12-19-97

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MEMORANDUM:

SUBJECT: Phosmet [(mercaptomethyl) phthalimide S-(O,O-dimethylphosphorodithioate]: Hazard Identification Committee Report.

CASRN: 732-11-6
PC Code: 059201
Caswell: 543

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

Thru: Clark Swentzel
Chairman, Hazard Identification Committee
Health Effects Division (7509C)

To: Susan Lewis, Chief PM 03
Insecticide-Rodenticide Branch
Registration Division (7505C)

The Health Effects Division-Hazard Identification Committee met on September 04, 1997 to evaluate the existing and/or recently submitted toxicology data in support of phosmet 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 (RfD) for this chemical.

Phosmet had already been evaluated by the HED-RfD Committee on March 3, 1994 (report dated May 11, 1994). Therefore, this Hazard Identification Committee report should be considered in conjunction with the RfD-Committee report of March 3, 1994.

Material available for review consisted of data evaluation

records (DERs) for combined chronic toxicity-carcinogenicity studies in rats **(83-5)**, a chronic toxicity study in dogs **(83-1b)**, a carcinogenicity study in mice **(83-2b)**, a reproductive toxicity study in rats **(83-4)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)**, a subchronic study in rats **(82-1a)**, and a battery of mutagenicity studies **(84-2)**.

## INDIVIDUALS IN ATTENDANCE

Hazard Identification Committee members present were David Anderson, Karl 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, and Clark Swentzel (Chairman, Hazard Identification Committee, HED).

In attendance also were Stephen Dapson and Christina Swartz, HED, as observers.

Hazard Identification Committee member(s) in absentia: Jess Rowland.

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.

William Greear _____

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A. Acute Toxicity

## I. TOXICOLOGY PROFILE:

### A. Carcinogenicity:

The carcinogenicity issue has been discussed by the Health Effects Division-Cancer Peer Review Committee. The Committee agreed that "phosmet should be classified as a "Group C", possible human carcinogen, and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk".

"This decision was based on an increased incidence of liver tumors in male B6C3F1 mice at the high dose, that was statistically significant by pair-wise comparison, with a statistically significant trend and which also had an apparent early onset. Female mice had a significant dose-related trend for liver tumors, and for mammary gland adenocarcinomas, as well. There was no evidence for carcinogenicity in an acceptable study in rats" (report dated May 25, 1994).

### B. Reproductive and Developmental Toxicity:

The reproductive and developmental toxicity issues had been recently addressed by the HED-RfD Committee (report dated May 11, 1994).

Developmental Neurotoxicity: In the attempt to develop a weight-of-evidence recommendation on the need for developmental neurotoxicity testing with phosmet, all the following information was considered:

1) Evidence that supports requiring a developmental neurotoxicity study:

Phosmet is a neurotoxic organophosphate associated with plasma, RBC and brain cholinesterase inhibition in various species. According to the one-liners, there is a positive acute delayed neurotoxicity study in hens with phosmet, and a neurotoxic esterase study which is also positive. The delayed neurotoxicity was not, however, repeated in subsequent studies. Adequate characterization of the cholinesterase inhibition has been conducted, although not in pregnant females or their offspring.

Phosmet may disrupt neuroendocrine function, as evidenced by reductions in fertility, mating performance in the two-generation reproduction study in rats, reduced testes and ovary weights, and histopathological evidence of moderately decreased spermatogenesis. Reproductive function was impaired more severely in the second generation than the first.

2) Evidence that does not support asking for a developmental neurotoxicity study:

No evidence of developmental anomalies, including abnormalities in the development of the fetal nervous system, were observed in the prenatal developmental toxicity studies in either Wistar rats or New Zealand white rabbits, at maternal gavage doses up to 15 mg/kg/day. The maternal doses were sufficient to elicit clinical signs of toxicity in the dams. (It is noted that assessment of differential response of offspring versus adults to cholinesterase inhibition following treatment with phosmet was not conducted.)

No evidence of alterations to brain weight or histopathology was observed in the chronic toxicity studies in rats, mice, and dogs.

3) Other Factors:

Acute and subchronic neurotoxicity studies in rats have not yet been submitted. Furthermore, comparative cholinesterase measurements in adult and neonatal animals (rats) have not been assessed.

Based on the above, the Committee agreed that there was insufficient data to determine the need for a developmental neurotoxicity in rats. Such a determination would depend on the results of an acute and/or subchronic neurotoxicity study in rats, in particular, upon the neuropathology data, which are more sensitive in detecting treatment-related effects than the data from a standard subchronic or chronic study. Neither of these two neurotoxicity studies has been submitted to the Agency yet.

The inability to assess the need for a developmental neurotoxicity study is considered a potential data gap for the assessment of hazard to infants.

C. 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 phosmet was evaluated by the Hazard Identification Committee. The Committee concluded the following:

**Adequacy of data:** The data base for phosmet included an acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits, meeting the basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. However, because of the lack of the necessary information, required to assess the need for a developmental neurotoxicity study in rats, it was determined that a data gap exists for the assessment of hazard to infants and children.

