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Critical Evaluation of Phosmet’s Breast Cancer Risk

by

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Critical Evaluation of Phosmet’s Breast Cancer Risk
Table of Contents

Table of Contents.................................................................................................................... iii
List of Tables........................................................................................................................... v

I. Introduction................................................................................................................. .1
   A. History of Use and Usage.................................................................................... 1
      1. History of Use and Nomenclature............................................................. 1
      2. Usage........................................................................................................... 1
   B. Chemical Information........................................................................................... 1

II. Regulatory Status
   A. Regulatory History............................................................................................ 1
   B. Clean Water Act Requirements............................................................................. 2
   C. Workplace Regulations......................................................................................... 2
   D. Food Tolerances..................................................................................................... 2

III. Summary of Evidence of Overall Carcinogenicity (non-Breast Sites)
   A. Human Studies
      1. Population-Based Case-Control Studies...................................................... 2
      2. Summary, Human Studies............................................................................. 2
   B. Experimental Animal Studies............................................................................... 2
      1. Mice............................................................................................................... 3
      2. Rats................................................................................................................ 3
      3. Dogs............................................................................................................... 3
      4. Summary, Animal Studies............................................................................. 3
   C. Current Classification of Carcinogenicity by Other Agencies
      1. IARC Classification....................................................................................... 4
      2. NTP Classification......................................................................................... 4
      3. EPA Classification......................................................................................... 4

IV. Critical Evaluation of Breast Cancer Risk
   A. Human Studies........................................................................................................ 4
   B. Experimental Animal Studies.................................................................................. 4
      1. Mice............................................................................................................... 4
      2. Rats................................................................................................................ 4
      3. Summary, Critical Evaluation on Breast Carcinogenicity............................. 4
   C. Other Relevant Data on Breast Cancer Risk
      1. Evidence of Endocrine Disruption.................................................................. 5
         a. In Vivo Studies........................................................................................ 5
         b. Effect on Spermatogenesis....................................................................... 5
      2. Reproductive and Teratogenic Effects........................................................... 5
      3. Tests of Mutagenicity and Genotoxicity......................................................... 6
         a. Studies in Humans and Animals............................................................. 6
         b. Studies in Bacteria and Yeast.................................................................. 6
         c. Studies in Isolated Human and Animal Cells......................................... 6
      4. Evidence of Tumor Promotion....................................................................... 7
      5. Immunological Effects................................................................................... 7
      6. Summary of Other Relevant Data on Breast Cancer Risk............................. 7

V. Other Information
   A. Environmental Fate and Potential for Human Exposure................................. 7
      1. Occupational Exposure............................................................................... 7
List of Tables and Figures

Figure 1. Chemical structure of phosmet.............................................................................................. 1
Table 1. Chemical information on phosmet.......................................................................................... 1
Table 2. Tumor incidence in the mammary gland/skin of phosmet-treated B6C3F1 mice................. 4
Table 3. Trade names of phosmet and phosmet pre-mixes (in Appendix C) ...................................... 20
Critical Evaluation of Phosmet’s Breast Cancer Risk

Author’s Note: The reader is encouraged to read the attached document, Appendix B, which includes an explanation of the BCERF Breast Cancer Risk Classification System, before reading this Critical Evaluation.

I. Introduction

Phosmet is a non-halogenated aromatic organophosphate insecticide. Like other organophosphate pesticides (OP), phosmet acts as a non-systemic insecticide by inhibiting cholinesterase enzymes of the nervous system of insects. It was chosen for this evaluation because of its high use on fruit trees in orchards, an important industry in New York State (NYS). It has been found in household dust in homes of orchard workers who live in close proximity to the orchards (Simcox et al., 1995). Hence, there is a potential for occupational and para-occupational exposure to this insecticide. While there is some evidence of a carcinogenic effect, phosmet has not been through a complete review for its carcinogenic potential by the International Agency for Research on Cancer (IARC), or the Environmental Protection Agency (EPA). Health effects from phosmet are undergoing a review at EPA, as part of the procedure for reassessment of tolerances for OP under the Food Quality and Protection Act of 1996 (FQPA) (EPA, 1998a).

A. History of Use and Usage

1. History of Use and Nomenclature:

   The insecticidal properties of phosmet were first reported in 1961. It was introduced commercially in 1966, by Stauffer Chemical Co. (now Zeneca Agrochemicals, a part of AstraZeneca) (EPA, 1986). Phosmet is available for agricultural and non-agricultural use, in the form of dusts, emulsifiable concentrates, wettable powders and treated articles such as flea collars. It is used to control beetles, worms, aphids and fruitflies on fruits and vines; Colorado beetles on potatoes; boll weevils on cotton; olive moths and olive thrips on olives; blossom beetles on oilseed rape; leaf beetles and weevils on alfalfa; European corn borers on corn and sorghum; and sweet potato weevils on sweet potatoes in storage (Tomlin, 1994). It is also used to control animal ectoparasites. Phosmet is used in nurseries to protect ornamental plants (EPA, 1986). Phosmet products can be used to control household insect pests including moths, beetles, weevils, lice, flies, fleas and ticks (EPA, 1998a).

2. Usage:

Phosmet is used in the production of alfalfa, potatoes, almonds, apples, pears, plums, cherries, blueberries, peaches, grapes and peas. Agricultural use of phosmet during the years 1990 to 1993 was estimated to be 941 thousand pounds (lbs.) of active ingredient (AI) per year (Gianessi and Anderson, 1995b). The use of this insecticide has increased and in 1995, 49 thousand lbs. of phosmet were applied for apple production alone in NYS (NASS, 1995).

B. Chemical Information:

Table 1. Chemical information on phosmet

<table>
<thead>
<tr>
<th>Common Names:</th>
<th>phosmet, phtalofos, PMP, Imidan, Prolate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Name:</td>
<td>$O,O$-dimethyl $S$-phthalimidomethyl phosphorodithioate (Tomlin, 1994).</td>
</tr>
<tr>
<td>Chemical Formula:</td>
<td>$C_{11}H_{12}NO_4PS_2$ (Montgomery, 1993).</td>
</tr>
<tr>
<td>CAS Registry Number:</td>
<td>732-11-6 (Montgomery, 1993).</td>
</tr>
</tbody>
</table>

| Major Metabolites: | Rapid metabolism in animals leads to phthalamic acid, phthalic acid and phthalic acid derivatives (Tomlin, 1994). Dialkyl phosphate metabolites such as $O,O$-dimethyl phosphorothionate are excreted in the urine of mammals (Mount, 1984; Stokes et al., 1995). |
| Mode of Action: | cholinesterase inhibitor |

![Figure 1. Chemical structure of phosmet](image)

II. Regulatory Status

A. Regulatory History:

Phosmet is a General Use Pesticide (GUP) (EXTOXNET, 1996). In June 1994, EPA revoked the processed food tolerance of phosmet in cottonseed oil (PMEP, 1994). In 1997, EPA’s Health Effects Division’s Hazard Identification Assessment Review Committee met to re-evaluate the toxicology data submitted in support of phosmet re-registration (EPA, 1997a). The committee re-evaluated the reference dose (RfD) for chronic dietary risk assessment, paying attention to the special sensitivity of infants and children, as required by FQPA. To increase the transparency of registration eligibility and tolerance reassessment decisions, EPA has opened...
public dockets on OPs, including phosmet. These public dockets include all documents developed by the Agency on the preliminary health and ecological risk assessments of phosmet, any rebuttals or comments on the risk assessments by the chemical registrants, and EPA’s responses to the rebuttals. According to the preliminary reports in the public docket, the aggregate exposure risk to phosmet from food, water, residential and other non-dietary sources could not be assessed since the residential and acute dietary exposure risk components alone exceed EPA’s level of concern (EPA, 1998a).

