weeks 1 to 13 were comparable to the control values in males and 11% greater than control value in females.

Neurobehavioral evaluations revealed treatment-related effects in high-dose males and females, with females being more affected than males. Treatment-related FOB effects consisted in part, of muscle fasciculations in both sexes and abnormal gait and decreased grip strength in females. Motor and locomotor activities were significantly decreased in high-dose females.

The incidences of gross and neuropathological finding of treated animals were comparable to controls.

Plasma, erythrocyte and brain ChE activities of mid- and high-dose animals were all significantly decreased. The evaluations at week 4 for mid-dose animals showed significant decreases in plasma (54% in males and 84% in females) and erythrocyte (64% in males and 81% in females) ChE activities. At week 14, mid-dose animals had decreases in plasma, erythrocyte and brain ChE activities of 54, 63 and 32% in males and respectively, and 88, 66 and 60% in females, respectively. At week 4, high-dose animals had decreases in plasma and erythrocyte ChE activities of 85 and 98%, in males, respectively and 97 and 100% (complete inhibition) in females, respectively. At week 14, plasma, erythrocyte and brain ChE activities of high-dose animals were decreased 84, 96, and 75% in males, respectively and 97, 97, and 89% in females, respectively.

**Based on the results of this study (inhibition of plasma, erythrocyte and brain ChE), the LOEL was established at 25 ppm (1.62 mg/kg/day in males, 2.07**

**mg/kg/day in females); the NOEL was established at 1 ppm (0.06 mg/kg/day in males, 0.09 mg/kg/day in females).**

**3) Subchronic Delayed Neurotoxicity Study in the Hen**: In a subchronic delayed neurotoxicity study (MRID Nos.: 00146887, 40459701, 41074101, HED Doc Nos: 005435, 006808, 007612), hens (10/group) were assigned to control groups [vehicle-treated and naive, untreated], isofenphos (92.5%) treatment groups, 0.25, 1.00 and 2.00 mg a.i./kg/day, or a positive control group [TOCP (tri-o-tolyl phosphate (TOCP) at 5 mg/kg/day]. Hens were treated daily by oral gavage for 90 days.

Mean body weights were significantly decreased at 2.0 mg/kg/day from week 1 through 13; non-significant decreases were observed in the positive control hens.

At day 26, plasma ChE activity was significantly decreased by 53% at 1 mg/kg/day and 65% at 2 mg/kg/day. At 2 mg/kg/day, erythrocyte ChE activity was significantly decreased by 24% on day 26. On day 55, whole blood ChE activity was decreased by 25% at 1 mg/kg/day and 36% at 2 mg/kg/day.

Compared to the vehicle control hens, isofenphos at 2 mg/kg/day did not produce any appreciable neuropathological effects in hens. There were no indications of delayed neurotoxicity due to isofenphos treatment. TOCP treatment produced the expected neural degeneration indicative of its delayed neurotoxicity in both the peripheral and central neurons.

**i. Dermal Absorption**

No study available

**j. Other Toxicological Considerations: Non FIFRA, Open Literature Publications**

**1) Human accidental exposure incident:** In a publication by Catz *et al.* (J. Neurology, Neurosurgery, and Psychiatry 51: 1338-1340, 1988), late onset neuropathy was described in an agricultural worker following the accidental ingestion of few milliliters of a mixture of isofenphos (0.75 mg/ml) and Maneb (2.0 mg/ml). The worker was treated by a physician with atropine and taken to a local hospital. Since there were no clinical signs of cholinergic toxicity and the serum ChE value was within the normal range, the worker was discharged. Cholinergic signs of toxicity (weakness, dyspnea, vomiting) developed within several hours of the exposure with recovery by 16 hours. The worker developed pain in the calves and gait impairment two weeks after the exposure and was readmitted to the hospital after three weeks. Clinical evaluation over the next few weeks revealed abnormal electromylographs and nerve conduction tests. These findings were described at distal, mainly axonal, motor neuropathy.

Although the toxicity was attributed to isofenphos, the worker was exposed to mixture of pesticides, making identification of the causative agent unclear. Additionally, prior-exposure to pesticides and medical history of the worker were not given in the



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publication.

**2) *In vitro* and *in vivo* studies with isofenphos and selected metabolites:** Chow *et al.* (Toxicol. Appl. Pharmacol. 83: 178-183 (1986) evaluated isofenphos and some of its metabolites for their ability to inhibit neurotoxic esterase (NTE) *in vitro*. This study showed that metabolic activation of isofenphos was necessary for the formation of NTE-inhibiting substance(s). Without metabolic activation, isofenphos and the oxon metabolite (an unexpected finding) were essentially inactive and inhibited NTE by 0.0% and 1.3%, respectively. Another metabolite, des-N-isopropyl isofenphos inhibited NTE by 16%, while des-N-isopropyl isofenphos oxon inhibited NTE by 99%. With microsomal activation, NTE was inhibited by 20%, 80%, and 73% for isofenphos, isofenphos oxon, des-N-isopropyl isofenphos, respectively (des-N-isopropyl isofenphos oxon was not assayed).

Isofenphos metabolites were further studied *in vivo* for their ability to cause delayed neurotoxicity in chickens. Chickens were dosed subcutaneously with a single dose with isofenphos oxon at 10, 25, 50, or 75/100 mg/kg or des-N-isopropyl isofenphos at 10, 25, or 50 mg/kg. Four weeks post-dosing, isofenphos oxon produced slight ataxia at 50 mg/kg and paralysis at 75/100 mg/kg. Des-N-isopropyl isofenphos produced ataxia at 25 mg/kg and paralysis at 50 mg/kg. Based on the results of these studies, des-N-isopropyl isofenphos oxon was proposed as the possible neurotoxic metabolite of isofenphos.

**3) Delayed neurotoxicity study in the hen:** In another publication, Francis *et al.* (J. Environ. Sci. Health B20(1): 73-95, 1985; also reviewed by EPA: Accession No.: 258240, HED Doc No.: 005428), hens were evaluated for neurotoxicity toxicity after repeated dermal dosing with isofenphos at 4.7, 4.9 or 5.2 mg/kg/day (1 hen/dose). Isofenphos was extracted from commercial sample of Amaze® granular insecticide (purity of final product not given) and formulated in xylene and 2% Triton X-100. Hens were unprotected by atropine and 2-PAM during the study. During treatment, hens were scored for the development of ataxia, ranging from irregular gait (T-1), ataxia (T-2), severely ataxic (T-3) to paraplegia (T-4). Dosing was discontinued when a hen became severely ataxic (T-3), and not started again until the hen recovered.

Hens were treated for 18 to 52 days, with ataxia occurring either during treatment or shortly after treatment was stopped. The hens progressed to paraplegia after 20 to 59 days, with death occurring one to two days later. Only one hen survived long enough after cession of dosing to experience a gradation in neurotoxic responses from T-3 to T-4. Ataxia seen in hens was a result of cumulative toxicity, and probably not due to delayed neurotoxicity. No histopathology or determination of NTE activity were performed in this study.

Deficiencies noted in the EPA review included: 1) too few hens were used (4 for oral study, 3 for dermal), 2) neurohistopathological evaluations were not performed, 3) hens were too young (6-7 months vs 8-14 months). This study was not submitted to satisfy regulatory requirements.

**4) Evaluation of the neuropathic potential of isofenphos in hens:** In another publication (Wilson *et al.* (Bull. Environ. Contam. Toxicol. 33: 386-394, 1984) the neuropathic potential of isofenphos was evaluated in hens. Hens protected with atropine/2-PAM survived a lethal challenge of isofenphos at 100 mg/kg (15 to 20 times the $LD_{50}$); symptoms consistent with organophosphate-induced delayed neuropathy (OPIDN) were observed. Although the hens had regained their ability walk, 10 to 14 days after the isofenphos challenge, the condition of the hens progressed to symptoms of leg ataxia and paralysis. NTE activity in the brains of hens, challenged with 100 mg/kg isofenphos, was inhibited by 64% one day dosing and 85% after three days. Histopathologic evaluation of the most severely affected hens revealed lesions in the peripheral and central nervous systems; similar lesions were observed in TOCP-treated (positive control) hens.

Although isofenphos appears to induce delayed neuropathy in hens, it should be noted that the doses used in this study greatly exceed those recommended for Agency guideline delayed neurotoxicity studies. Although the results obtained from unconventional studies such as this are scientifically intriguing, isofenphos, when evaluated using Agency-approved protocols, did not induce delayed neuropathology in the subchronic hen study.

**2. Dose/Response Assessment**

On October 23 and 30, 1997 and December 10 and 17, 1997 (document dated January 13, 1997), the Health Effects Division Hazard Identification Assessment Review Committee evaluated the toxicology data base for isofenphos and selected doses and endpoints for acute dietary, chronic dietary (RfD) as well as occupational and residential exposure risk assessments [short-, intermediate and long-term exposure (dermal and inhalation)], assessed the carcinogenic potential and addressed the sensitivity of children and infants from exposure to isofenphos as required by the Food Quality Protection Act (FQPA).

**a. Special Sensitivity to Infants and Children**

Under P.L. 104-170, FQPA was promulgated as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA). This directed the Agency to "ensure that there is a reasonable certainty that no harm will result to infants and children" from aggregate exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this reasonable certainty of no harm, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Pursuant to the language and intent of the FQPA directive regarding infants and

children, the applicable toxicity database for isofenphos was evaluated by the Hazard Identification Assessment Review Committee. The following discussion represents the information that was considered and the conclusions that were drawn by the Committee:

**1) Adequacy of the data**: The data base for isofenphos included an acceptable two-generation reproduction studies in rats and prenatal development toxicity studies in rats and rabbits, meeting the FIFRA basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. Additionally, the Committee reviewed several open literature publications which suggested that isofenphos caused delayed neuropathy in the hen.

**2) Susceptibility issues:** In evaluating the susceptibility issues for isofenphos and the recommendation for a developmental neurotoxicity, the Hazard Identification Assessment Review Committee reviewed the toxicology database for studies submitted to the Agency and open literature publications dealing with the development of delayed neurotoxicity in a human exposure and three studies in the hen.