**Susceptibility:** The available data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to phosmet.

**Uncertainty factor:** The inability to assess the need for a developmental neurotoxicity study is considered a potential data gap for the assessment of hazard to infants and children.

The Committee evaluated the data as described and concluded that the 10-fold uncertainty factor for the protection of infants and children can be reduced to 3-fold. This decision to reduce the 10-fold uncertainty factor to 3-fold was based on the following:

On one hand, the data base, which includes acceptable developmental toxicity studies in two species and a two-generation reproduction study in rats, demonstrate no evidence of increased sensitivity to young animals following pre- and/or post-natal exposure to phosmet. Furthermore, results from studies conducted to evaluate the potential for delayed neurotoxicity and neurotoxic esterase assays did not support classification of phosmet as a delayed neurotoxicant.

On the other hand, since acute and subchronic neurotoxicity studies in rats have not been submitted to the Agency at the time of this review, a full characterization of the neuropathological potential for phosmet is not available. Positive results from these studies could potentially lead to a data requirement for a developmental neurotoxicity study in rats. These studies, i.e. the acute and subchronic neurotoxicity studies in rats, are considered a data gap for the assessment of hazard to infants and children, for which a 3-fold uncertainty factor was recommended.

**D. Mutagenicity:**

The mutagenicity issue has been addressed as part of the weight of the evidence evaluation of the carcinogenic potential of this chemical. Phosmet was determined to be a potent, direct-acting mutagen.

**E. Dermal Absorption:**

In a dermal absorption study (MRID 40122201), phosmet (Imidan 50-WP, 50%, Lot #10 RSEE 300 10) was applied to the shaved skin on the back of 4 male Sprague-Dawley (CD) rats/group. Dilutions used were 1:2, 1:10 and 1:100 applied at a rate of 300 $\mu$l rat. Administered doses were 2.67, 0.52 and 0.058 mg/cm$^2$ skin. The dosing solutions contained 20-50 uCi of labeled compound. The radioactive test material had a specific activity of 26.6 mCi/mmol and was 97% pure. Phosmet was poorly absorbed when applied to the shaved skin of rats. The percent of radioactive dose found in the carcass, skin, urine, feces, and blood (combined) after 24 hours

was 0.9, 3.8, and 11.8% of administered doses of .67, 0.5% and 0.058 mg/Cm skin, respectively. The skin at the dosing site contained much of the radioactivity. The amount in the carcass and excreta reached a maximum at 24 hours and accounted for 7.9, 1.7 and 0.3% of the administered radioactivity at the low-, mid- and high-doses, respectively. Excretion of the absorbed radioactivity was primarily urinary; **0.1%** of the high-dose (1:2 dilution), **1.1%** of the mid-dose (1:10 dilution), and 5.4% of the low dose (1:100 dilution) radiolabel was found in the urine between 10 and 24 hours. Much lesser amounts were found in the feces.

**The Committee estimated that the dermal absorption rate is about or no greater than 10%.**

## II. HAZARD IDENTIFICATION:

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

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 uncertainty associated with intraspecies variability, interspecies extrapolation, route to route conversion, or variable durations extrapolation are also addressed.

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

### DIETARY EXPOSURE:

### A. Chronic Dietary Exposure-Reference Dose (RfD):

**Reference Dose ($R_fD$):** 0.003 mg/kg/day.

**Critical Study:** Chronic toxicity study in rats (83-1a), MRID No(s): 41916401.

**Executive Summary:**

In a 2-year chronic toxicity/carcinogenicity study (MRID 41916401) phosmet (Lot # EHC-0866-24, WRC-4921-42-8) was administered to Sprague-Dawley Crl:CD(R) SD BR rats in the diet at 0, 20, 40, 200 or 400 ppm (400 ppm terminated at 12 months) (doses of: males - 0, 1.1, 1.8, 9.4 and 23 mg/kg/day; females - 0 1.1, 2.1, 10.9 and 27 mg/kg/day) for 2 years.

At 20 ppm there was marginal RBC cholinesterase (ChE) inhibition (16%) noted at 6 months in males only. At 40 ppm RBC (about 15-20%) and serum ChE (5-36%- M; 15-25%- F) was inhibited in both males and females. Brain cholinesterase was inhibited (>34%) in males and females at 200 ppm. **The LOEL for ChE inhibition was < 20 ppm based on RBC ChE in males (marginal - only at 6 months). The NOEL for (ChE) inhibition was < 20 ppm.**

Systemic toxicity was limited to increased incidence of fatty change in the liver of males at all doses. In addition, at 200 ppm and above (males) there were increases in the incidences of depressed hepatic foci, hyperkeratosis of the stomach; (females) fatty change in the liver, mineralization of the thyroid. At 400 ppm (males and females) body weight and body weight gain were decreased; (females) decreased kidney weight and increased BUN. **The systemic LEL is < 20 ppm based on an increased incidence of fatty change in the liver of males. the systemic NOEL < 20 ppm.**

**Endpoint and Dose Level Selected for use in risk assessment**: NOEL = 1.1 mg/kg/day, based on RBC and serum cholinesterase inhibition observed at the next higher dose level of 1.8 mg/kg/day.