B. Clean Water Act Requirements:
There has been no maximum contaminant level (MCL), or health advisories set for levels of phosmet in public drinking water supplies (USEPA, 1996).

C. Workplace Regulations:
Workplace exposure limits, or Threshold Limit Values (TLV) have not been defined for phosmet. Phosmet was one of 21 chemicals that were put on an “emergency order” list by the Occupational Safety and Health Administration (OSHA) in 1973 for which re-entry dates had to be set. Opposition from agricultural industries persuaded OSHA to drop nine chemicals, including phosmet, from that list. These chemicals were removed from the “emergency order” list with the following comment from OSHA: “It is proposed that re-entry times should still be set for the nine excluded pesticides in the permanent standard since these substances, while not presenting grave danger to employees, can be hazardous” (ANON, 1973). California State regulations require a re-entry safety interval of five days before workers can enter phosmet-treated orchards (Kahn, 1980). In a recent occupational exposure assessment, EPA found 13 scenarios of worker exposures to have unacceptable risk levels (EPA, 1998a).

D. Food Tolerances:
EPA sets the maximum amount of a pesticide that is permitted to occur on the edible portion of raw agricultural commodities and in processed foods, called tolerances. Tolerances set for phosmet and its oxygen analog are 5 to10 parts per million (ppm) in fruits; 0.2 ppm in meat; and 0.1 ppm in potatoes (USEPA, 1998). In June 1994, EPA revoked the processed food tolerance of phosmet in cottonseed oil (PMEP, 1994).

III. Summary of Evidence of Overall Carcinogenicity (non-breast sites)

A. Human Studies:
Epidemiological studies that specifically evaluate the risk of cancer in populations exposed to phosmet were not found in the scientific literature. There have been two case-control studies in Iowa and Minnesota that have observed an increase in cancer risk in association with exposure to OPs, including phosmet. The number of cases and controls exposed were too small in these studies to allow for an evaluation of the chemical-specific contribution of phosmet to cancer risk.

B. Experimental Animal Studies:
Animal studies have been presented in unpublished reports.
Some of these unpublished reports were provided to us by Gowan Company, the current registrant for phosmet. We have included brief abstracts of other studies, as reviewed in the report from the Joint Food and Agricultural Organization (FAO) and World Health Organization (WHO) Meeting on Pesticide Residues (JMPR, 1994).

1. Mice:
B6C3F1 mice (60/sex/dose) were treated with 0, 5, 25 or 100 ppm Imidan® technical (94.7% phosmet) in diet for two years in an oncogenicity study conducted for Stauffer Chemical Co. (Katz et al., 1984). Ten animals from each group were killed after 12 months of exposure and evaluated for cholinesterase inhibition. Phosmet treatments did not affect the survival rates of the mice adversely. There was a dose-dependent increase in incidence of liver tumors (adenomas and carcinomas combined) in phosmet-treated males: 13/60 (22%) of the controls, 10/60 (17%) of the 5 ppm, 14/60 (23%) of the 25 ppm, and 26/60 (45%) of the males fed 100 ppm phosmet had liver adenomas. The incidence of adenomas, and the combined incidence of adenomas and carcinomas was significantly increased in male mice fed 100 ppm phosmet (p < 0.05). Among female mice, the incidence of liver adenomas was observed in 6/60 (10%) of the controls, 4/60 (7%) of the 5 ppm, 5/59 (8%) of the 25 ppm, and 11/60 (18%) of the 100 ppm phosmet groups. The small increase in incidence of liver adenomas in female mice fed 100 ppm phosmet was not statistically significant (Katz et al., 1984).

Stauffer Chemical Co. submitted an addendum to the initial report to EPA, to demonstrate that the increase in incidence of liver adenomas in the high dose phosmet-treated males was not significantly different from the incidence of these tumors in historical controls (Sprague and Turnier, 1986). The historical controls were comprised of mice purchased from the same supplier and housed at the laboratory at the same time as the oncogenicity study, but were from a different breeding laboratory. This argument to dismiss the significance of the increase in liver tumor effect of phosmet in male mice is weak, since concurrent controls from the same breeding laboratory are more suitable controls for comparison. EPA has considered the evidence from this study (Katz et al., 1984) as positive for carcinogenicity (EPA, 1998a).

Independent researchers have proposed that for tumors that occur spontaneously in experimental animals, a p value equal to or less than 0.01 should be used as an indicator of biological significance (Haseman et al., 1986). Results of the above study in mice would be regarded as of questionable significance. However, results from studies of phosmet’s potential to promote liver tumors (presented in Section V.C.4) add weight to the evidence supporting that phosmet increases the risk for liver tumors.

2. Rats:
In a chronic toxicity/carcinogenicity study, Sprague-Dawley rats (60 to 70/sex/dose) were fed 0, 20, 40 or 200 ppm R-1504® technical (95.2% phosmet) for up to 24 months. Ten animals from each treatment group and 20 animals from the controls were killed after a 12 month exposure period. A high dose satellite group (20/sex) was fed 400 ppm for 12 months. Survival rates of the rats were not affected by the phosmet treatments (Chang et al., 1991). Tumor incidences in males and females in the phosmet-treated groups were not significantly different from in the controls.

Groups of albino (strain unspecified) rats (25/sex/dose) were fed 0, 20, 40 or 400 ppm of phosmet in diet for two years in an unpublished study conducted for Stauffer Chemical Co. at Woodard Research Corp. (reviewed in JMPR, 1994). Body weight gain was depressed at the highest dose (statistical analysis not available). Pituitary adenomas were more frequent in some of the treated groups. The incidence of pituitary adenomas was 36% in controls, 21% in the group fed 20 ppm, 46% in the group fed 40 ppm and 56% in the group fed 400 ppm (details on surviving number of animals in each group, the incidence rates separated by sex, and p values were not available). The authors of the review commented that small number of survivors made this study difficult to interpret.

3. Dogs:
Groups of beagle dogs (three/sex/dose) were given 0, 20, 40 or 400 ppm phosmet in diet for two years in an unpublished study conducted for Stauffer Chemical Co. at Woodard Research Corp. (reviewed in JMPR, 1994). The very small group sizes in the study made it difficult to draw any conclusions about the carcinogenicity of phosmet.

4. Summary, Animal Studies:
B6C3F1 mice that were fed phosmet had a dose-related increase in incidence of liver adenomas when compared to concurrent controls, which was significant (p < 0.05) at the highest dose of 100 ppm. This increase in incidence of liver adenomas was not different than the incidence rate of these tumors in historical controls. There was no increase in the incidence of liver tumors in female mice (Katz et al., 1984; Sprague and Turnier, 1986). Two studies in rats (see Section V.C.4) have indicated a liver tumor promotion effect of phosmet. The results of carcinogenicity study in mice and tumor promotion effects in rats combined, provide evidence for liver tumor promotion potential of phosmet.

