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

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MAY 31, 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review of Phosphamidon (CAS No. 13171-21-6)

FROM: George Z. Ghali, Ph.D. G. Ghali
Scientific Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: William H. Miller, PM 16
Insecticide-Rodenticide Branch
Registration Division (H7504C)

The Health Effects Division Peer Review Committee met on January 9, 1989 to discuss and evaluate the weight-of-the-evidence on phosphamidon with particular reference to its oncogenic potential. The Committee classified phosphamidon as a Category C - Possible Human Carcinogen. Quantification of oncogenicity risk was not recommended.

A. Individuals in Attendence

1. Peer Review Committee (signatures indicate concurrence with conclusions of the Committee unless otherwise stated):

Reto Engler

Robert Beliles

Judith Hauswirth

Marcia van Gemert

John Quest

Marion Copley

Leonard Slaughter

Esther Rinde

Kerry Dearfield

Richard Levy

William Sette

George Ghali

2. Peer Review Committee members in absentia (Committee members who were not able to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee):

William Burnam

Richard Hill

Diana Beal

3. Non-Panel Members (Responsible for data presentation; signatures indicate technical accuracy of panel report):

Ed Budd

Krystyna Locke

C.J. Nelson

B. Material Reviewed

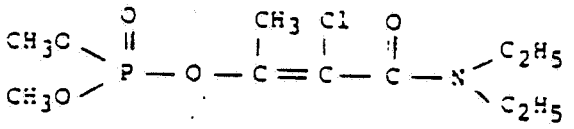
The material available for review consisted of DERs for an oncogenicity study in Sprague-Dawley rats, an NCI report for oncogenicity studies in Osborne-Mendel rats and B6C3F1 mice in addition to relevant information on metabolism, mutagenicity, and structure-activity relationship.

C. Background Information

Phosphamidon [O,O-Dimethyl O-(2-chloro-2-diethylcarbamoyl-1-methylvinyl)phosphate] is a systemic organophosphorous pesticide. It is considered toxic on an acute basis. The acute oral $LD_{50}$ in rats is 17 to 30 mg/kg and the acute dermal $LD_{50}$ in rabbits is 267 mg/kg (Farm Chemical Handbook, 1986). It was first

registered by Ciba-Geigy in 1963, and marketed in the US by Chevron. A Registration Standard was completed in 1987.

It is mainly used to control pests on apples, grapefruit, lemons, oranges, tangerines, broccoli, cauliflower, cucumbers, peppers, cantaloups, watermelons, cotton, potatoes, sugarcane, tomatoes, walnuts, corn, peanuts, sweet potatoes, and soybeans. The residue levels on these agricultural food commodities range from 0.1 to 1.0 ppm. The chemical is considered of short half-life in and on plants under field conditions. The half-life ranges from 1 to 5 days.



Phosphamidon

D. Evaluation of Oncogenicity Data

1. Twenty-Four Month Combined Chronic Oral Toxicity/ Oncogenicity Study in Rats. Unpublished report prepared by American Biogenics Corporation, Report No. 410-1056, dated February 28, 1986. EPA Accession Nos. 261913 through 261925.

   Technical phosphamidon was administered in the diet to groups of male and female Sprague-Dawley rats at 0, 1.0, 30, or 80 ppm for 2 years.

   The treatment was associated with increase in the incidence of transitional cell carcinomas of the urinary bladder in the mid- and high-dose males. Of concern also were the increased incidences of adrenal cortical adenomas and hepatocellular carcinomas in males, and ovarian granulosa-theca cell tumors in females (Table 1).