**(i) The Hazard Identification Assessment Review Committee evaluated the following evidence to support the recommendation for a developmental neurotoxicity study:**

- Administration of isofenphos, like most other organophosphate pesticides, to various species results in plasma, erythrocyte and brain ChE inhibition.

- Isofenphos is considered to be relatively acutely toxic, with oral $LD_{50}$ values ranging from 29 to 39 mg/kg in two rat studies and from 91 to 127 mg/kg in a mouse study. The dermal $LD_{50}$ ranged from 70 to 191 mg/kg in rats and 315 to 1172 mg/kg/day in rabbits. The $LC_{50}$ for inhalation exposure ranged from 0.14 to 0.53 mg/L over 5 separate studies.

- A report of delayed neuropathy in an agricultural worker [see section I.1) above] described clinical manifestations, electromylographs, and nerve conduction assays which suggested a pathology of a distal, mainly axonal, motor neuropathy following accidental isofenphos ingestion.

- In a non-guideline open literature publication, isofenphos was shown to inhibit NTE at very high concentrations in an *in vitro* chicken brain assay [section I.2), above]. This group also demonstrated that oxon and des-N-isopropyl metabolites of isofenphos, at very high doses, produced symptoms of delayed neurotoxicity in hens.

**(ii) The Hazard Identification Assessment Review Committee evaluated the following evidence which were insufficient to support the recommendation for a developmental neurotoxicity study:**

- In two guideline developmental toxicity studies in the rat and rabbit, no evidence

that isofenphos produced developmental abnormalities in the fetal nervous system at maternally toxic oral doses (4.0 mg/kg/day in the rat and 7.5 mg/kg/day in the rabbit).

- In the developmental toxicity study in the rat, evaluation of fetal brain ChE at gestation day 20 was not different from the control value, although in maternal, erythrocyte and brain cholinesterase were significantly inhibited at that time point.

- In guideline acute and subchronic neurotoxicity studies in the rat, there was no evidence that isofenphos produced alterations in either brain weight or the incidence of neuropathological lesions.

- In a guideline subchronic delayed neurotoxicity study in the hen, there was no evidence for the development of OPIDN.

**3) Uncertainty factor (UF)**: The Committee determined that for isofenphos the 10-fold uncertainty factor for the protection of infants and children would be retained because of the lack of a developmental neurotoxicity study in rats.

**4) Recommendation for a developmental neurotoxicity study**: Based on the evaluation of the toxicology database, the Hazard Identification Assessment Review Committee determined that a developmental neurotoxicity study in rats is required for isofenphos in order to assess functional development following prenatal exposure. This is considered a data gap for the assessment of the effects of isofenphos following *in utero* and/or early postnatal exposure.

**b. Reference Dose (RfD)**

$$RfD = \frac{0.08 mg/kg/day (NOEL)}{1000 (UF)} = 0.00008 mg/kg/day$$

**Critical Study:** 2-Generation Reproductive Toxicity Study in Rats (83-4), MRID 41609902 [see section B.1.e, above].

**Endpoint and Dose Selected for Use in Risk Assessment**

The NOEL for parental animals was established at 1 ppm (0.08 to 0.16 mg/kg/day); the LOEL was established at 5 ppm (0.44 to 0.69 mg/kg/day) based on inhibition of plasma and erythrocyte ChE in both sexes and brain ChE in males.

Further, the reproductive NOEL is 1 ppm (0.08-0.16 mg/kg/day), based on clinical signs of toxicity (small to very small and emaciated pups) and increased pup mortality (reductions in the lactation indices and mean litter sizes) observed at 5 ppm (0.44-0.69 mg/kg/day).

**Uncertainty Factor (UF)**: A UF of 1000 was applied; this includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability. An additional UF of 10 was recommended because of FQPA considerations.

**Comments and Rationale**: The NOEL and the effects observed in this study are supported by similar findings (ChE inhibition) in the chronic dog study (MRID No. 92085016, 43198001).

**Chronic Dietary Risk Assessment:** There is potential for chronic dietary exposure to isofenphos from drinking water sources. A screening level chronic dietary risk assessment for isofenphos in drinking waster sources is required. A chronic dietary (food source) risk assessment is not required for isofenphos because currently there are no isofenphos end-use products registered for food/feed uses; thus, there is no potential for chronic dietary exposure to isofenphos from food sources at this time.

**c. Acceptable Daily Intake (FAO/WHO)**

Isofenphos was evaluated for acceptable daily intake (ADI) in 1986 (87 JMPR 1986). The estimate of the ADI for humans was established at 0 to 0.001 mg/kg. The ADI was based on a no effect level for plasma ChE inhibition of 1 ppm (equivalent to 0.05 mg/kg/day) in both the rat and dog and an uncertainty factor of 50.

**d. Carcinogenicity Classification and Risk Quantification:** At an October 30, 1997 meeting, the Hazard Identification Assessment Review Committee, based on the toxicology data available, determined that isofenphos did not alter the spontaneous tumor profile in the mouse under the testing conditions. Therefore, it was recommended that isofenphos be classified as a **"Group E"**, indicating evidence of non-carcinogenicity for humans; i.e., the chemical is characterized as **"Not Likely"** to be carcinogenic in humans via relevant routes of exposure.

This weight of the evidence judgement was largely based on the absence of significant tumor increases in an adequate carcinogenicity study in mice [see section B.1.c.2), above]. This classification was also supported by the lack of mutagenic activity in several mutagenicity assays [see sections B.1.f.1), 2), and 3), above].

It should be noted, however, that designation of an agent as being in **"Group E"** or **"Not Likely"** was based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

**e. Dermal Absorption**: There were no dermal absorption studies appropriate for use for the purpose of risk assessment. Therefore, the default value of 100% will be used for the dermal absorption rate.

**f. Other Toxicological Endpoints for Use in Human Risk Assessment**

**1) Acute Dietary Exposure (one day)**



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**Critical Study**: Acute Oral Neurotoxicity Study in Rats (81-8), MRID No. 44285601 [see section B.2.h.1), above].

**Endpoint and Dose Level Selected for Use in Risk Assessment**: The NOEL was not established in this study. The LOEL is 2.0 mg/kg/day based on inhibition of plasma, erythrocyte and brain ChE with clinical signs (muscle fasciculation) in females.

**Uncertainty Factor (UF)**: The Committee determined that the 10X factor to account for enhanced sensitivity to infants and children (as required by FQPA) should be retained. For acute dietary risk assessment, a MOE of 3000 is required. This MOE is based on a UF of 100 to account for both interspecies extrapolation and intraspecies variability, an additional UF of 3 to account for the lack of a NOEL, and a UF of 10 for FQPA considerations.

**Comments:** The effect of concern is the acute inhibition of ChE, which this study demonstrates, and the length of the study (acute exposure) is appropriate for the exposure scenario.

**Acute Dietary Risk Assessment**: There is a potential for acute dietary exposure to isofenphos from drinking water sources. An acute dietary (food source) risk assessment in not required for isofenphos because currently there are no isofenphos end-use products registered for food/feed uses; thus, there is no potential for acute dietary exposure from food sources at this time. However,.a screening level acute dietary risk assessment for isofenphos in drinking water is required.

**2) Short Term Occupational or Residential Exposure (1-7 days)**

**Critical Study**: Acute oral neurotoxicity study (81-8), MRID No. 44285601 [see section B.1.h.1), above].

**Endpoint and Dose Level Selected for Use in Risk Assessment**: The NOEL was not established in this study. The LOEL is 2.0 mg/kg/day based on inhibition of plasma, erythrocyte and brain ChE inhibition in both sexes with clinical signs (muscle fasciculation) in females.

**Uncertainty Factor (UF)**: A UF of 3000 was applied; this includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability, an additional UF of 3 to account for the lack of a NOEL, and an additional UF of 10 for FQPA considerations.

**Comments**: Although two 21-day and a 90-day dermal toxicity studies were available on isofenphos, and although these studies cover the time points of 1-7 days, the Committee recommended the use of an oral study for this purpose. This conclusion was based on the fact that the 21-day dermal toxicity studies were conducted with isofenphos formulations not with the technical material (in the rabbit), and the 90-day dermal toxicity study, though conducted with the technical material, was also performed in the rabbit. The rabbit is considered inappropriate to conduct dermal studies with



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organophosphorus compound requiring metabolic activation, i.e., thiophosphates, phosphorothioates, and phosphorodithioates which are normally activated to the corresponding phosphates by the hepatic microsomal enzymes. (Robert Zendzian, HED memo dated March 31, 1997).

Because of the lack of a dermal absorption study and because of the similarity of toxic effects via the oral and dermal routes as evidenced in several acute oral and dermal toxicity studies, the Committee recommended the use of a dermal absorption rate of 100%. The Committee recommended that the dermal absorption rate may be changed with the submission and favorable review of either a 21-day dermal study with technical isofenphos in the rat or a dermal penetration study in the rat.

**Short- and Intermediate-Term Occupational and Residential Risk Assessment**: Based on the currently registered use pattern, short-term occupational and residential risk assessment is required.

**3) Intermediate Term Occupational or Residential Exposure (one week to several months)**

**Critical Study**: Subchronic Neurotoxicity Screening Study in Wistar Rats (82-7), MRID No.: 44236601 [see section B.1.h.2), above].

**Endpoint and Dose Level Selected for Use in Risk Assessment**: The NOEL of 1 ppm (0.06 mg/kg/day, males; 0.09 mg/kg/day, females), based on inhibition of plasma, erythrocyte and brain ChE observed at the next higher dose level of 25 ppm (1.62 mg/kg/day, males; 2.07 mg/kg/day, females).

**Uncertainty Factor (UF)**: A UF of 1000 was applied. This includes a UF of 100X to account for both interspecies extrapolation and intraspecies variability and 10X to account for enhanced sensitivity of infants and children (as required by FQPA) was retained.