In other studies, no treatment-related increases in tumor incidences were reported in Sprague-Dawley rats fed phosmet in diet over two years (Chang et al., 1991). It was not possible to draw conclusions on the cancer causing potential of phosmet from another two year exposure study in albino rats and dogs (unpublished, summarized in JMPR, 1994).
C. Current Classification of Carcinogenicity by Other Agencies

1. IARC Classification:
Phosmet has not been evaluated for its carcinogenic potential by IARC (IARC web site: www.iarc.fr/).

2. NTP Classification:
The National Toxicology Program has not classified phosmet by its carcinogenic potential (USDHHS, 1998).

3. EPA Classification:
In a recent Re-registration Eligibility Decision Document on phosmet, the Human Effects Division (HED) Cancer Peer Review Committee of EPA agreed that “phosmet should be classified in Group C, or possibly human carcinogen” (EPA, 1997b). 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 an apparently early onset. Female mice had a significant dose-related trend for liver tumors and for mammary gland adenocarcinomas, as well. There is no evidence for carcinogenicity in an acceptable study in rats” (EPA, 1997b).

IV. Critical Evaluation of Breast Cancer Risk

A. Human Studies:
The few epidemiological studies of cancer risk that have been done in association with OP exposures have not addressed the risk of breast cancer among women exposed to phosmet.

B. Experimental Animal Studies:
There has been only one study done on chronic exposure effects of phosmet in each species (mice and rats). Laboratory rats tend to be more prone to developing mammary tumors. In rats exposed to phosmet, the incidence of mammary tumors was increased, but not significantly. Experimental mice exposed to phosmet were found to have an increased incidence of mammary tumors. While this increase was also not statistically significant, it was remarkable since mammary tumors are rare in experimental mice. The study of mice that were chronically exposed to phosmet was flawed and needs to be repeated.

1. Mice:
As described earlier (Section IV. B.), a two year carcinogenicity study was conducted for Stauffer Chemical Co., in which B6C3F1 mice (60/sex/dose) were treated with 0, 5, 25 or 100 ppm Imidan® technical (94.7% phosmet) in diet (Katz et al., 1984; Sprague and Turnier, 1986). Mammary gland tissue from the controls, females in the group fed the highest dose, and any animals with gross lesions were examined microscopically. Incidence of malignant mammary tumors was recorded in 4/60 (6%) controls and 6/60 (10%) females fed 100 ppm phosmet. Mammary glands of eleven animals from the group fed 25 ppm were examined microscopically: six of these animals (54% of mice examined; 10% of the group) had malignant (lymphomas and adenocarcinomas) mammary tumors. There was an increase in incidence of adenocarcinomas observed in 5/49 (10%) of the mice in the group fed 100 ppm, compared to 1/45 (2%) control rats (see Table 1 below). The small number of animals examined microscopically in most groups made a dose-related comparison in incidence of mammary tumors difficult. Mammary adenocarcinomas are rare in mice. These results suggest the need for a bioassay in mice, with detailed histopathological analysis of the mammary glands of all animals.

<table>
<thead>
<tr>
<th>Dose level (ppm)</th>
<th>0</th>
<th>5</th>
<th>25</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of mice/group</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Number of mice examined</td>
<td>45</td>
<td>15</td>
<td>11</td>
<td>49</td>
</tr>
<tr>
<td>Adenocarcinomas (malignant)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Lymphoma (malignant)</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hemangioma (benign)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

2. Rats:
In a study described earlier (Section IV. B.), Sprague-Dawley rats (60 to 70/sex/dose) were fed 0, 20, 40 or 200 ppm R-1504® technical (95.2% phosmet) for up to 24 months. Ten animals from each treatment group and 20 animals from the controls were terminated after 12 months. A high dose satellite group (20/sex) was fed 400 ppm for 12 months. The survival rates were not adversely affected by the phosmet treatments (Chang et al., 1991). Malignant adenocarcinomas were recorded in the mammary glands of 6/70 (9%) controls, 8/60 (13%) of the 20 ppm, 9/60 (15%) of the 40 ppm, and 4/60 (6%) of the 200 ppm dose females. In addition, one female in the 200 ppm had a mammary gland sarcoma. While there was a slight increase in incidence of mammary tumors in some of the phosmet-treated groups, the increase was not consistently dose-related or statistically significant.

3. Summary, Critical Evaluation on Breast Carcinogenicity:
While increase in incidence of mammary tumors has been observed in phosmet-treated female rats and mice, the increases were not consistently dose-related or statistically significant (Chang et al., 1991; Katz et al., 1984). The Cancer Peer Review Committee of EPA’s Health Effects Division has based its decision to classify phosmet in “Group C” or possibly human carcinogen, in part, on
the significant dose-related trend for mammary gland carcinomas in B6C3F1 mice (EPA, 1997b). Mice exposed to phosmet had an increased incidence of mammary adenocarcinomas. The very small number of animals examined in this study do not allow for a conclusion to be made about phosmet’s potential to cause mammary adenocarcinomas in mice.

C. Other Relevant Data on Breast Cancer Risk

1. Evidence of Endocrine Disruption:
Many of the risk factors associated with breast cancer, such as early age of menarche and late age at menopause, indicate that increased lifetime exposure to estrogen plays a role in increasing a woman’s risk for the disease. Hence, it is important to evaluate a chemical’s ability to mimic estrogen, or cause endocrine disruption that may affect the body hormone levels.

a. In Vivo Studies:
A phosmet emulsion in Tween 80 (10%) injected intraperitoneally (i.p.) in neonatal rats (strain not specified) was found to increase the mean relative weight of uteri and squamous cell metaplasia of the endometrial epithelium. These are characteristic estrogen-mediated events (Vargova et al., 1994). However, the Tween 80 treated control rats revealed the same changes, indicating that the estrogenic effects may have been caused by the surfactant, Tween 80 rather than phosmet (Vargova et al., 1994). Hence, this study was not very useful to determine if phosmet injected into rats has an estrogenic effect.

b. Effect on Spermatogenesis:
Endocrine disruptive effects could disrupt steroidogenesis, which could lead to a suppression of spermatogenesis. Phosmet treatments of (C3H X C57BL/6) F1 hybrid mice (6/group) using two different routes (per os and i.p.) for five consecutive days did not induce teratospermia or frequency of morphologically visible sperm abnormalities (Quinto et al., 1989).

Phosmet does not seem to be an endocrine disruptor in these studies.

2. Reproductive and Teratogenic Effects:
Reproductive toxicity is sometimes a result of endocrine disruption. In an unpublished two-generation reproductive toxicity study in rats, phosmet caused a reduction in fertility and mating performance accompanied by reduced testes and ovary weights. The reproductive effect was more severe in the second generation (as reported in EPA, 1997). Details of this evaluation were not available to assess if the reduced fertility and mating performance were due to endocrine disruption.

Other studies on reproductive toxicity of phosmet summarized briefly below, provide some evidence for its embryotoxicity and teratogenicity, but do not indicate endocrine disruption effects.