Table 1. Incidence* of Neoplastic Lesions in Male and Female Sprague-Dawley Rats

| Neoplastic Lesion | Historical Controls | Dose Level (ppm) 0 | 1.0 | 30 | 80 |
|---|---|---|---|---|---|
| | | Males | | | |
| Bladder transitional cell carcinoma | (0.0) | 0/79 (0.0) | 0/69 (0.0) | 1/68 (1.5) | 3/77 (3.9) |
| Adrenal cortical adenoma | (6.7-13.3) | 1/80 (1.2) | 3/70 (4.3) | 3/70 (4.3) | 5/79 (6.3) |
| Hepatocellular carcinoma | (0.0-4.4) | 1/80 (1.2) | 1/68 (1.5) | 5/70 (7.1) | 5/80 (6.2) |
| | | Females | | | |
| Ovarian granulosa-theca cell tumor | (0.0-5.1) | 2/30 (2.5) | 2/70 (2.8) | 3/70 (4.3) | 5/80 (6.2) |

*Number of neoplasms/number of tissues examined.
() = percent.

Table 2. Phosphamidon - Male Rat liver and Bladder Tumor Rates+ and Trend or Fisher's Exact Test Results

| Dose (ppm) | 0 | 1 | 30 | 80 |
|---|---|---|---|---|
| Urinary bladder carcinoma[a/] | 0/62* | 0/60 | 1/57 | 3/68 |
| Hepatocellular carcinoma[a/] | 1/62* | 1/62 | 5/62 | 5/69 |

+ Number of tumor bearing animals/number of animals at risk (excludes all animals that died before the week of the appearance of the first tumor).
a/First bladder tumor appeared at week 78 (day 546) in 80 ppm dose.
a/First liver carcinoma appeared at week 73 (day 512) in 30 ppm dose.
**$p < .01$ and *$p < .05$.
Significance of trend analysis denoted at Control.
Significance of pairwise comparison between control and dosed groups denoted at Dose level.

a. Discussion of Tumor Data:

In this study, survival was higher in the high dose group than other groups including control. A time adjusted survival analyses (Thomas, Breslow, Cart) revealed a statistically significant negative trend ($p = .0128$) in mortality. The low- and mid-dose groups had poorer survival than the control group, but there was no statistically pairwise difference between the treated and control groups. Under these conditions, a time-to-tumor analysis was not warranted, and the Cochran-Armitage test for trend, and Fisher's Exact test for pairwise comparison were used in this analysis (Table 2).

The incidence of transitional cell carcinomas of the urinary bladder in males receiving 30 and 80 ppm phosphamidon was 1.5 and 3.9 percent respectively, compared to 0 percent for the concurrent controls. Statistical analysis of data indicated a significant ($p < 0.05$) trend for urinary bladder transitional cell carcinomas in males, but no significant pairwise comparison between control and dosed groups was observed for this tumor category. Although the increased incidence was not statistically significant for pairwise comparison ($p = 0.05$), the Committee considered this tumor to be treatment-related. The Committee based its decision on the fact that bladder tumor of this type is uncommon in rats with spontaneous incidences of 0 to <0.5 percent.

There was an apparent increase in the incidence of hepatocellular carcinoma with statistically significant trend ($p < 0.05$) in dosed males; 1.5, 7.1, 6.2 percent respectively for the 1.0, 30, and 80 ppm groups compared with 1.2 percent for the control. This increase was not statistically significant for pairwise comparison with the control, but was marginally higher than the incidence of the historical control provided by the registrant (0.0 to 4.4 percent).

The increases in the incidence of adrenal cortical adenoma in males, and the ovarian granulosa-theca cell tumors in females were not statistically significant neither for trend nor for pairwise comparison with the concurrent controls.

It should be noted also that all the transitional cell carcinomas of the bladder occurred in the male rats, which were either found dead or were moribund and had to be sacrificed during the last 6 months of the study (test days 546 to 736). Each rat with transitional cell carcinoma in the high-dose group also had bladder stones. The mid-dose male with transitional cell carcinoma had kidney stones. No animal had a bladder tumor without evidence of calculi formation.