**Comments and Rationale**: See comments and rationale for Section 2.f.2), above, for the explanation of why an oral toxicity was used for dermal risk assessment although dermal studies were available covering the range of 1-90 days, and what is the dermal absorption rate to be used for the derivation of the dermal equivalent dose in this case and why.

**4) Chronic Occupational and Residential Exposure (Non-cancer)**

**RfD = 0.00008 mg/kg/day**

**Critical Study**: 2-Generation Reproductive Toxicity Study in Rats (83-4), MRID 41609902 [see section B.1.e, above]

**Endpoint and Dose Selected for Use in Risk Assessment**



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For parental animals; the ChE NOEL was established at 1 ppm (0.08 to 0.16 mg/kg/day); the LOEL was established at 5 ppm (0.44 to 0.69 mg/kg/day) based on inhibition of plasma and erythrocyte ChE in both sexes and brain ChE in males.

Further, the reproductive NOEL is 1 ppm (0.08-0.16 mg/kg/day), based on clinical signs of toxicity (small to very small and emaciated pups) and increased pup mortality (reductions in the lactation indices and mean litter sizes) observed at 5 ppm (0.44-0.69 mg/kg/day).

**Uncertainty Factor (UF)**: A UF of 1000 was applied; this includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability. A UF of 10X to account for enhanced sensitivity of infants and children (as required by FQPA) was retained.

**Comments and Rationale:** The NOEL and the effects observed in this study (ChE inhibition) are supported by similar findings in the chronic dog study [see Section B.1.c.1 above for details].

**Chronic Occupational and Residential (non-cancer) Risk Assessment:** Based on the currently registered use pattern, chronic dermal exposure in not anticipated and thus the long term dermal risk assessment is not required.

**5) Inhalation Exposure (variable duration)**

For the purpose of inhalation risk assessment of short and intermediate duration, the Committee recommended that the inhalation exposure be converted from mg/L to the equivalent mg/kg/day dose assuming an inhalation absorption rate of 100%. This dose should be compared to the oral LOEL of 2 mg/kg/day from the acute neurotoxicity study [see section B.1.h.1), above], in the case of short term and compared to the oral NOEL of 0.06 mg/kg/day from the subchronic neurotoxicity study [see section B.1.h.2), above] in the case of the intermediate-term risk assessment. Based on the use pattern and exposure profile, the Committee determined that the long-term inhalation risk assessment would not be required.

A UF of 3000 was recommended for the short-term exposure. This includes a UF of 100 to account for both interspecies extrapolation and intraspecies variability, an additional UF of 3 to account for the lack of a NOEL, and the 10X factor for enhanced sensitivity of infants and children (as required by FQPA) was retained.

An UF of 1000 was recommended for the intermediate-term exposure. This includes an UF of 100 to account for both interspecies extrapolation and intraspecies variability, and the 10x factor for enhanced sensitivity of infants and children (as required by FQPA) be retained.

**Comments and Rationale**: Since there was no appropriate subchronic inhalation study, but there was concern about potential inhalation exposure, the inhalation exposure was converted to an equivalent oral dose assuming 100% lung absorption.

This was added to the dermal exposure (after assuming 100% dermal absorption) and compared to the oral neurotoxicity endpoint of either 2 or 0.06 mg/kg/day depending on the exposure duration.

### 6) Aggregate Risk

Because of the similarity of the endpoints identified both in the dermal and inhalation exposure, i.e. ChE inhibition, the following equation is appropriate in expressing the aggregate risk for isofenphos.

$$\textit{Combined Dermal and Inhalation Risk} = \frac{1}{\frac{1}{MOE_{dermal}} + \frac{1}{MOE_{inhalation}}}$$

**SUMMARY of TOXICOLOGICAL ENDPOINTS for Isofenphos**

| Exposure Duration | Exposure Route | Endpoint and Toxicological Effect | MOE |
|---|---|---|---|
| Acute | Dietary | NOEL = not established, LOEL = 2 mg/kg<br><br>Uncertainty Factors 10x = Interspecies<br>10x = Intraspecies<br>10x = FQPA<br>3x = Lack of NOEL (FIFRA)<br><br>Based on inhibition of plasma, erythrocyte and brain ChE activity in an acute neurotoxicity study in the rat | 3000 |
| Short-Term (1-7 Days) Occupational/Residential | Dermal and Inhalation | NOEL = not established, LOEL = 2 mg/kg<br><br>Uncertainty Factor 10x = Interspecies<br>10x = Intraspecies<br>10x = FQPA<br>3x = Lack of NOEL (FIFRA)<br><br>Based on inhibition of plasma, erythrocyte and brain ChE activity in an acute neurotoxicity study in the rat. Assume 100% dermal and inhalation absorption. | 3000 |
| Intermediate-Term (7-90 days) Occupational/Residential | Dermal and Inhalation | NOEL = 0.06 mg/kg/day, males; 0.09 mg/kg/day, females<br><br>Uncertainty Factor 10x = Interspecies<br>10x = Intraspecies<br>10x = FQPA<br><br>Based on inhibition of plasma, erythrocyte and brain ChE activity in a subchronic neurotoxicity study in the rat. Assume 100% dermal and inhalation absorption. | 1000 |

ATTACHMENT 4: Occupational and Residential Exposure Assessment. Jonathan Becker (02/18/98)



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February 18, 1998

MEMORANDUM

SUBJECT: OCCUPATIONAL AND RESIDENTIAL EXPOSURE ASSESSMENT AND RECOMMENDATIONS FOR THE REREGISTRATION ELIGIBILITY DECISION DOCUMENT FOR ISOFENPHOS

FROM: Jonathan Becker, Ph.D., Environmental Health Scientist
Reregistration Branch II
Health Effects Division (7509C)

TO: Margaret Rice / Ruby Whiters
Accelerated Reregistration Branch
Special Review and Reregistration Division (7508W)

THRU: Alan Nielsen, Senior Scientist
Reregistration Branch II
Health Effects Division (7509C)

Please find attached the the occupational and residential exposure assessment for Isofenphos.

DP Barcode: D242474

Pesticide Chemical Codes: 109401

EPA Reg Nos: 4-361, 70-271, 538-162, 538-225, 557-1995, 557-1996, 557-1997, 557-2008, 557-2009, 769-822, 769-830, 829-257, 869-203, 961-343, 961-344, 961-351, 3125-326, 3125-330, 3125-331, 3125-339, 3125-342, 3125-350, 3125-435, 7401-410, 8660-15, 8660-131, 8660-137, 8660-142, 9198-76, 9198-88, 10404-45, 10404-47, 28293-272, 32802-23, 32802-25, 34704-249, 35512-22, 51036-157, and 52287-4.

EPA MRID No.: N/A

PHED: Yes, Version 1.1

## Summary of Toxicity Concerns Impacting Occupational and Residential Exposures

### Acute Toxicology Categories

The toxicological data base for isofenphos is adequate and will support reregistration. Guideline studies for acute toxicity indicate that the technical grade of isofenphos is classified as category I for acute oral toxicity, category I for acute dermal toxicity, category III for primary eye irritation, category IV for primary skin irritation, and category II for acute inhalation toxicity. Isofenphos is not classified as a skin sensitizer.[4]

### Other Endpoints of Concern

The isofenphos hazard identification committee report, dated January 6, 1998, indicates that there are toxicological endpoints of concern for isofenphos. Dermal endpoints of concern have been identified for short-term and intermediate-term dermal exposures. The short-term dermal LOEL was 2 mg/kg/day based on inhibition of plasma, RBC and brain cholinesterase inhibition with clinical signs (muscle fasciculation) in females. The intermediate-term dermal NOEL was 0.06 mg/kg/day (1 ppm) based on inhibition of plasma, RBC and brain cholinesterase inhibition seen at the next higher dose level of 25 ppm. The above endpoints were based on oral studies. No appropriate dermal absorption study was available; therefore, the default value of 100 percent was indicated for the dermal absorption rate.[4]

The short- and intermediate-term endpoints of 2 mg/kg/day and 0.06 mg/kg/day, respectively, were also identified as inhalation endpoints for isofenphos. No appropriate inhalation studies were available; therefore, inhalation exposure was converted to an equivalent oral dose, assuming 100 percent lung absorption. A body weight of 70 kg was used to calculate the short- and intermediate-term doses.

An uncertainty factor (UF) of 100 was applied to account for both interspecies extrapolation and intraspecies variablilty. An additional factor of 10X was retained in accordance with the Food Quality Protection Act (FQPA) related to concerns for neurotoxicity and neuropathy and the need for a developmental neurotoxicity study. An UF of 3 was also required under FIFRA for the short-term endpoint to account for the lack of a NOEL. Because of these committee recommendations, MOEs of 3,000 and 1,000 were used for the short- and intermediate-term risk assessments, respectively.

Because the dermal and inhalation endpoints are similar (i.e., based on cholinesterase inhibition) the dermal and inhalation MOEs were combined in this risk assessment to identify a total MOE.

### Epidemiological Information

**Jerry Blondell (OPP/HED/CEB2) to provide information to complete this section.**



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application: 2 acres for handgun, belly grinder, and push-type lawn drop spreader application; 5,000 square feet for application by backpack sprayer and low pressure handwand; 1 one-pound can for application by hand and shaker can; and 2 cubic yards for application by hand to potting soil.

**Residential Handler Exposures**

Based on the use patterns, EPA has identified five major isofenphos exposure scenarios for residential handlers: (1) loading/applying granules by hand to fire ant mounds; (2) loading/applying granules to potting soil by hand; (3) loading/applying granules with a shaker can to fire ant mounds (4) loading/applying granules with a belly grinder; and (5) loading/applying granules with a push-type lawn drop spreader.

Short-term dermal and inhalation exposures (developed using PHED Version 1.1 surrogate data and chemical-specific data) are presented in Table 6. Table 7 presents the risk assessment for short-term dermal and inhalation exposures. Table 8 summarizes the caveats and parameters specific to each exposure scenario and corresponding risk assessment.