In 1976, Soviet and American investigators independently conducted parallel studies on the reproductive toxicity and teratogenic potential of phosmet in rat. In the American study, CD rats were given 0, 5, 10, 20, 25 and 30 mg/kg/day of Imidan® (95.8% phosmet) in either diet, or by gavage from day six through 15 of gestation in one study (Staples et al., 1976). The highest two doses were lethal to the most sensitive dams and toxic to the rest. However, there were no teratogenic effects observed. These results were in contrast with the Soviet study in which groups of pregnant Wistar rats (8 to 10 rats/group) were given 30 mg/kg phosmet by gavage on either the ninth or thirteenth day of gestation; additional groups were given 1.5 mg/kg or 0.06 mg/kg phosmet every other day throughout the pregnancy. Rats that received 30 mg/kg on the ninth day, or 1.5 mg/kg phosmet every other day, had a significantly increased rate of post-implantation mortality (p < 0.05) (Martson and Voronina, 1976). The number of corpora lutea and implantation sites were not significantly affected in the treated females, indicating that estrogen-dependent events were not affected.

Phosmet was one of the chemicals evaluated for embryotoxicity in a study in New Zealand rabbits. Pregnant female rabbits (n = 5) were administered 35 mg/kg dose of phosmet daily by stomach tube on days seven through 12 of pregnancy. There was no increase in number of resorptions or malformed fetuses in the rabbits treated with phosmet (Fabro et al., 1966).

An unusually high incidence of abortions and congenital abnormalities was observed in a beef herd in United Kingdom (UK) in the summer of 1980 (Nicolson et al., 1985). Exposure to a teratogen during early pregnancy was suspected as the cause for the abnormalities. The cows involved had been treated with a pour-on warble fly dressing (20% phosmet), a vaccine against bovine rhinotracheitis and fenbendazole in November of the previous year. The deformed calves were born over a period of three months in summer, indicating the most effective window for teratogen exposure to lie between October and December of the previous year. There were many potential teratogens involved and whether the one-time exposure to phosmet had any causative role could not be ascertained from this study. The silage fed to animals in the previous year were not available for a toxicological evaluation.

Studies of reproductive toxicity and teratogenicity of phosmet have given equivocal results. Two studies in rats have reported reproductive toxicity (EPA, 1997; Martson and Voronina, 1976), while a third study observed toxicity to dams, but no teratogenicity or reproductive toxicity (Staples et al., 1976). Phosmet was not found to affect the number of normal fetuses in New Zealand rabbits (Fabro et al., 1966). There was a case-report of high incidence of abortions and congenital abnormalities in a beef herd that had been exposed to phosmet (Nicolson et al., 1985), but phosmet was only one of several possible teratogens that may have been involved.
3. Tests of Mutagenicity and Genotoxicity:

A wide variety of in vivo and in vitro test systems have been developed to assay a chemical's ability to induce mutations or genotoxic damage and thus affect the risk for cancer. None of these assays alone provide sufficient evidence for the mutagenicity of an agent. Collective evidence from several assays in different systems is useful for evaluating a chemical's genotoxic potential. Below, we have divided the assays of mutagenicity and genotoxicity based on the test systems used.

a. Studies in Humans and Animals:

Increased chromosome damage in the blood cells of humans has been used as a screening method to detect exposure to mutagens. Peripheral blood lymphocytes of manufacturing workers (25 males) at a plant in Budapest were examined for chromosome aberrations (Kiraly et al., 1977; Kiraly et al., 1979). The workers wore face masks during work hours and the concentration of phosmet in the air of the workshop was measured at 0.26 mg/m³. Workers exposed at a plant in Budapest were examined for chromosome aberrations (Kiraly et al., 1977; Kiraly et al., 1979). The workers wore face masks during work hours and the concentration of phosmet in the air of the workshop was measured at 0.26 mg/m³. Workers exposed to phosmet were found to have a three-fold increase in frequency of chromatid-type aberrations when compared to factory employees who did not work in manufacture or handling of chemicals. Stable chromosome aberrations of workers in phosmet production were not significantly different from in controls. There was no reliable information on previous exposure histories or disease conditions of the manufacturing workers to assess the exposure contribution of phosmet.

In an in vivo assay, CD-1 mice fed 17 mg/kg of phosmet were not observed to have an increase in micronuclei or chromosome aberrations in their bone marrow cells, indicating a lack of a genotoxic effect for the insecticide (unpublished study, as reported in EPA, 1997b).

Diseases have long been regarded as caused by either mutations in DNA, or by pathogens. Bovine spongiform encephalopathy (BSE) and the related scrapie disease in sheep, both affecting the central nervous system, challenge this dogma. An irreversible modification of the prion protein has been implicated as the causative agent for these diseases. The following papers present a unique medical hypothesis that a mutagenic trigger (phosmet) led to the post-translational covalent modification of prion proteins, and the onset of the BSE epidemic in the UK (Purdy, 1998; Purdy, 1996). The correlation between the use of phosmet and the onset of the BSE epidemic has been outlined as evidence. However, the BSE epidemic also coincided in timing with scrapie-infected cattle feed being used in the UK. The epidemiological survey above does not provide sufficient evidence to dismiss the role of the scrapie-infected cattle feed in the spread of the disease.

b. Studies in Bacteria and Yeast:

Phosmet did not induce reverse mutations in three different bacterial systems used in one study: Salmonella typhimurium, Escherichia coli and Bacillus subtilis (Shirasu et al., 1976). In other studies however, phosmet, with or without metabolic activation with S9, was found to induce reverse mutations in Salmonella (Moriya et al., 1983; Vlckova et al., 1993) and Saccharomyces (Vlckova et al., 1993). In an unpublished study reviewed by EPA, phosmet induced revertant mutations in a dose-related manner, with or without metabolic activation (EPA, 1997b). Hence, two out of three studies in bacteria and yeast indicate a mutagenic potential of phosmet.

c. Studies in Isolated Human and Animal Cells:

Results of unpublished studies of phosmet's mutagenic potential in mouse lymphoma cells and human fibroblasts have been summarized in a report of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) on phosmet (1994) and in EPA's assessment of its toxicity (EPA, 1997b). Most studies done on phosmet in isolated human and animal cells have indicated some mutagenic potential. In a study of mouse lymphoma cells, phosmet induced sister chromatid exchanges (SCE) in a dose-related manner, with or without S9-activation. In another study, phosmet, without any metabolic activation, induced mutations at the tk locus in a dose-related manner (EPA, 1997b). The presence of S9 in this assay reduced the mutagenic effect of phosmet. Three different concentrations of phosmet used in a cell transformation assay of BALB/3T3 cells (6, 8 and 14 µg/ml) caused at least a two-fold increase in the number of foci (EPA, 1997b).

Phosmet induced single-strand breaks in the DNA of exponentially growing hamster cells V79, indicating the potential to cause DNA damage (Slamenova et al., 1992). In the same study, it also caused a significant increase (p value not stated) in morphologically transformed colonies of Syrian hamster embryo cells (SHE).