The Committee discussed the registrant's claim that the formation of urinary bladder tumors might probably be secondary to calculi formation and is not directly due to treatment with phosphamidon. It has been suggested that formation of calculi may cause bladder tumors through physical irritation and/or tissue damage. However, although one might argue that high doses of phosphamidon may facilitate stone formation, there are no scientific data to support such an argument.

b. Consideration of Adequate Dosing for Oncogenicity Assessment.

Considering the toxic signs seen in the high-dose group, it appears that an adequate top dose for the assessment of oncogenic potential was reached. The toxic signs included:

1) Muscle tremors in 71 percent of the females ($p < 0.01$),
2) Decreased body weight gains 9 to 14% in males ($p < 0.01$), and
3) significant plasma and brain cholinesterase inhibition in males and females ($p < 0.01$).

2. Oncogenicity Study in Osborne-Mendel Rats. National Cancer Institute. Report No. 16, dated 1979.

In this study, Osborne-Mendel rats were administered phosphamidon in the diet at 0, 80, or 160 ppm for 80 weeks and then placed on phosphamidon-free diet for 30 to 31 weeks before sacrifice. Fifty animals per sex per dose level were assigned to the treated groups, whereas there were only 10 animals per sex per dose in the control group.

In male rats, the incidence of adrenal cortical adenoma in the low-dose group was significantly higher ($p = 0.023$) than that in the control group (controls 0/8, low dose 6/49, high dose 2/49). However, the incidence in the high-dose group was not significant, and the occurrence of the tumor was not considered to be related to administration of the test chemical. Transitional cell carcinoma of the bladder was observed only in one high-dose male (1/47), whereas single incidences of ovarian granulosa cell tumor were observed in mid-dose females (1/49) and high-dose females (1/49). Hepatocellular carcinomas were not observed in the male rats.

The data obtained in the bioassay with Osborne-Mendel rats were insufficient and could not be considered a reliable assessment of the oncogenic potential of this chemical.

3. Oncogenicity Study in B6C3F1 Mice. National Cancer Institute. Report No. 16, dated 1979.

In this study, B6C3F1 mice were fed diets containing phosphamidon as follows: low-dose males, for 71 weeks; high-dose males, for 62 weeks; and low-dose and high-dose females, for 80 weeks. Following the termination of treatment, the observation period for these animals was 19, 28, and 10 or 11 weeks, respectively. The levels of phosphamidon fed were 0, 80, and 160 ppm. Fifty males and 50 females per dose level were assigned to the treated groups, whereas there were only 10 males and 10 females in the control group.

In this study, the treatment did not alter the spontaneous tumor profile in this strain of mice under the test conditions. However, according to the Phosphamidon Registration Standard, 1987, this study did not meet the Agency's current standards, and therefore another oncogenicity study in the mouse will be required according to the Registration Standard of 1987.

E. Additional Toxicology Data

1. Metabolism

Studies concerned with the mammalian metabolism of phosphamidon are inadequate. However, the existing studies indicated that phosphamidon was rapidly absorbed from the gastrointestinal tract, was almost completely degraded enzymatically, and the metabolites were rapidly excreted in urine. The major urinary metabolite was dimethylphosphate, which is nontoxic. Neither phosphamidon nor its metabolites accumulated in tissues.

2. Mutagenicity

There are no mutagenicity studies submitted to the Agency. However, published literature suggests that there is a mutagenicity concern associated with phosphamidon.

The National Toxicology Program (NTP) reported that phosphamidon was positive in the Salmonella test in strain TA100 with hamster S-9 (Haworth et al., Environ. Mutagen. 5: 3-142, 1983).

Phosphamidon induced chromosomal aberrations in cultured human lymphocytes (Georgian, Mutat. Res. 31: 103-108, 1975), and in rat and mouse bone marrow (Georgian, 1975; Patankar and Vaidya, Ind. J. Exp. Biol. 18:1145-47, 1980; Adhikari and Grover, Environ, Molec. Mutagen. 12:235-42, 1988).