The following assumptions were made in the exposure calculations:

- Average body weight of an adult handler is 70 kg.
- The amount handled is based on 1,000 square feet for application by hand and shaker can; 0.25 cubic yard for application by hand to potting soil; and 0.5 acre for application with a belly grinder and push-type lawn drop spreader.
- Due to a lack of scenario-specific data, HED calculated unit exposure values using generic data from the Pesticide Handler Exposure Database (PHED). The details for each scenario are discussed in Table 8.
- Generally, the use of PPE and engineering controls are not considered acceptable options for products sold for use by homeowners because they are not available and/or are inappropriate for the exposure scenario.

Potential inhalation and dermal daily exposures for both occupational and residential handlers were calculated using the following formulas (100 percent dermal and inhalation absorption were assumed):

$$\text{Daily Inhalation Exposure}\left(\frac{mg\ ai}{day}\right) = \text{Unit Exposure}\left(\frac{\mu g\ ai}{lb\ ai}\right) \times \text{Conversion Factor}\left(\frac{1mg}{1{,}000\ \mu g}\right) \times \text{Use Rate}\left(\frac{lb\ ai}{A}\right) \times \text{Daily Acres Treated}\left(\frac{A}{day}\right)$$

$$\text{Daily Dermal Exposure}\left(\frac{mg\ ai}{day}\right) = \text{Unit Exposure}\left(\frac{mg\ ai}{lb\ ai}\right) \times \text{Use Rate}\left(\frac{lb\ ai}{A}\right) \times \text{Daily Acres Treated}\left(\frac{A}{day}\right)$$



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**Post Application:**

**Occupational Postapplication Exposures and Assumptions**

Except for termiticide (a use which has been voluntarily canceled[1]) studies, chemical-specific postapplication exposure data have not yet been submitted by the registrant in support of reregistration of isofenphos. In lieu of these data, a surrogate rangefinder postapplication exposure assessment was conducted to determine potential risks for two representative scenarios. The surrogate assessment presented in Table 9 is based on the application rate recommended for turf in isofenphos labels, and activities that bracket the reentry exposure levels anticipated from isofenphos use on turf. The two scenarios addressed by the calculations are described below:

- Low Exposure Reentry Activity (golf course mowing): transfer coefficient (Tc) = 500 $cm^2$/hour, and

- High Exposure Reentry Activity (turf farm harvesting): Tc = 10,000 $cm^2$/hour.

The DFR is derived from the application rate for turf, using an estimated 20 percent of the rate applied as initial dislodgeable residues, and an estimated 10 percent dissipation rate per day. This estimate may be a lower bound as environmental fate data suggests that isofenphos has a half-life of 72 days on sandy loam exposed to sunlight. The equation used for the calculations in Table 9 are presented below:

$$DFR\left(\frac{\mu g}{cm^2}\right) = AR\left(\frac{lb\ ai}{A}\right) \times CF\left(\frac{\mu g/cm^2}{lb\ ai/A}\right) \times F \times (1 - DR)^t$$

Where:
AR = Application rate is 2.0 lb ai/A
CF = Conversion factor is 11.2 lb per $cm^2$/lb per A
F = Fraction retained on foliage is 20 percent
DR = Daily dissipation rate (10 percent/day)
t = Days after treatment

$$Dose\ (mg/kg/d) = \frac{(DFR\ (\mu g/cm^2) \times Tc\ (cm^2/hr) \times CF\left(\frac{1\ mg}{1{,}000\ \mu g}\right) \times Abs \times ED\ (hrs/day))}{BW}$$

Where:
DFR = Initial DFR or daily DFR
Tc = Transfer coefficient; 500 $cm^2$/hr or 10,000 $cm^2$/hr

The equations and assumptions used for each of the scenarios were taken from the Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments guidance document[6], and are given below. The following general assumptions were made for all scenarios:

- On the day of application, it was assumed that 20 percent of the application rate are available from the turfgrass as dislodgeable residue.
- Postapplication was assessed on the same day the pesticide is applied because it was assumed that the homeowner could be exposed to turfgrass immediately after application. Therefore, postapplication exposures were based on day 0.
- Adults were assumed to weigh 70. Toddlers (3 years old), used to represent the 1 to 6 year old age group, were assumed to weigh 15 kg.

**Dermal exposure:**

$$ADD = (DFR_t * CF1 * Tc * ET) / BW$$

where:

| | | |
|---|---|---|
| ADD | = | average daily dose (mg/kg/day) |
| $DFR_t$ | = | dislodgeable foliar residue on day "t" ($\mu g/cm^2$) |
| CF1 | = | weight unit conversion factor to convert $\mu g$ units in the DFR value to mg for the daily dose (0.001 mg/$\mu g$) |
| Tc | = | transfer coefficient ($cm^2/hr$) |
| ET | = | exposure time (hr/day) |
| BW | = | body weight (kg) |

and

$$DFR_t = AR * F * (1-D)^t * CF2 * CF3$$

where:

| | | |
|---|---|---|
| AR | = | application rate (lb ai/acre) |
| F | = | fraction of ai retained on foliage (0.20, unitless) |
| D | = | fraction of residue that dissipates daily (0.10, unitless) |
| t | = | postapplication day on which exposure is being assessed (day 0) |
| CF2 | = | weight unit conversion factor to convert the lbs ai in the application rate to $\mu g$ for the DFR value (4.54E8 $\mu g$/lb) |



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**Turfgrass ingestion:**

$$ADD = (GR_t * IgR * CF1) / BW$$

where:

| | | |
|---|---|---|
| ADD | = | average daily dose (mg/kg/day) |
| $GR_t$ | = | grass (and plant matter) residue on day "t" ($\mu g/cm^2$) |
| IgR | = | ingestion rate of grass ($cm^2$/day) |
| CF1 | = | weight unit conversion factor to convert the $\mu g$ of residues on the grass to mg to provide units of mg/day (1E-3 mg/$\mu g$) |
| BW | = | body weight (kg) |

and

$$GR_t = AR * F * (1-D)^t * CF2 * CF3$$

where:

| | | |
|---|---|---|
| AR | = | application rate (lb ai/acre) |
| F | = | fraction of ai available on the grass (unitless) |
| D | = | fraction of residue that dissipates daily (unitless) |
| t | = | postapplication day on which exposure is being assessed |
| CF2 | = | weight unit conversion factor to convert the lbs ai in the application rate to $\mu g$ for the grass residue value (4.54E8 $\mu g$/lb) |
| CF3 | = | area unit conversion factor to convert the surface area units ($ft^2$) in the application rate to $cm^2$ for the grass residue value (2.47E-8 acre/$cm^2$ if the application rate is per acre) |

- The assumed ingestion rate for grass for toddlers (age 3 years) was 25 $cm^2$/day (i.e., 2 x 2 inches or 4 $in^2$). This value was intended to represent the approximate area from which a child may grasp a handful of grass.

**Incidental Soil Ingestion:**

$$ADD = (SR_t * IgR * CF1) / BW$$

where:

| | | |
|---|---|---|
| ADD | = | average daily dose (mg/kg/day) |
| $SR_t$ | = | soil residue on day "t" ($\mu g/g$) |
| IgR | = | ingestion rate of soil (mg/day) |
| CF1 | = | weight unit conversion factor to convert the $\mu g$ of residues on the soil to grams to provide units of mg/day (1E-6 g/$\mu g$) |
| BW | = | body weight (kg) |

- The calculations based on combined dermal and inhalation risks indicate that the MOEs are not more than 3,000 at **additional personal protective equipment** (double layer body protection and chemical-resistant gloves) for any scenarios.

- The calculations based on combined dermal and inhalation risks indicate that the MOEs are not more than 3,000 at **engineering controls** for all scenarios except scenario (2) loading granules for tractor-drawn/mechanical spreader application.

Intermediate-Term

Dermal and inhalation MOEs were combined and risk was calculated using the intermediate-term dermal NOEL of 0.06 mg/kg/d. The acceptable MOE was assumed to be 1,000.

- The calculations based on combined dermal and inhalation risks indicate that the MOEs are not more than 1,000 at **baseline** for any scenarios.

- The calculations based on combined dermal and inhalation risks indicate that the MOEs are not more than 1,000 at **additional personal protective equipment** (double layer body protection and chemical-resistant gloves) for any scenarios.

- The calculations based on combined dermal and inhalation risks indicate that the MOEs are not more than 1,000 at **engineering controls** for any scenarios.

**Residential**

Short-Term

Dermal and inhalation MOEs were combined and risk was calculated using the short-term dermal LOEL of 2.0 mg/kg/day. The acceptable MOE was assumed to be 3,000.

- The calculations based on combined dermal and inhalation risks indicate that the MOEs are not more than 3,000 at **baseline** for any scenarios.

In summary, the calculations of risk are not over the MOE for any of the short-term and intermediate-term scenarios except occupational scenario (2), which exceeds the short-term MOE with the use of engineering controls for risk mitigation.

**Summary of Combined Dermal and Inhalation Risk from Postapplication Exposures**



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## Additional Occupational/Residential Exposure Studies

### Handler Studies

Two studies were performed in 1988 to monitor mixer / loader / applicator exposure to isofenphos during typical use as a termiticide (MRID 419904-01, 419904-02) by Mobay Corporation to satisfy the requirements of Subdivision U of the Pesticide Assessment Guidelines. A total of 17 replicates were included in four distinct types of homes. Each replicate consisted of treating a single building in or around the Kansas City metropolitan area. Exposure levels were estimated using passive dosimetry (dermal and inhalation) as well as biological monitoring techniques.