The results from two available studies of phosmet’s genotoxic potential in vivo are different. While the epidemiological survey of humans exposed to phosmet indicates a genotoxic potential (Kiraly et al., 1979), phosmet tested negative in an assay for genotoxicity in experimental mice (EPA, 1997b). The routes of exposure were different: occupational exposure in humans was mainly inhalation and dermal, while the mice were fed the insecticide. No studies of inhalation exposure of experimental animals were found. A hypothesis implicating phosmet exposure of cattle as the trigger for the BSE epidemic in the UK (Purdy, 1998; Purdy, 1996) was based on inadequate evidence. The results of studies in isolated cells indicate that phosmet has the potential to induce mutations and DNA damage in the absence of metabolic activation (JMPR, 1994; Slamenova et al., 1992). One study in isolated cells indicates that metabolic activation may actually decrease phosmet’s mutagenic potential. This result is supported by the lack of genotoxic effects in the bone marrow of mice fed phosmet, an in vivo study described earlier (unpublished studies, as reported in EPA, 1997b).
4. Evidence of Tumor Promotion:
Agents that act as tumor promoters, i.e. increase the effect of known carcinogens, could increase the life-time risk of cancer. Assays have been developed to evaluate the tumor promotion effect of chemicals in animals that have already been treated with known carcinogens. In one tumor promotion assay, two groups of Fischer 344 rats (five, male) were injected (i.p.) with 200 mg/kg of the liver carcinogen diethylnitosamine (DEN). A third group was injected with saline. One of the groups of DEN-treated rats and the control rats were fed 400 ppm phosmet (99.8% phosmet) in diet for six weeks, starting from week two. All rats had a partial hepatectomy during week three. Rats were sacrificed after six weeks of treatment. The group of rats treated with phosmet had a significant increase (p < 0.05) in the number and area of pre-neoplastic lesions assayed as glutathione S-transferase positive (GST-P) foci in the liver, compared to the rats that were exposed to DEN, but no phosmet (Cabral et al., 1991). This study adds weight to the results of the chronic toxicity study described in Section IV.B.1, in which phosmet exposures through diet increased the frequency of liver adenomas in male mice (Katz et al., 1984).

In a multi-organ tumor promotion assay, two groups of F344 rats (16, male) were initiated using an injection (i.p.) with 100 mg/kg DEN, followed with injections of 20 mg/kg N-methyl-N-nitrosourea (MNU) on days 2, 5, 8, 11, and then given 1% N-bis(2-hydroxypropyl)nitrosamine (DHPN) in drinking water for two weeks. A third group of rats (10) received none of the three carcinogens and served as controls. The carcinogen treated groups of rats were fed 0 or 400 ppm phosmet (99.8% phosmet) for 16 weeks following the treatments with the carcinogens. Phosmet treatments were found to significantly increase (p < 0.01) the number of GST-P foci in the liver and as pepsinogen-1 altered pyloric gland (PAPG) lesions in the stomach, indicating a potential for phosmet to act as a multi-organ tumor promoter (Hasegawa et al., 1993).

5. Immunological Effects:
A compromised immune system may fail to detect or fight cancer cells in the body and thus increase the risk of cancer. Studies of immunological effects of phosmet in experimental animals were not found. Immune-mediated skin lesions have been reported in pets treated with phosmet-containing flea dips. There were two case-reports of immune-mediated toxic epidermal necrolysis, in a female Himalayan cat and a female Corgi dog (Frank et al., 1992). These case reports do not provide adequate evidence for the immunotoxicity of phosmet, but indicate the need for an evaluation of immune effects of phosmet in experimental animals and occupationally-exposed humans.

6. Summary of Other Relevant Data on Breast Cancer Risk:
Estrogenic effects were observed in one study in rats treated with phosmet, but the effects were later found to be associated with the surfactant (Tween 80) used along with the insecticide (Vargova et al., 1994). Most studies of reproductive toxicity of phosmet have not observed reduced fertility or mating performance in treated animals. There has been one report of reduced fertility and mating performance, in a two-generation study in rats (as reported in EPA, 1997b). Details of this study were not available to determine if the cause may have been phosmet-induced endocrine disruption. Phosmet has tested positive for mutagenicity in the majority of assays in bacteria and yeast, as well as in isolated mammalian cells (JMPR, 1994; EPA, 1997b). However, results of its genotoxic potential in in vivo assays have been equivocal (EPA, 1997b). Phosmet has been found to act as a liver tumor promoter and a multi-organ tumor promoter in experimental rats (Cabral et al., 1991; Hasegawa et al., 1993). Phosmet has not been evaluated for its immuno-toxicity in experimental animals.

V. Other Information

A. Environmental Fate and Potential for Human Exposure:
Phosmet exposure can occur through dermal contact, inhalation or ingestion (EPA, 1987). Exposure risk for phosmet is being evaluated by EPA for the process of its re-registration eligibility decision and tolerance reassessments (EPA, 1998). Preliminary analyses on occupational and non-occupational exposure risks are available for phosmet at EPA's web site: http://www.epa.gov/pesticides/op/phosmet.htm. Some of the results from EPA's assessment of exposure potential to phosmet, and other studies on occupational and non-occupational exposures are summarized below.

1. Occupational Exposure:
In the absence of adequate studies that have evaluated levels of exposure to phosmet in handlers, EPA has conducted an occupational handler risk assessment for phosmet using data from the Pesticides Handlers Exposure Database (PHEP). PHEP is a database designed by representatives from EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection association. It contains voluntarily submitted empirical exposure data for workers handling or applying pesticides for over 2,000 monitored events. Although not chemical specific for phosmet, this data allows for estimate of exposure in various exposure scenarios, based on the application rates and the equipment used for application and personal protection. For phosmet, when appropriate protective equipment is used, the anticipated exposure risk estimates are below EPA's level of concern. However, exposure and risk for occupational handlers involved in 13 scenarios that involve mixing, loading
and applying wettable powders using air-blast sprayers or fixed-winged aircraft, or flagging for aerial applications, exceeded EPA’s level of concern (EPA, 1998a).

There are very few studies that have evaluated chemical-specific exposure levels for phosmet. In a study that evaluated chromosome aberrations in manufacturing workers, researchers detected 0.26 mg/m³ phosmet residues in the air of the workshops (Kiraly et al., 1979). In an epidemiological survey for neurotoxicity, urine samples collected from a cohort of 90 male pesticide applicators of apple orchards in NYS were assayed for OP metabolite O,O-dimethyl phosphorothionate (DMTP) (Stokes et al., 1995). Phosmet was one of the five most used OP by these applicators. DMTP levels in the urine of applicators were found to be proportional to the number of tanks loaded, acres sprayed, and the number of hours applicators sprayed. However, exposure to phosmet itself could not be estimated from this study.

Leaf and ground cover residues were monitored after phosmet spraying application at the recommended rate of 1.68 kg AI/hectare (ha) to an orchard in a study that was evaluating the extent of drift from such operations. Phosmet residues persisted for several weeks after application, with levels on ground cover samples > 100 ppm for the first week, indicating the potential for post-application exposure for orchard workers (MacNeil and Hikichi, 1986). In 1973, clinical symptoms of OP poisoning were reported in 32 men who had worked for three days in vineyards in California that had been sprayed with OPs, including phosmet. Records indicated that three months had elapsed since phosmet application. Dislodgeable phosmet residues on grape leaves were measured to be 30 ppm. Many OPs were involved in this incident, which together may have caused the clinical symptoms (Maddy, 1976). Another case-report documented OP toxicity symptoms in a female pet groomer who had treated 8 to 12 dogs each day for three years, with a phosmet-containing flea dip product (Rosenberg and Quenon, 1988). The flea-dip was improperly used in this case: a concentrated solution was sponged on directly on the flea-infested areas, instead of being properly diluted.

These studies indicate that occupational exposure to phosmet can occur during manufacture, application, or on re-entry into treated areas. However, specific data on levels of phosmet exposure during mixing, loading and spraying operations is lacking.