**Uncertainty Factor (UF)**: An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability. The use of a UF of 100 was justified based on the availability of a chronic toxicity study in a second species (MRID No. 00062651, 00075419, 00076436, 00080431, 00080556) and a reproductive toxicity study in rats (MRID No. 41520001) in accordance with the rules established by the Agency-IRIS (Integration Risk Information System) Work Group.

Pursuant to the FQPA, an additional UF of 3 was recommended to account for the lack of acute and subchronic neurotoxicity studies in rats. A full characterization of the neuropathological potential for phosmet is not available. Positive results from these studies could potentially lead to a data requirement for a developmental neurotoxicity study in rats. These studies are considered a data gap for the assessment of hazard to infants and children, for which a 3-fold uncertainty factor was recommended.

**B. Acute Dietary Exposure (one day):**

**Critical Study**: Chronic toxicity study in rats (83-1a), MRID No(s): 41916401.

**Executive Summary**: See Section II-A, above.

**Endpoint and Dose Level Selected for Use in Risk Assessment**: NOEL = 1.1 mg/kg/day, based on RBC and serum cholinesterase inhibition observed at the next higher dose level of 1.8 mg/kg/day.

**Uncertainty Factor (UF)**: Same as Section II-A, above.

**Comments and Rationale**: Although the chronic toxicity study in rats is a long-term study, it was considered appropriate to use for the acute exposure risk assessment since the endpoint selected (cholinesterase inhibition) occurs as early as 2-4 weeks and because the NOEL/LOELs are lower than those in the rat subchronic studies.

**Supportive Data**: The Committee recommended the use of the reproductive toxicity study in rats (MRID No. 41520001) as a supportive study. In this two-generation reproductive toxicity study, Sprague-Dawley (Crl:CD SD BR) rats, 25 per sex were treated with 0 (control), 20, 80 or 300 ppm (0, 1.5, 6.1 or 23.4 mg/kg/day) of phosmet (95.%, Lot #EHC-0866-14; WRC-4921-42- 8) in the diet continuously. Parental toxicity consisted of RBC ChE inhibition at 20 ppm (6-16%), 80 ppm (>37%), and 300 ppm (>74%). Serum ChE was inhibited at 80 ppm (34%) and 300 ppm (65%). There were clinical signs (tremors) noted at 300 ppm). The parental LEL is equal to or less than 20 ppm. The parental **NOEL is equal to 20 ppm.** Reproductive toxicity consisted of decreased fertility, number of live pups/litter, pup weights, lactation index and fertility index (e.g., 88% versus 48%, control and high dose). **The reproductive NOEL is 20 ppm. The reproductive LEL is 80 ppm based on decreased fertility.**

**NON-DIETARY EXPOSURE:**

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

**Critical Study**: Chronic toxicity study in rats (83-1a), MRID No(s): 41916401.

**Executive Summary**: See Section II-A, above.

**Endpoint and Dose Level Selected for Use in Risk Assessment**: NOEL = 1.1 mg/kg/day, based on RBC and serum cholinesterase inhibition observed at the next higher dose level of 1.8 mg/kg/day.

**Uncertainty Factor (UF)**: Same as Section II-A, above.

**Comments and Rationale**: Although this study is an oral, long-term

study, it was considered appropriate to use for the short-term exposure dermal risk assessment since the endpoint selected (cholinesterase inhibition) occurs as early as 2-4 weeks and because the NOEL/LOELs are lower than those in the rat subchronic studies. A dermal absorption rate of 10% should be considered in the calculation of the dermal equivalent dose.

**Supportive Data:** The Committee recommended the use of the reproductive toxicity study in rats (MRID No. 41520001) as a supportive study (see executive summary under Section II-B, above).

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

**Critical Study:** Chronic toxicity study in rats (83-1a), MRID No(s): 41916401.

**Executive Summary:** See Section II-A, above.

**Endpoint and Dose Level Selected for Use in Risk Assessment:** NOEL = 1.1 mg/kg/day, based on RBC and serum cholinesterase inhibition observed at the next higher dose level of 1.8 mg/kg/day.

**Uncertainty Factor (UF):** Same as Section II-A, above.

**Comments and Rationale:** Although the chronic toxicity study in rats is a long-term study, it was considered appropriate to use for the shorter duration exposure risk assessment since the endpoint selected (cholinesterase inhibition) occurs as early as 2-4 weeks and because the NOEL/LOELs are lower than those in the rat subchronic studies.

**Supportive Data:** The Committee recommended the use of the reproductive toxicity study in rats (MRID No. 41520001) as a supportive study (see executive summary under Section II-B, above).

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

**Critical Study:** None identified.

**Executive Summary:** None.

**Endpoint and Dose Level selected for use in risk assessment:** None.

**Comments**: Since there are no studies available for inhalation exposure, it is appropriate to assume 100% absorption of the inhalation exposure estimates via the lungs.

cc: Stephanie Irene
Marion Copley
William Greear
Christina Swartz
Michael Metzger
Karen Whitby
Jess Rowland
Amal Mahfouz (OW)
Hazard ID file
Caswell File