Neither study met the requirements of Subdivision U because of many issues, including the following: inadequate number of replicates performed per home type, lack of adequate description of application equipment, test subjects wearing rubber gloves (not required by label), lack of laboratory recovery samples generated and analyzed with the field samples, insufficient information concerning storage stability, and no description of the field spike preparation procedures. It should be noted that the acceptability of these studies is moot because the use of isofenphos as a termiticide has been voluntarily canceled by the registrant.[1]

Notwithstanding the Subdivision U guideline issues described above, the data from these studies form the complete basis for the termiticide mixer/ loader / applicator scenario unit exposure estimates in the Pesticide Handlers Exposure Database (PHED). Based on these data, the dermal unit exposure is 0.36 mg / lb ai handled and the inhalation unit exposure is 2.2 μg / lb ai handled. These values should not be considered worst case in comparison with that from other exposure scenarios, as they are well within the observed range for both inhalation and dermal unit exposures from PHED.

### Postapplication Studies

One dislodgeable residue from turf study (MRID 00159625) was submitted. This study was conducted in 1980, prior to the issuance of guidelines for conducting dislodgeable residue studies. In this study, the isofenphos formulation was diluted with water and applied to bluegrass turf at the rate of two lbs ai per acre using a tractor-mounted boom. Triplicate samples of grass clippings were taken at 0, 1, 3, and 7 days post-treatment from two treatment plots and one control plot. Immediately after sampling, residues were dislodged from a 10 gram aliquot of grass clippings and analyzed for both Oftanol and its oxygen analog. Results showed that over the 7 day sampling period, dislodgeable Oftanol residues declined from approximately 280 ppm on day 0 to about 3-4 ppm on day 7. Oftanol oxygen analog levels were constant over time at less than 12 ppm.

Under current guidelines this study is not considered acceptable. The technical registrant, Bayer, is a member of the Outdoor Residential Exposure Task Force (ORETF) and plans to submit dislodgeable residue data for isofenphos under this task force.

Two indoor air monitoring studies were submitted. One study (MRID 410075-01) measured the indoor air concentration of isofenphos in nine residential homes in and around Kansas City treated with Pryfon 6 termiticide during application and up to one year after application. The other study (MRID 419013-02) measured indoor air concentrations of isofenphos in eight residential homes in eastern Massachusetts treated with Pryfon 6 Termiticide.

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Table 1: Occupational Handler Short- and Intermediate-term Dermal and Inhalation Exposures to Isofenphos

| Exposure Scenario (Scenario #) | Baseline Dermal Unit Exposure (mg/lb ai)[a] | Baseline Inhalation Unit Exposure (µg/lb ai)[b] | Range of Application Rates (lb ai/acre)[c] | Daily Acres Treated[d] | Daily Dermal Exposure (mg/day)[e] | Daily Inhalation Exposure (mg/day)[f] |
|---|---|---|---|---|---|---|
| **Mixer/Loader Exposure** | | | | | | |
| Mixing/loading liquids for groundboom application (1a) | 2.9 | 1.2 | 2.0 lb ai/A | 80 acres | 460 | 0.19 |
| Mixing/loading liquids for rights-of-way sprayer (1b) | | | | 40 acres | 230 | 0.096 |
| Mixing/loading liquids for chemigation application (1c) | | | | 40 acres | 230 | 0.096 |
| Mixing/loading liquids for handgun application (1d) | | | | 5 acres | 29 | 0.012 |
| Loading granules for tractor drawn/mechanical spreader application (2) | 0.0084 | 1.7 | 2.0 lb ai/A | 80 acres | 1.3 | 0.27 |
| **Applicator Exposure** | | | | | | |
| Applying sprays with a groundboom sprayer (3) | 0.014 | 0.74 | 2.0 lb ai/A | 80 acres | 2.2 | 0.12 |
| Applying sprays to rights-of-way (4) | 1.3 | 3.9 | 2.0 lb ai/A | 40 acres | 100 | 0.31 |
| Applying sprays with a handgun sprayer (5) | 0.34 (gloves) | 1.4 | 2.0 lb ai/A | 5 acres | 3.4 | 0.014 |
| Applying granules with tractor-drawn sprayer (6) | 0.0099 | 1.2 | 2.0 lb ai/A | 80 acres | 1.6 | 0.19 |
| **Mixer/Loader/Applicator Exposure** | | | | | | |
| Loading/applying granules by hand to fire ant mounds (7) | 71 (gloves) | 470 | 0.015 lb ai/can | 1 lb can | 1.1 | 0.007 |
| Mixing/loading/applying liquids with a backpack sprayer (8) | 2.5 | 30 | 2.0 lb ai/A | 5000 $ft^2$ | 0.57 | 0.0069 |
| Mixing/loading/applying liquids with a low pressure handwand (9) | 100 | 30 | 2.0 lb ai/A | 5000 $ft^2$ | 23 | 0.0069 |
| Loading/applying granules to potting soil by hand (10)[g] | 71 (gloves) | 470 | 0.020 lb ai/$yd^3$ | 2 $yd^3$ | 2.8 | 0.019 |
| Loading/applying granules with a shaker can to fire ant mounds (11)[g] | 71 (gloves) | 470 | 0.015 lb ai/can | 1 lb can | 1.1 | 0.007 |
| Loading/applying granules with a belly grinder (12) | 10 | 62 | 2.0 lb ai/A | 2 acres | 40 | 0.25 |
| Loading/applying granules with a push type lawn drop spreader (13) | 2.9 | 6.3 | 2.0 lb ai/A | 2 acres | 11.6 | 0.025 |

[a] Baseline dermal unit exposure represents long pants, long sleeved shirt, no gloves, open mixing/loading, open cab tractor. The exceptions are scenarios 5 (applying sprays with a handgun), 7 (loading/applying granules by hand), 10 (loading/applying granules to potting soil by hand), and 11 (loading/applying granules with a shaker can), for which the PHED unit exposure value includes the use of protective gloves.

[b] Baseline inhalation exposure represents no respirator.

[c] Application rates are maximum rate values found on isofenphos labels.

Table 2: Occupational Handler Short-term and Intermediate-term Risks from Isofenphos at Baseline

| Exposure Scenario (Scenario #) | Baseline Dermal | | | Baseline Inhalation | | | Baseline Total | |
|---|---|---|---|---|---|---|---|---|
| | Daily Dose (mg/kg/day)[a] | Short-term MOE[b] | Int.-term MOE[c] | Daily Dose (mg/kg/day)[d] | Short-term MOE[e] | Int.-term MOE[f] | Short-term MOE[g] | Int.-term MOE[h] |
| **Mixer/Loader Exposure** | | | | | | | | |
| Mixing/loading liquids for groundboom application (1a) | 6.6 | 0.30 | 0.0091 | 0.0027 | 740 | 22 | 0.30 | 0.0091 |
| Mixing/loading liquids for rights-of-way sprayer (1b) | 3.3 | 0.61 | 0.018 | 0.0014 | 1,400 | 43 | 0.61 | 0.018 |
| Mixing/loading liquids for chemigation application (1c) | 3.3 | 0.61 | 0.018 | 0.0014 | 1,400 | 43 | 0.61 | 0.018 |
| Mixing/loading liquids for handgun application (1d) | 0.41 | 4.9 | 0.15 | 0.00017 | 12,000 | 350 | 4.9 | 0.15 |
| Loading granules for tractor drawn/mechanical spreader application (2) | 0.019 | 110 | 3.2 | 0.0039 | 510 | 15 | 90 | 2.6 |
| **Applicator Exposure** | | | | | | | | |
| Applying sprays with a groundboom sprayer (3) | 0.030 | 67 | 2.0 | 0.0017 | 1,200 | 35 | 63 | 1.9 |
| Applying sprays to rights-of-way (4) | 1.4 | 1.4 | 0.043 | 0.0044 | 460 | 14 | 1.4 | 0.043 |
| Applying sprays with a handgun sprayer (5) | 0.049 | 41 | 1.2 | 0.00020 | 10,000 | 300 | 41 | 1.2 |
| Applying granules with tractor-drawn sprayer (6) | 0.023 | 87 | 2.6 | 0.0027 | 740 | 22 | 78 | 2.3 |
| **Mixer/Loader/Applicator Exposure** | | | | | | | | |
| Loading/applying granules by hand to fire ant mounds (7) | 0.016 | 130 | 3.8 | 0.0001 | 20,000 | 600 | 130 | 3.8 |
| Mixing/loading/applying liquids with a backpack sprayer (8) | 0.0081 | 250 | 7.4 | 0.000099 | 20,000 | 600 | 250 | 7.4 |
| Mixing/loading/applying liquids with a low pressure handwand (9) | 0.33 | 6 | 0.18 | 0.000099 | 20,000 | 600 | 6 | 0.18 |
| Loading/applying granules to potting soil by hand (10) | 0.040 | 50 | 1.5 | 0.00027 | 7,400 | 220 | 50 | 1.5 |
| Loading/applying granules with a shaker can to fire ant mounds (11) | 0.016 | 130 | 3.8 | 0.0001 | 20,000 | 600 | 130 | 3.8 |
| Loading/applying granules with a belly grinder (12) | 0.57 | 3.5 | 0.11 | 0.0036 | 560 | 17 | 3.5 | 0.11 |
| Loading/applying granules with a push type lawn drop spreader (13) | 0.17 | 12 | 0.35 | 0.00036 | 5,600 | 170 | 12 | 0.35 |

[a] Daily Dermal Dose (mg/kg/day) = Daily Dermal Exposure (mg/day)/ Body weight (70 kg).
[b] Short-term Dermal MOE = LOEL (2 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).
[c] Intermediate-term Dermal MOE = NOEL (0.06 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).