2. Potential of Exposure for the General Population:
The FQPA mandates that EPA conduct an aggregate exposure and concomitant risk assessment from food, water, residential and other non-dietary sources. According to a preliminary risk assessment document in the public docket, the Health Effects Division of EPA has not conducted an aggregate exposure and risk assessment for phosmet. This is because two of the exposure estimates which would be combined for an aggregate exposure estimate for phosmet, residential and acute dietary exposure estimate, by themselves exceed the Agency’s level of concern (EPA, 1998a). The lack of appropriate neurotoxicological studies required the Agency to use an additional safety factor of 3X for the risk assessments for phosmet. Availability of an adequate neurotoxicity study would allow for the elimination of the additional 3X uncertainty factor. Further, more refined exposure estimates may also reduce the Agency’s level of concern for the acute dietary exposure risk of phosmet. The main concern stated in EPA’s assessment report was the risk of residential post-application exposure. This could include exposure of household members, including children to residues of phosmet on floors and surfaces for days after its use. However, actual studies evaluating the extent of such exposures were not found.

a. Food and Water:
The US Department of Agriculture (USDA) collects information on pesticide residues in raw agricultural produce through the Pesticide Data Program (PDP). This program collects information on the nationwide pesticide use and pesticide residues on foods, and provides the information to EPA. Phosmet residues were not detected in samples of milk, canned peaches, potatoes, sweet corn, sweet peas or tomatoes analyzed for PDP. Phosmet residues were detected in 6% of the apple samples (ranging from 0.01 ppm to 1.4 ppm); in 1% grape samples (0.01 to 0.5 ppm); 0.1% orange samples (0.01 to 0.04 ppm); 16% of fresh peach samples (0.01 to 1.4 ppm); 19% of pear samples (0.008 to 0.72 ppm); and 6% of sweet potato samples (0.01 to 0.42 ppm) (EPA, 1999). None of these residue levels violated the established tolerances for phosmet. EPA performed acute and chronic dietary risk analyses for phosmet, using the PDP data from the 1995 to 1996 survey (EPA, 1998b). The chronic dietary risk for phosmet was below EPA’s level of concern for all population subgroups.

Acute dietary exposure risk estimates were also calculated by EPA. The tolerance-levels of phosmet for single serving commodities and anticipated residue levels for blended commodities were used for the acute dietary risk assessments. The acute dietary risk estimate for phosmet was above the Agency’s level of concern for infants and children (EPA, 1998b). The registrant (Gowan Co.) has recently submitted a more refined Monte Carlo analysis (based on probabilistic risk assessment technique) to estimate acute dietary exposure and risk, which is under review. Results of EPA’s reassessment of the acute dietary risk after incorporating this analysis are not yet available. If refined exposure estimates still indicate an acute dietary risk above the Agency’s level of concern, EPA may modify the tolerances for phosmet, and/or restrict the use of phosmet.

Phosmet undergoes rapid hydrolysis in water, with its half-life ranging from 7.5 to 9.7 days at pH 5, to 5.5 minutes at pH 9 (JMPR,
applicator families, a higher frequency of detectable DMTP was
employed as an agricultural worker. Among children of
their urine (p = 0.015) than children from families where no
pesticide applicator, had significantly higher levels of DMTP in
assayed in the urine of the children as an indicator of exposure.
most used dimethyl OP. DMTP, a metabolite of dimethyl OP, was
spraying period January to July of 1995, making it the second
applicators surveyed for this study, 33% had used phosmet during
on small family orchards (Loewenherz et al., 1997). Of the 48
farm-workers in central Washington State who worked primarily
ancestors of applicators, were analyzed for four OPs including phosmet. The farm
families lived within 200 ft of an operating apple or pear orchard,
while all reference homes were within a mile from an orchard.
Residues of all four OP were found in 62% of the household dust
samples, indicating the potential for exposure to phosmet in such
residential settings (Simcox et al., 1995). However, airborne
residues of phosmet were not assayed by these studies.

b. Air:
While evaporation of phosmet is negligible, inhalation of airborne
particles carrying residues of phosmet is a potential route of
exposure, especially during spraying or dispersal. There have been
no studies of phosmet residues in the air of residential settings.
Studies summarized in the next section document the presence of
phosmet in the dust of homes that are within 200 feet (ft) of orchards
(Loewenherz et al., 1997; Simcox et al., 1995). However, airborne
residues of phosmet were not assayed by these studies.

c. Residential Dust/Surface Residues:
There have been two studies indicating residential exposure to
phosmet in homes of applicators, especially those that lie within
close proximity to an orchard or vineyard. These studies indicate
the potential of para-occupational exposure risk, especially for
children and infants living in these homes.

Household dust and soil samples from children’s play areas from
59 residences, of 26 farming, 22 farm-worker and 11 non-farming
families were analyzed for four OPs including phosmet. The farm
families lived within 200 ft of an operating apple or pear orchard,
while all reference homes were within a mile from an orchard.
Residues of all four OP were found in 62% of the household dust
samples, indicating the potential for exposure to phosmet in such
residential settings (Simcox et al., 1995).

The above group of investigators conducted a follow-up study to
assess the actual exposure of children (infants to six years of age)
of farm-workers in central Washington State who worked primarily
on small family orchards (Loewenherz et al., 1997). Of the 48
applicators surveyed for this study, 33% had used phosmet during
the spraying period January to July of 1995, making it the second
most used dimethyl OP. DMTP, a metabolite of dimethyl OP, was
assayed in the urine of the children as an indicator of exposure.
Children from families with at least one member working as a
pesticide applicator, had significantly higher levels of DMTP in
their urine (p = 0.015) than children from families where no one
was employed as an agricultural worker. Among children of
applicator families, a higher frequency of detectable DMTP was
observed in the urine of children who lived within 200 ft of an
orchard (p = 0.036), than those who lived further away. Also,
younger children were observed to have higher levels of exposure
than the older siblings. This study documents para-occupational
exposure of children in families of applicators who live in close
proximity to the application site to OP, including phosmet.
However, since only one common metabolite was assayed, the
study does not indicate the chemical-specific exposure levels. Air
borne residues of OP were not measured in these residences.

d. Field Soil:
Half-life of phosmet in soil has been estimated at six days in soils
above pH 8 (JMPR, 1997). Phosmet remains in the top 10 cm
layer of soil. Some studies have detected trace amounts of phosmet
oxon in treated soils, while others have not. Studies on phosmet
residues in plants grown on phosmet treated soils show
undetectable levels of the insecticide or its oxygen analogue
(JMPR, 1997).

3. Storage and Excretion of Phosmet in Mammals
a. Lactation and Breast Milk:
There were no reports found on phosmet residues in human milk.

In one study, pour-on treatments of dairy cows (5% phosmet
preparation) resulted in phosmet residues in dairy milk, with peak
level concentration of 0.04 mg/kg at 12 hours after treatment
(O’Keefe et al., 1983). Phosmet residues were eliminated in milk
over 40 to 50 hours after treatments. In another study, four lactating
Jersey cows fed 0.22 mg/kg bd wt of phosmet (92.6% phosmet)
per day in silage for 42 days, had no detectable levels of phosmet
or phosmet oxon in their milk (assay time not specified) (Johnson
and Bowman, 1968).