As no mutagenicity tests have been submitted to support the registration of phosphamidon, a full battery of mutagenicity testing is required according to Part 158 of 40 CFR. Since published information suggests activity in the Salmonella and rodent in vivo aberration assays, those tests should be required as part of the mutagenicity data requirements.

3. Developmental and Reproductive Toxicity

Phosphamidon was not teratogenic in Sprague-Dawley rats and New Zealand rabbits. However, developmental toxicity (increased incidence of runts) was observed at the highest dose tested in the rat, but not in the rabbit up to the highest dose tested (10 mg/kg).

In a 2-generation reproduction study in the rat, reproductive and developmental effects including reduced pup survival, body weights, organ (liver, kidneys, and testes) to brain ratio and pregnancy rates were observed in the mid- (30 ppm) and high-dose (50 ppm) groups.

4. Structure-Activity Data

Phosphamidon has some structural similarity to akton, gardona, dichlorvos, diallate, triallate, and telone based on the presence of the dialkyl-carbamoyl and/or a vinyl chloride, vinylidene chloride, or trichloroethylene moiety in their molecular structure.

Phosphamidon has two major sites for hydrolytic cleavage: 1) the ester bond, and 2) the amide bond. Cleavage of either bond will result in metabolites that are structurally similar and more likely to behave biologically in a manner similar to some of these chemical analogues mentioned above.

Studies on these chemical analogues provide evidence of mutagenic and oncogenic activity. Triallate, dichlorvos, telone, and gardona all have shown to be positive mutagens with clastogenic activity like phosphamidon.

Dichlorvos was reported to cause pancreatic adenomas and mononuclear cell leukemia in male rats and forestomach squamous cell papillomas in female mice and was classified as a category B-2 oncogen(Peer Review Memo, 6.27.1988).

Gardona is classified as a C oncogen on the basis of increased incidence of combined hepatocellular adenomas and carcinomas and renal adenomas and carcinomas in mice(Peer Review Memo, 2.12.1988).

Telone was classified as a B-1 oncogen (Peer Review Memo, 11.21.1985) according to proposed Guideline criteria in effect at that time, on the basis of increased incidence of forestomach squamous cell papillomas, and the combined adenomas and carcinomas in male and female rats; increased incidence of urinary bladder transitional cell carcinomas in male and female mice and combined adenomas and carcinomas of the lung in male mice. However, under final Guideline criteria, the chemical should be classified as B-2.

Information available on diallate ond triallate are currently under evaluation by the Agency. These two chemicals have never been evaluated by the HED Peer Review Committee.

Vinyl Chloride, vinylidine chloride or trichloroethylene are common moieties in the structure of these pesticidal chemicals. These moieties exist as terminal groups in the parent molecule or may become as such through hydrolytic cleavage of the ester bond of the pesticidal molecule. In essence, these pesticidal molecules may be viewed as substituted vinyl chloride, vinylidene chloride, or trichloroethylene and may react qualitatively similar.

The mutagenic and oncogenic potential of vinyl chloride, vinylidene chloride and trichloroethylene is well documented in the open literature. The mutagenic / oncogenic potential of vinyl chloride, vinylidene chloride, trichloroethylene may be attributable to the initial formation of unstable oxiranes (Greim et al, Biochem. Pharmacol., 24 (1975) 2013; Bonse and Henschler, CRC Crit. Revs Toxicol., 4 (1976) 395-409.)

F. Weight-of-the-Evidence Considerations

The Committee considered the following facts to be of importance in the weight-of-the-evidence determination of the oncogenic potential of phosphamidon.

1. Administration of phosphamidon to Sprague-Dawley rats at dietary levels of 0, 1.0, 30, or 80 ppm was associated with a significant dose-response trend for transitional cell carcinoma of the urinary bladder ($p = .0105$) in males. This increase was not statistically significant by pairwise comparison with the concurrent control ($p < 0.05$), but higher than the spontaneous tumor incidence for this tumor type in this strain of rats. Bladder transitional cell carcinoma is an uncommon tumor in this strain of rats with a spontaneous incidence of 0 to < 0.5 percent in males. Renal stones were neither proven nor ruled out as a possible cause of this tumor for the lack of scientific data.