Table 3: Occupational Handler Short-term and Intermediate-term Risks from Isofenphos with Additional PPE

| Exposure Scenario (Scenario #) | Dermal - Additional PPE | | | | Inhalation - Additional PPE | | | | Total - Additional PPE | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Unit Exposure (mg/lb ai)[a] | Daily Dose (mg/kg/day)[b] | Short-term MOE[c] | Int.-term MOE[d] | Unit Exposure (µg/lb ai)[a] | Daily Dose (mg/kg/day)[e] | Short-term MOE[f] | Int.-term MOE[g] | Short-term MOE[h] | Int.-term MOE[i] |
| **Mixer/Loader Exposure** | | | | | | | | | | |
| Mixing/loading liquids for groundboom application (1a) | 0.017 | 0.039 | 51 | 1.5 | 0.24 | 0.00055 | 3,600 | 110 | 50 | 1.5 |
| Mixing/loading liquids for rights-of-way sprayer (1b) | | 0.019 | 110 | 3.2 | | 0.00027 | 7,400 | 220 | 110 | 3.2 |
| Mixing/loading liquids for chemigation application (1c) | | 0.019 | 110 | 3.2 | | 0.00027 | 7,400 | 220 | 110 | 3.2 |
| Mixing/loading liquids for handgun application (1d) | | 0.0024 | 830 | 25 | | 0.000034 | 59,000 | 1,800 | 820 | 25 |
| Loading granules for tractor drawn/ mechanical spreader application (2) | 0.0034 | 0.0078 | 260 | 7.7 | 0.34 | 0.00078 | 2,600 | 77 | 240 | 7.0 |
| **Applicator Exposure** | | | | | | | | | | |
| Applying sprays with a groundboom sprayer (3) | 0.014 | 0.032 | 63 | 1.9 | 0.15 | 0.00034 | 5,900 | 180 | 62 | 1.9 |
| Applying sprays to rights-of-way (4) | 0.29 | 0.33 | 6.1 | 0.18 | 0.78 | 0.00089 | 2,200 | 67 | 6.1 | 0.18 |
| Applying sprays with a handgun sprayer (5) | 0.19 | 0.027 | 74 | 2.2 | 0.28 | 0.000040 | 50,000 | 1,500 | 74 | 2.2 |
| Applying granules with tractor-drawn sprayer (6) | 0.0042 | 0.010 | 200 | 6.0 | 0.24 | 0.00055 | 3,600 | 110 | 190 | 5.7 |
| **Mixer/Loader/Applicator Exposure** | | | | | | | | | | |
| Loading/applying granules by hand to fire ant mounds (7) | 40 | 0.0086 | 230 | 7.0 | 94 | 0.00002 | 100,000 | 3000 | 230 | 7.0 |
| Mixing/loading/applying liquids with a backpack sprayer (8) | 1.6 | 0.0052 | 3.8 | 12 | 6 | 0.00002 | 100,000 | 3000 | 380 | 12 |
| Mixing/loading/applying liquids with a low pressure handwand (9) | 0.37 | 0.0012 | 1700 | 50 | 6 | 0.00002 | 100,000 | 3000 | 1700 | 50 |
| Loading/applying granules to potting soil by hand (10) | 40 | 0.023 | 87 | 2.6 | 94 | 0.000054 | 37,000 | 1,100 | 87 | 2.6 |

Table 4: Occupational Handler Short-term and Intermediate-term Risks from Isofenphos with Engineering Controls

| Exposure Scenario (Scenario #) | Dermal - Engineering Controls | | | | Inhalation - Engineering Controls | | | | Total - Eng. Controls | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Unit Exposure (mg/lb ai)[a] | Daily Dose (mg/kg/day)[b] | Short-term MOE[c] | Int.-term MOE[d] | Unit Exposure (µg/lb ai)[a] | Daily Dose (mg/kg/day)[e] | Short-term MOE[f] | Int.-term MOE[g] | Short-term MOE[h] | Int.-term MOE[i] |
| **Mixer/Loader Exposure** | | | | | | | | | | |
| Mixing/loading liquids for groundboom application (1a) | 0.0086 | 0.020 | 100 | 3.0 | 0.083 | 0.00019 | 11,000 | 320 | 99 | 3.0 |
| Mixing/loading liquids for rights-of-way sprayer (1b) | | 0.0098 | 200 | 6.1 | | 0.000095 | 21,000 | 630 | 200 | 5.9 |
| Mixing/loading liquids for chemigation application (1c) | | 0.0098 | 200 | 6.1 | | 0.000095 | 21,000 | 630 | 200 | 5.9 |
| Mixing/loading liquids for handgun application (1d) | | 0.0012 | 1,700 | 50 | | 0.000012 | 170,000 | 5,000 | 1,700 | 50 |
| Loading granules for tractor drawn/ mechanical spreader application (2) | 0.00017 | 0.00039 | 5,100 | 150 | 0.034 | 0.000078 | 26,000 | 770 | 4,300 | 130 |
| **Applicator Exposure** | | | | | | | | | | |
| Applying sprays with a groundboom sprayer (3) | 0.005 | 0.011 | 180 | 5.5 | 0.043 | 0.000098 | 20,000 | 600 | 180 | 5.5 |
| Applying sprays to rights-of-way (4) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |
| Applying sprays with a handgun sprayer (5) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |
| Applying granules with tractor-drawn sprayer (6) | 0.0021 | 0.0048 | 420 | 13 | 0.22 | 0.00050 | 4,000 | 120 | 380 | 12 |
| **Mixer/Loader/Applicator Exposure** | | | | | | | | | | |
| Loading/applying granules by hand to fire ant mounds (7) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |
| Mixing/loading/applying liquids with a backpack sprayer (8) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |
| Mixing/loading/applying liquids with a low pressure handwand (9) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |
| Loading/applying granules to potting soil by hand (10) | NF | NF | NF | NF | NF | NF | NF | NF | NF | NF |

Table 5: Exposure Scenario Descriptions for the Use of Isofenphos

| Exposure Scenario (Number) | Data Source | Standard Assumptions[a] (8-hr work day) | Comments[b] |
|---|---|---|---|
| **Mixer/Loader Descriptors** | | | |
| Mixing/Loading Liquid Formulations (1a/1b/1c/1d) | PHED V1.1 | 80 acres for groundboom, 40 acres for rights-of-way sprayer and chemigation, and 5 acres for handgun | **Baseline:** Hand, dermal, and inhalation data are AB grades. Hand - 72 to 122 replicates; dermal - 53 replicates, and inhalation = 85 replicates. High confidence in hand/dermal and inhalation data. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively. Hand data are AB grades, with 59 replicates. High confidence in hand/dermal data.<br><br>**Engineering Controls:** Hand, dermal, and inhalation data are AB grades. Hand = 31 replicates; dermal = 16 to 22 replicates; inhalation = 27 replicates. High confidence in hand/dermal and inhalation data. |
| Loading granules for tractor drawn/mechanical spreader application (2) | PHED V1.1 | 80 acres | **Baseline:** Hand data are All grades, and dermal and inhalation are ABC grades. Hand = 10 replicates; dermal 33 to 78 replicates; and inhalation = 58 replicates. Low confidence in hand/dermal data, and high confidence in inhalation data. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** Hand data are AB grades, and dermal data are ABC grades. The same inhalation data are used as for the baseline coupled with an 80% protection factor to account for the use of a dust/mist respirator. Hand = 45 replicates and dermal = 12 to 59 replicates. Low confidence in hand/dermal data.<br><br>**Engineering Controls:** Hand data are All grades; dermal are ABC grades; and inhalation are AB grades. Hand = 10 replicates; dermal =33 to 78 replicates; inhalation = 58 replicates. Low confidence in hand/dermal data and high confidence in inhalation data. |
| **Applicator Exposure** | | | |
| Applying sprays with a groundboom sprayer (3) | PHED V1.1 | 80 acres | **Baseline:** Hand, dermal, and inhalation data are AB grades. Hand = 29 replicates; dermal = 23 to 42 replicates; and inhalation = 22 replicates. High confidence in hand/dermal and inhalation data. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively. Hand data are ABC grades, with 21 replicates. Medium confidence in hand/dermal data.<br><br>**Engineering Controls:** Hand and dermal data are ABC grades, and inhalation are AB grades. Hand = 16 replicates; dermal =20 to 31 replicates; inhalation = 16 replicates. Medium confidence in hand/dermal data, and high confidence in inhalation data. |
| Applying sprays to rights-of-way (4) | PHED V1.1 | 40 acres | **Baseline:** Hand data are AB grades, dermal are ABC grades, and inhalation data are A grades. Hand = 16 replicates; dermal = 4 to 30 replicates; and inhalation = 16 replicates. Low confidence in hand/dermal data , and high confidence inhalation data. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively. Hand data are AB grades, with 4 replicates. Low confidence in hand/dermal data.<br><br>**Engineering Controls:** Not feasible for this scenario. |

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| Exposure Scenario (Number) | Data Source | Standard Assumptions[a] (8-hr work day) | Comments[b] |
|---|---|---|---|
| Loading/applying granules to potting soil by hand (10)[c] | PHED V1.1 | 2 yd[3] | **Baseline:** Hand, dermal, and inhalation data are ABC grades. Hand = 15 replicates; dermal = 16 replicates, and inhalation = 16 replicates. Medium confidence in hand/dermal and inhalation data. Baseline data includes chemical resistant gloves. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively. Hand data are ABC grades, with 15 replicates. Medium confidence in hand/dermal data.<br><br>**Engineering Controls:** Not feasible for this scenario. |
| Loading/applying granules with a shaker can to fire ant mounds (11)[c] | PHED V1.1 | One 1-lb can<br>(assume that if more than 1 can is to be used, then different application equipment would be used). | **Baseline:** Hand, dermal, and inhalation data are ABC grades. Hand = 15 replicates; dermal = 16 replicates, and inhalation = 16 replicates. Medium confidence in hand/dermal and inhalation data. Baseline data includes chemical resistant gloves. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing, and an 80% protection factor to account for the use of a dust/mist respirator, respectively. Hand data are ABC grades, with 15 replicates. Medium confidence in hand/dermal data.<br><br>**Engineering Controls:** Not feasible for this scenario. |
| Loading/applying granules with a belly grinder (12) | PHED V1.1 | 2 acres | **Baseline:** Hand and dermal data are ABC grades, and inhalation data are AB grades. Hand = 23 replicates; dermal = 29 to 45 replicates; and inhalation = 40 replicates. Medium confidence in hand/dermal data, and high confidence in inhalation data. No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same hand and dermal data are used as for the baseline coupled with a 90% protection factor to account for chemical resistant gloves, and a 50% protection factor to account for an additional layer of clothing, respectively. The same inhalation data are used as for the baseline coupled with an 80% protection factor to account for the use of a dust/mist respirator.<br><br>**Engineering Controls:** Not feasible for this scenario. |
| Loading/applying granules with a push type lawn drop spreader (13) | PHED V1.1 | 2 acres | **Baseline:** Hand and dermal data are C grade, and inhalation data are B grade. Hand = 15 replicates; dermal = 0 to 15 replicates; and inhalation = 15 replicates. Low confidence in hand/dermal data, and high confidence in inhalation data No protection factor was needed to define the unit exposure value.<br><br>**PPE:** The same hand and dermal data are used as for the baseline coupled with a 90% protection factor to account for chemical resistant gloves, and a 50% protection factor to account for an additional layer of clothing, respectively. The same inhalation data are used as for the baseline coupled with an 80% protection factor to account for the use of a dust/mist respirator.<br><br>**Engineering Controls:** Not feasible for this scenario. |