Adult female lactating goats fed 5 mg/kg (low dose) or 10 mg/kg
(high dose) for seven days, or a single acute dose (200 mg/kg) of
phosmet, through a stomach tube did not have any detectable levels
diethyl phosphate metabolites in the milk (Mount, 1984).

b. Tissue Distribution and Excretion:
The primary route for excretion of phosmet in mammals is through
the urine (JMPR, 1997). In rats fed radioactive phosmet (three
males and two females), 79% of the administered radioactivity
was excreted in the urine, and 19% in feces, 72 hours after
treatment. The main metabolite was phthalamic acid. Less than
1% of the excreted radioactivity appeared as phosmet or its oxon.
Tissue residues accounted for 2.6% of the radioactivity (Ford et
al., 1966).

Another study in rats identified phthalamic acids and phthalic acids
to account for 62% of the excreted metabolites (McBain et al.,
1968). Phosmet oxon was detected following incubation of
phosmet with rat liver microsomes and reduced nicotinamide
adenine dinucleotide phosphate (NADPH) enzyme system in vitro (McBain et al., 1968).

Goats that were fed phosmet had the highest levels of O,O-dimethyl phosphorodithioate (DMDTP) and DMTP in the urine during the first 24 hours after treatment (Mount, 1984). In another study, goats (strain unspecified) treated with 8 ppm radiolabeled phosmet in diet for four days had most of the dose excreted in the urine within 24 hours of each dose. Less than 6% of the dose remained in the edible tissues at slaughter, 13 to 14 hours after the final dose. Phosmet residues are not found to be retained in the fat (JMPR, 1994).

Trans-placental transfer of phosmet was reported in albino pregnant rats that were treated with radioactively labeled insecticide by gavage. Intact phosmet and phosmet oxon were detected in the fetus, and the half-life of phosmet in the removed fetuses was calculated to be 50 to 70 minutes (Ackermann et al., 1976).

VI. Summary and Recommendation for Breast Cancer Risk Classification

According to this evaluation, phosmet should be classified in Group 3, not classifiable as to its breast carcinogenicity in humans (please see Appendix B for an explanation of the BCERF Breast Cancer Risk Classification Scheme). This is based on the following:

- **Human studies:** There have been no published studies on breast cancer incidences in women who may have been exposed to this insecticide in the past.
- **Animal studies:** No significant increase in incidence of mammary gland neoplasms was reported in phosmet-fed mice or rats (Chang et al., 1991; Katz et al., 1984).
- **Related mechanisms:** There is limited evidence for phosmet’s potential to affect cancer risk through other mechanisms. There is evidence for the mutagenic potential of phosmet in bacteria, yeast and isolated animal cells (EPA, 1997b; JMPR, 1994). There is evidence for its ability to act as a liver and multi-organ tumor promoter in rats (Cabral et al., 1991; Hasegawa et al., 1993). This evidence adds weight to the results of a carcinogenicity study, in which long-term exposure to phosmet was associated with increased incidence of liver adenomas and carcinomas in mice (Katz et al., 1984). Hence, there is limited evidence that phosmet may affect cancer risk by acting as a tumor-promoter. However, phosmet has not been tested for its ability to promote mammary tumors and thus affect breast cancer risk.

VII. Identification of Research Gaps, and Other Recommendations

- Epidemiological studies have observed an increased risk for leukemia and NHL in association with OP exposure (Brown et al., 1990; Cantor et al., 1992). However, the number of cases and controls who had used phosmet in these studies was small. Exposure to different OPs, including phosmet, and cancer risk needs to be followed in larger case-control studies.
- The epidemiological survey of humans exposed to phosmet through inhalation and dermal routes indicated a genotoxic potential. This result indicates the need for a study on the effects of inhalation exposure to phosmet in experimental animals.
- Phosmet fed to laboratory mice caused an increased incidence of mammary gland adenocarcinomas in one study. A detailed histopathological analysis was not carried out on all animals in this study. Mammary gland adenocarcinomas are rare in mice. This study needs to be repeated, with more careful histopathological analysis of the mammary glands of all animals.
- Phosmet has been found to be a multi-organ tumor promoter in experimental rats. It should be tested for its ability to promote mammary tumors in rats exposed to mammary carcinogens.
- Phosmet’s effects on the immune system have not been evaluated in experimental animals.
- Studies are needed to assess the occupational exposure to phosmet during manufacture, mixing and application.

VIII. Summary of New Human Studies Currently Being Conducted

**Strategy to Identify Non-Additive Response to Chemicals**

**Principal Investigator:** Vogel, J.S., University of California, Livermore (extracted from the CRISP Database)

In this study, mice will be exposed to different multiple combinations of OP at environmentally realistic doses to evaluate if there is a non-additive or synergistic effect to multiple chemicals in the OP family at low doses.

**Organophosphate Exposure in Migrant FarmWorker Children**

**Principal Investigator:** Woody, M., US Department of Health and Human Services (from the CRISP Database)

The study will determine the prevalence of OP exposure and neurobehavioral problems in children of migrant farm workers who live in State of California-run Migrant Housing Centers. Relationships between mother’s work and exposure, and the exposure and neurobehavior of her children will be assessed.
Occupational Injury in Hispanic Farmworker Families
Principal Investigator: McCurdy, S.A., University of California, Davis (extracted from the CRISP Database).
Migrant and seasonal workers in California will be evaluated for occupational injury in association with OP exposure, piece-work versus hourly pay, language appropriate safety training, and the role of multiple employment. The cohort is expected to consist of 500 farmworker families who live in six Migrant Housing Centers close to Davis, California.

Pesticide Risks to Normal Development and Learning
Principal Investigator: Faustman, E., University of Washington, Seattle (from the CRISP Database)
A risk research center at the University of Washington is conducting two laboratory based and two field based projects to 1) identify mechanisms for developmental neurotoxicity of pesticides and 2) identify the impact of genetic polymorphisms for paraoxonase enzyme, on the developmental neurotoxicity of organophosphate pesticides. The two field based projects will 1) identify critical exposure pathways for children and 2) design ways to intervene, to reduce children’s exposure to pesticides.

Exposure of Indoor Pesticides and Effects on Growth and Neurodevelopment
Principal Investigator: Berkowitz, G. S., Mount Sinai School of Medicine, New York, NY
Neurodevelopmental impact of organophosphate pesticide exposure of children living in inner cities will be evaluated in a five-year prospective epidemiological study of an ethnically diverse birth cohort. Maternal serum, maternal urine, cord blood, and infant urine will be analyzed to assess environmental exposures. Questionnaires will be used to assess indoor pesticide use, residential history, dietary intake (especially fish consumption), as well as other relevant characteristics. Carpet dust, as well as “hand wipe” samples and wipe samples of toys will be assessed for chlorpyrifos, a frequently used OP which has been a special concern for residential exposure of children.
IX. Bibliography


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Maddy, K. (1976). Current considerations on the relative importance of conducting additional studies on hazards of field worker exposure to pesticide residues as compared to studying other occupational safety hazards on the farm. In Pesticide residue hazards to farm workers (Salt Lake City, UT: National Institute for Occupational Safety and Health), pp. 125-142.