2. The treatment was associated with increase in the incidence of hepatocellular carcinoma with statistically significant dose-response trend ($p = .0365$) in male rats. This increase was not statistically significant in the pairwise comparison with the concurrent control ($p < 0.05$). This increase was marginally higher than the spontaneous historical incidence provided by the registrant (4 studies), but still within the range of historical control incidence known for this strain of rats (0 to 7 percent).

3. The increases in the incidence of adrenal cortical adenoma in males, and the ovarian granulosa-theca cell in females were not statistically significant neither for trend nor for pairwise comparison with the concurrent controls.

4. Based on toxicity signs exhibited by both males and females, the high-dose tested is considered adequate.

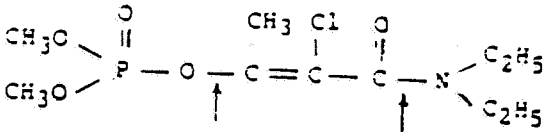
5. Phosphamidon is structurally related to chemical oncogens.

6. The chemical was shown to be a positive mutagen and clastogenic agent. Chemical analogues discussed under the structure-activity section also have positive mutagenic activity including clastogenicity.

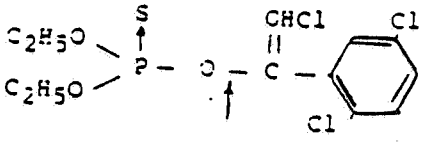
G. Classification of Oncogenic Potential

Pursuant to criteria contained in the EPA Guidelines [FR 51:33992-34003, 1986] for the classification of chemical carcinogens, the Committee concluded that the data available on phosphamidon provide evidence for the classification of this chemical as a "Category C oncogen", possible human carcinogen. The Committee's decision was based on the significant dose-response trend for liver and urinary bladder carcinoma reported in one sex of one strain of rodent, i.e. male Sprague-Dawley rats.

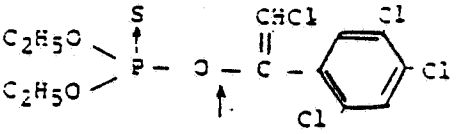
The "C Category" classification was supported by the findings from mutagenicity studies and SAR data.



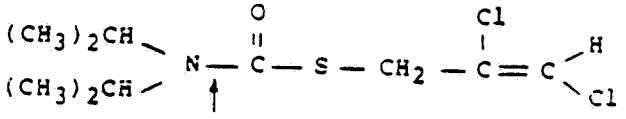
Phosphamidon



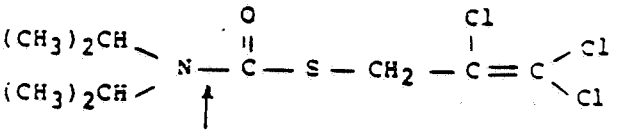
Akton*



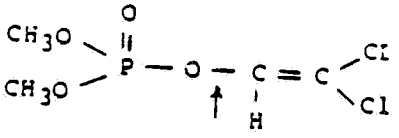
Gardona



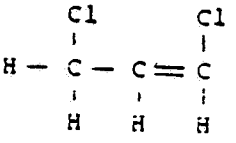
Diallate



Triallate



Dichlorvos



Telone

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* Akton has been discontinued by Shell Chemical Co., no information are currently available on this chemical in HED files.

Arrows denotes sites of hydrolytic cleavage.

The treatment did not alter the spontaneous tumour profile in either female rats or mice of either sex. However, the mouse study was considered inadequate and another study should be performed according to the Registration Standard completed in 1987.

Quantification of oncogenicity risk was not recommended since the evidence was limited and the oncogenic response was confined to one sex of one strain of one species, i.e. male Sprague-Dawley rats. Furthermore, the increase in the incidence of tumors were not statistically significant by pairwise comparison.