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

[b] All handler exposure assessments in this document are based on the "Best Available" data as defined by OREB SOP for meeting Subdivision U Guidelines. Best available grades are assigned to data as follows: matrices with grades A and B data and a minimum of 15 replicates; if not available, then grades A, B and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality (i.e., All Grade Data) and number of replicates. High quality data with a protection factor take precedence over low quality data with no protection factor. Generic data confidence categories are assigned as follows:

High = grades A and B and 15 or more replicates per body part
Medium = grades A, B, and C and 15 or more replicates per body part
Low = grades A, B, C, D and E or any combination of grades with less than 15 replicates

[c] Unit exposure data for application of granules by hand were used as surrogate values for these scenarios.

Table 7: Residential Handler Short-term Risks from Isofenphos

| Exposure Scenario (Scenario #) | Baseline Dermal | | Baseline Inhalation | | Baseline Total |
|---|---|---|---|---|---|
| | Daily Dose (mg/kg/day)[a] | Short-term MOE[b] | Daily Dose (mg/kg/day)[c] | Short-term MOE[d] | Short-term MOE[e] |
| Mixer/Loader/Applicator Exposure | | | | | |
| Loading/applying granules by hand to fire ant mounds (1) | 0.093 | 21 | 0.0001 | 20,000 | 21 |
| Loading/applying granules to potting soil by hand (2) | 0.029 | 68 | 0.000031 | 65,000 | 68 |
| Loading/applying granules with a shaker can to fire ant mounds (3) | 0.093 | 21 | 0.0001 | 20,000 | 21 |
| Loading/applying granules with a belly grinder (4) | 1.6 | 1.3 | 0.00089 | 2,200 | 1.3 |
| Loading/applying granules with a push type lawn drop spreader (5) | 0.043 | 47 | 0.000090 | 22,000 | 47 |

[a] Daily Dermal Dose (mg/kg/day) = Daily Dermal Exposure (mg/day)/ Body weight (70 kg).
[b] Short-term Dermal MOE = LOEL (2 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).
[c] Daily Inhalation Dose (mg/kg/day) = Daily Inhalation Exposure (mg/day)/ Body weight (70 kg).
[d] Short-term Inhalation MOE = LOEL (2 mg/kg/day)/ Daily Inhalation Dose (mg/kg/day).
[e] Total Short-term MOE = 1/ ((1/ Short-term Dermal MOE) + (1/ Short-term Inhalation MOE)).

Table 9. Isofenphos Intermediate-Term Surrogate Occupational Postapplication Assessment (Range Finder).

| DAT[a] | DFR ($\mu g/cm^2$)[b] | Dermal Dose (mg/kg/day)[c] | | MOE[d] | |
|---|---|---|---|---|---|
| | | Low | High | Low | High |
| 0 | 4.5 | 0.26 | 5.1 | 0.23 | 0.012 |
| 50 | 0.023 | 0.0013 | 0.026 | 46 | 2.3 |
| 80 | 9.8E-4 | 5.6E-5 | 0.0011 | 1,100 | 55 |
| 100 | 1.2E-4 | NA | 1.4E-4 | NA | 430 |
| 108 | 5.1E-5 | NA | 5.9E-5 | NA | 1,000 |

a DAT is "days after treatment"

b Initial DFR = Application rate (2.0 lb ai/A) x Conversion factor (1 lb ai/acre = 11.209 ug/cm2) x fraction of initial ai retained on foliage

$$DFR\left(\frac{\mu g}{cm^2}\right) = AR\left(\frac{lb\ ai}{A}\right) \times CF\left(\frac{\mu g/cm^2}{lb\ ai/A}\right) \times F \times (1 - DR)^t$$

Where : Assumed percent DFR after initial treatment is 20%, and each day after the percent dissipation per day is 10%.

c Dose = DFR (ug/cm2) x Transfer coefficient (low is 500, high is 10,000 $cm^2$/hr ) x Conversion Factor (1mg/1000 ug) x Dermal Absorption (1) x Hrs worked per day (8hrs)/ Body weight (70 kg)

d MOE = NOEL ( mg/kg/day)/ Dermal Dose (mg/kg/day). Where: intermediate-term NOEL is 0.06 mg/kg/day.

## References


1) Notice of Receipt of Request to Voluntarily Cancel Certain Pesticide Registrations. Federal Register. Vol. 60, No.190, p.51468. October 1, 1997.

2) Isofenphos labels

3) U.S. EPA 1997. Isofenphos LUIS Table for Exposure Assessors (PRD report dated 11/6/96 and report run date 8/5/97.

4) Isofenphos 1-Methylethyl 2-[[ethoxy[(1-methylethyl)amino] phosphinothioyl] oxy] benzoate: Hazard Identification Committee Report dated January 6, 1998.

5) Pesticide Handler Exposure Database Version 1.1 Surrogate exposure Table (newly organized). E-mailed to Versar, Inc. in late December, 1997, and printed December 26, 1997.

6) U.S. EPA 1997. Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments.

7) Oftanol (Isofenphos) Reregistration Product Use Meeting, September 18, 1997.


cc: Paula Deschamp, OPP/HED/RRB2
OREB Files



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ATTACHMENT 5: Review of Isofenphos Incident Reports. Blondell and Spann (03/04/98)





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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

March 4, 1998

MEMORANDUM

SUBJECT: Review of Isofenphos Incident Reports
DP Barcode D243363, Chemical #109401, Reregistration Case #2345

FROM: Jerome Blondell, Ph.D., Health Statistician
Chemistry and Exposure Branch 2
Health Effects Division (7509C) Jerome Blondell

Monica F. Spann, M.P.H., Environmental Health Scientist
Chemistry and Exposure Branch 2 Monica F. Spann
Health Effects Division (7509C)

THRU: Susan V. Hummel, Senior Scientist
Chemistry and Exposure Branch 2
Health Effects Division (7509C)

TO: Jonathan Becker, Environmental Health Specialist
Reregistration Branch 2
Health Effects Division (7509C)

BACKGROUND

The following data bases have been consulted for the poisoning incident data on the active ingredient Isofenphos (PC Code: 109401):

1) OPP Incident Data System (IDS) - reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992. Reports submitted to the Incident

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Data System represent anecdotal reports or allegations only, unless otherwise stated. Typically no conclusions can be drawn implicating the pesticide as a cause of any of the reported health effects. Nevertheless, sometimes with enough cases and/or enough documentation risk mitigation measures may be suggested.

2) Poison Control Centers - as the result of Data-Call-Ins issued in 1993, OPP received Poison Control Center data covering the years 1985 through 1992 for 28 organophosphate and carbamate chemicals. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System which obtains data from about 70 centers at hospitals and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings, involving drugs, household products, pesticides, etc.

3) California Department of Food and Agriculture (replaced by the Department of Pesticide Regulation in 1991) - California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided.

4) National Pesticide Telecommunications Network (NPTN) - NPTN is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive has been prepared. The total number of calls was tabulated for the categories human incidents, animal incidents, calls for information, and others.

## ISOFENPHOS REVIEW

### I. Incident Data System

There were no reports involving isofenphos alone in the Incident Data System. A few incidents were reported involving exposures to mixtures of pesticides which included isofenphos. However, it was not possible to distinguish which pesticide was responsible for the alleged health effects.

## II. Poison Control Center Data

Isofenphos was one of 28 chemicals for which Poison Control Center (PCC) data were requested. The following text and statistics are taken from an analysis of these data; see December 5, 1994 memo from Jerome Blondell to Joshua First.

The 28 chemicals were ranked using three types of measures: (A) number and percent occupational and non-occupational adult exposures reported to PCCs requiring treatment, hospitalization, displaying symptoms or serious life-threatening effects; (B) California data for handlers and field workers comparing number of agricultural poisonings to reported applications; and (C) ratios of poisonings and hospitalization for PCC cases to estimated pounds reported in agriculture for pesticides used primarily in agriculture.

### A. Occupational and Non-occupational Exposure

There were a total of 351 isofenphos cases in the PCC data base. Of these, 47 cases were occupational exposure; 36 (77%) involved exposure to isofenphos alone and 11 (23%) involved exposure to multiple chemicals, including isofenphos. There were a total of 194 adult non-occupational exposures; 165 (85%) involved this chemical alone and 29 (15%) were attributed to multiple chemicals.[1] In this analysis, four measures of hazard were developed based on the Poison Control Center data, as listed below.

1. Percent of all accidental cases that were seen in or referred to a health care facility (HCF).

2. Percent of these cases (seen in or referred to HCF) that were admitted for medical care.

3. Percent of cases reporting symptoms based on just those cases where the medical outcome could be determined.

4. Percent of those cases that had a major medical outcome which

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[1] Workers who were indirectly exposed (not handlers) were classified as non-occupational cases.

could be defined as life-threatening or resulting in permanent disability.

Exposure to isofenphos alone or in combination with other chemicals was evaluated for each of these categories, giving a total of 8 measures. A ranking of the 28 chemicals was done based on these measures with the lowest number being the most frequently implicated in adverse effects. Table 1 presents the analyses for occupational and non-occupational exposures.

Table 1: Measures of Risk From Occupational and Non-occupational Exposure to Isofenphos Using Poison Control Center Data from 1985-1992[a]

| | Occupational Exposure | Non-occupational Exposure |
|---|---|---|
| Percent Seen in HCF | | |
| Single chemical exposure | 58.3 (68.2) | 43.0 (44.0) |
| Multiple chemical exposure | 61.7 (69.8) | 43.3 (46.1) |
| Percent Hospitalized | | |
| Single chemical exposure | 9.5 (12.2) | 5.6 (9.9) |
| Multiple chemical exposure | 13.8 (14.3) | 6.0 (12.6) |
| Percent with Symptoms | | |
| Single chemical exposure | 69.2 (85.8) | 77.2 (74.0) |
| Multiple chemical exposure | 71.4 (85.8) | 81.0 (75.2) |
| Percent with Life-threatening Symptoms | | |
| Single chemical exposure | 0.0 (0.0) | 0.0 (0.0) |
| Multiple chemical exposure | 2.9[b] (0.5) | 0.9[b] (0.05) |

a Extracted from Tables 2, 3, 5 and 6 in December 5, 1994 memo from Jerome Blondell to Joshua First; number in parentheses is median score for that category. Top 25% of chemicals are ranked with a superscript of 1 to 7

b The percent calculated here is based on a single case where a mixture was involved in the exposure.

Compared to other organophosphate and carbamate insecticides, isofenphos had average or below average evidence of effects (Table 1). Only one life-threatening case was reported for isofenphos and that case involved exposure to other products, so it can not be used to evaluate hazard. Among cases seen in a health care facility, isofenphos cases were much less likely to be hospitalized than the other insecticides. On other measures of hazard (percent seen in a health care facility or percent with symptoms), isofenphos had percents similar to the median for other cholinesterase-inhibitors.

B. Ratios of poisoning - California Data

It is not possible to compare numbers of isofenphos poisoning in California to the number of applications because there have not been any reports of systemic poisonings from 1982 through 1995. However, there have been almost no reports of isofenphos used in California. From 1990 through 1994, only one use is reported in their annual reports concerning commercial use.

C. Exposure in Children

A separate analysis of the number of exposures in children five years of age and under from 1985-1992 was conducted. For isofenphos, there were 110 incidents; 101 involved exposure to isofenphos alone and 9 involved other pesticides as well. Compared to 16 other organophosphates and carbamates that 25 or more children were exposed to, isofenphos cases were half as likely to be seen in a health care facility or require hospitalization. Symptoms, however, occurred just as often for isofenphos, though there were no life-threatening cases reported in children under age six. This suggests that most isofenphos cases result in relatively minor symptoms that do not require serious medical care.

III. California Data - No Data

IV. NPTN

On the list of the top 200 chemicals for which NPTN received calls from 1984-1991 inclusively, isofenphos was ranked 43rd with 89 incidents in humans reported and 30 incidents in animals (mostly pets).

V. Conclusions

Due to absence of commercial use in California, there is relatively little information on confirmed poisonings due to isofenphos. The Incident Data System did not have any cases where isofenphos alone was responsible for an incident. The only information available comes from the Poison Control Centers. Compared to other organophosphate and carbamate insecticides, isofenphos had average or below average evidence of effects.

VI. Recommendations

Measures to reduce risk to applicators and handlers of isofenphos should be consistent with other organophosphate and carbamates.

cc: Correspondence
Isofenphos file (chemical no. 109401)
SRRD - Ruby Whiters (7508W)

RDI: BRSrSci:SHummel:

ISOFENPHOS



ATTACHMENT 6: Drinking Water Assessment for Isofenphos. Nelson Thurman (02/13/98)



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U. S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

February 13, 1998

**MEMORANDUM**

**SUBJECT:** Drinking Water Assessment for **Isofenphos**
PC Code No. **109401**; RED Case No. **2345**

**TO:** Paula Deschamp, Risk Assessor
Health Effects Division 07509C

**FROM:** Nelson Thurman, Environmental Engineer Nelson Thurman
Environmental Fate and Effects Division (7507C)

**THROUGH:** Mah T. Shamim, Ph.D., Chief
Environmental Risk Branch IV / EFED (7507C)

EFED has conducted both a Tier 1 screening assessment and a qualitative evaluation of the potential impact of the use of isofenphos on drinking water resources. The initial screening assessment provides likely upper bound estimates of the concentration of isofenphos that might be found in ground- and surface-water sources of drinking water (DWECs). Surface water sources of drinking water are most likely to be impacted by the use of isofenphos. The tier 1 screening, using GENEEC for surface water modeling, suggests that upper-bound estimates of isofenphos concentrations in surface water (acute $DWEC_{sw}$ of 52 ug/L; chronic $DWEC_{sw}$ of 37 ug/L) may exceed HED's acute and chronic drinking water levels of concern.

Since the Tier 1 models serve only as a screening tool, exceedances using these model predictions mean a refined assessment is needed (refined modeling or monitoring data). Currently, EFED does not have Tier 2 screening models that adequately model runoff from golf courses or residential lawns; existing surface water monitoring data is very limited and not of much use in assessing the extent of isofenphos occurrences in water. However, EFED believes the overall impact of isofenphos on drinking water resources is likely to be less than what would be estimated in the Tier 1 screens due to its apparent susceptibility to enhanced degradation by soil microorganisms; its limited uses (primarily lawns and golf courses) and limited acreage, and label recommendations which would minimize off-target movement to surface water. The impact of these factors cannot be sufficiently quantified to generate a refined $DWEC_{sw}$. However, EFED believes that, on a qualitative basis, any risk to drinking water resources from isofenphos use would be highly localized in space and time. On a national basis, isofenphos is not expected to be a concern for drinking water resources.

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Modeled Data: A preliminary ground water assessment was made using SCI-GROW[2] (Screening Concentrations In GROund Water) to estimate concentrations of pesticides in ground water under highly vulnerable conditions. SCI-GROW uses fate properties of the pesticide (aerobic soil half-life and sorption coefficients), the maximum application rate, and the existing body of data from small-scale ground-water monitoring studies. The model assumes the pesticide is applied at its maximum rate in areas where the ground water is particularly vulnerable to contamination. The highly-vulnerable ground water upon which the SCI-GROW estimates is believed to represent only a small percentage of drinking water in the pesticide use area. Because SCI-GROW is a regression model, it does not account for site-specific hydrology, soil properties, climatic conditions, or agronomic practices. Overestimates are particularly likely for foliarly-applied pesticides that are susceptible to photolysis or for volatile pesticides. As such, SCI-GROW is likely to provide high-end estimates of acute or chronic exposure and should be used only for screening purposes.

Isofenphos was modeled with a $K_{oc}$ of 972 (mean value), an aerobic soil metabolism half-life of 352 days, and an application rate of 2 lb ai/A applied twice. SCI-GROW predicts that the ground water concentration for isofenphos is not expected to exceed 0.8 ug/L.

Because isofenphos oxon is structurally similar and is likely to be at least as toxic as the parent, SCI-GROW was run for the combined isofenphos plus oxon residues. A $K_{oc}$ of 230 (mean value for the more mobile moiety) and an aerobic soil metabolism half-life of 1,044 days for the combined residues were used, resulting in a ground water EEC of 22.8 ug/L for the combined isofenphos and isofenphos oxon residues. This modeled EEC contains a high degree of uncertainty because of uncertainties in the fate and persistence of isofenphos oxon.

### *ii. Surface Water Assessment*

Insufficient monitoring data is available to provide estimates of isofenphos concentrations in surface water sources of drinking water. Surface water data reported in STORET is too limited in area (NY) and size (237 samples) to provide a reasonable estimate. No additional data is available. The only modeling data available for predicting estimated environmental concentrations of isofenphos in surface water comes from the preliminary screening model GENEEC. Given the use patterns, the turf scenario is best applicable to modeling for drinking water assessments.

Monitoring Data: The STORET database reported no detections of isofenphos in a limited number of sediment and surface water samples taken in Florida, Illinois, and New York. In Florida, isofenphos was not detected (limits of detection ranging from 1.2 to 36 mg/kg, dry weight) in 68 sediment samples taken from lakes, estuaries, streams and outflows. No concentration was reported for one stream sample in Illinois. Isofenphos was not found above the limit of detection/quantification (0.03 to 0.5 ug/L) in 237 New York water samples (231 stream, 4 canal, and 2 lake samples). The utility of this data is uncertain because of the wide

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[2] Barrett, M. 1997. SCI-GROW; "A proposed method to determine screening concentrations estimates for drinking water from ground water sources." Draft. USEPA/OPP/EFED, September 1997.



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### *B. Tier 2 (Refined) Screening Assessment*

EFED does not have a Tier 2 model for ground water assessments. For surface water, EFED currently does not have Tier 2 screening models that adequately model runoff from golf courses or residential lawns. Therefore, a reliable Tier 2 refinement is not possible for isofenphos.

### *C. Qualitative Assessment*

The overall impact of isofenphos on potential drinking water sources is likely to be much less than what is estimated in the Tier 1 screens, particularly for surface water sources, for the following reasons:

- an apparent susceptibility to enhanced degradation by soil microorganisms in subsequent years of application. Although we do not have adequate data to quantify the degree and extent of such degradation, we incorporated it qualitatively in our assessment.
- Isofenphos has no food/feed uses; existing uses (primarily lawns and golf courses) cover a limited acreage (approximately 132,000 acres treated nationally). It should be noted, however, that the limited use area may reduce overall risk on a national basis, but it does not preclude risk in the localized areas where the pesticide is used.
- Application recommendations on the existing label (1-2 applications in a season, wet-in, and ground rather than aerial application) can minimize off-target movement to surface water.

The impact of these factors cannot be sufficiently quantified to generate a refined $DWEC_{sw}$. However, EFED believes that, on a qualitative basis, any risk to drinking water resources from isofenphos use would be highly localized in space and time. On a national basis, isofenphos is not expected to be a concern for drinking water resources.

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