## X. Appendix A. Common Abbreviations, Acronyms and Symbols

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACGIH</td>
<td>American Conference of Governmental Industrial Hygienists</td>
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<tr>
<td>ADI</td>
<td>acceptable daily intake</td>
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<tr>
<td>AI</td>
<td>active ingredient</td>
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<td>ATSDR</td>
<td>Agency for Toxic Substances and Disease Registry</td>
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<tr>
<td>BCERF</td>
<td>Program on Breast Cancer and Environmental Risk Factors in New York State, based in Cornell’s Center for the Environment, Institute for Comparative and Environmental Toxicology</td>
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<tr>
<td>bd wt</td>
<td>body weight</td>
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<tr>
<td>BSE</td>
<td>bovine spongiform encephalopathy</td>
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<td>CAS</td>
<td>Chemical Abstract Service</td>
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<tr>
<td>CDC</td>
<td>Center for Disease Control and Prevention</td>
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<tr>
<td>CFE rats</td>
<td>Carworth Farm E strain rats</td>
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<tr>
<td>CIE</td>
<td>Cornell University’s Center for the Environment</td>
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<td>CHO</td>
<td>Chinese hamster ovary</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>Cl</td>
<td>chloride</td>
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<td>cm</td>
<td>centimeter</td>
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<td>Co.</td>
<td>company</td>
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<td>Corp</td>
<td>corporation</td>
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<tr>
<td>CRISP</td>
<td>Computer Retrieval of Information on Scientific Projects; database of scientific intra and extramural projects supported by the Dept. of Health and Human Services (i.e., NIH, EPA, USDA)</td>
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<tr>
<td>DEN</td>
<td>diethylnitrosamine</td>
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<tr>
<td>DHPN</td>
<td>N-bis(2-hydroxypropyl)nitrosamine</td>
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<td>DMDTP</td>
<td>O,O-dimethyl phosphorodithioate</td>
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<tr>
<td>DMTP</td>
<td>O,O-dimethyl phosphorothionate</td>
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<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<tr>
<td>EPA</td>
<td>Environmental Protection Agency</td>
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<tr>
<td>E-SCREEN</td>
<td>screening assay for estrogenicity that measures proliferative response in estrogen-dependent breast tumor cells</td>
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<tr>
<td>FAO</td>
<td>World Food and Agricultural Organization</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FQPA</td>
<td>Food Quality and Protection Act of 1996</td>
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<td>ft</td>
<td>foot</td>
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<tr>
<td>GST-P</td>
<td>glutathione S-transferase P</td>
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<tr>
<td>GUP</td>
<td>General Use Pesticide</td>
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<tr>
<td>ARC</td>
<td>International Agency for Research on Cancer, headquartered in Lyon, France</td>
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<tr>
<td>ICET</td>
<td>Institute for Comparative and Environmental Toxicology</td>
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<tr>
<td>i.p.</td>
<td>interperitoneal</td>
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<tr>
<td>JMPR</td>
<td>Joint FAO/WHO Meeting on Pesticide Residues</td>
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<tr>
<td>kg</td>
<td>kilogram</td>
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<td>L</td>
<td>liter</td>
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<td>lbs</td>
<td>pounds</td>
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<td>m</td>
<td>meter</td>
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<tr>
<td>MCF-7</td>
<td>Michigan Cancer Foundation; cells derived from human breast tumor</td>
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<tr>
<td>MCS</td>
<td>multiple chemical sensitivity</td>
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<td>MDA</td>
<td>malondialdehyde</td>
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<td>mdr</td>
<td>multidrug resistance</td>
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<td>µg</td>
<td>microgram</td>
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<tr>
<td>mg</td>
<td>milligram</td>
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<tr>
<td>MNU</td>
<td>N-methyl-N-nitrosourea</td>
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<tr>
<td>MTD</td>
<td>maximum tolerated dose</td>
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<tr>
<td>n</td>
<td>number of subjects/animals in the group</td>
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<tr>
<td>NADPH$_2$</td>
<td>reduced nicotinamide adenine dinucleotide phosphate</td>
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<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
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<tr>
<td>NHL</td>
<td>non-Hodgkin’s lymphoma</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>NOAEL</td>
<td>no observable adverse effect level</td>
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<tr>
<td>NTIS</td>
<td>National Technical Information Service; repository for federal agency technical reports</td>
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<tr>
<td>NTP</td>
<td>National Toxicology Program</td>
</tr>
<tr>
<td>NY</td>
<td>New York</td>
</tr>
<tr>
<td>NYS</td>
<td>New York State</td>
</tr>
<tr>
<td>OP</td>
<td>organophosphate pesticide</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>OSHA</td>
<td>Occupational Safety and Health Administration</td>
</tr>
<tr>
<td>PDP</td>
<td>Pesticide Data Program</td>
</tr>
<tr>
<td>P-gp</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td>PHEP</td>
<td>Pesticides Handlers Exposure Database</td>
</tr>
<tr>
<td>ppb</td>
<td>parts per billion</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>RFd</td>
<td>reference dose</td>
</tr>
<tr>
<td>SCE</td>
<td>sister chromatid exchange</td>
</tr>
<tr>
<td>SLRL</td>
<td>sex-linked recessive lethals</td>
</tr>
<tr>
<td>TCP</td>
<td>3,5,6-trichloro-2-pyridinol</td>
</tr>
<tr>
<td>TLV</td>
<td>threshold limit value</td>
</tr>
<tr>
<td>TWA</td>
<td>time-weighted average</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>USDA</td>
<td>United States Department of Agriculture</td>
</tr>
<tr>
<td>USEPA</td>
<td>United States Environmental Protection Agency</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Symbols:
α  alpha
β  beta
γ  gamma
μg  microgram
μM  micromolar
ng  nanogram
<  less than
>  greater than
%  percent
p  p value
±  plus or minus
=  equal to
®  registered trademark
XI. Appendix B. Critical Evaluations of Breast Cancer Risk

This includes an overview of the Critical Evaluations and explanation of the BCERF Breast Cancer Risk Classification Scheme

The Process

Starting Point - Existing Critical Evaluations on Evidence of Carcinogenicity
- IARC Monographs (International Agency for Research on Cancer)
- NTP ARC (National Toxicology Program, Annual Report on Carcinogens)
- ATSDR (Agency for Toxic Substances and Disease Registry)

Conduct Literature Searches using databases to obtain historical and the most recent information; i.e. Toxline, Medline, Biosis, Cancerlit
  - Peer-reviewed scientific literature-available through Cornell libraries and interlibrary loans
  - Technical Reports-NTIS-National Technical Information Service
  - TOXNET databases—EPA’s IRIS database source of oncogenicity and regulatory status information
  - Grey literature—Studies submitted to EPA that are not published:
    - Industry generated oncogenicity studies
    - Some abstracts (short summaries) are on line (IRIS database)
    - Request reports from industry
    - Request reports from EPA through Freedom of Information Act

The Critical Evaluation will include some general background information, including chemical name, CAS#, trade name, history of use, and current regulatory status.

Evidence of cancer in other (non-breast) organ systems will be provided in synopsis form with some critical commentary, along with the current overall carcinogenicity classification by international (IARC) and US Federal Agencies (NTP, EPA).

Human epidemiological studies, animal studies, and other relevant studies on possible mechanisms of carcinogenesis are critically evaluated for evidence of exposure to agent and breast cancer risk based on “strength of evidence” approach, according to a modification of IARC criteria as listed in the IARC Preamble. (See below for a more detailed explanation of the BCERF Breast Cancer Risk Classification scheme)

The emphasis of the document is the Critical Evaluation of the evidence for breast cancer carcinogenicity, classification of the agent’s breast cancer risk, identification of research gaps, and recommendations for future studies. A section will also be devoted to brief summaries of new research studies that are in progress. A bibliography with all cited literature is included in each critical evaluation. Major international, federal and state agencies will be provided with copies of our report.
General Outline of BCERF Critical Evaluations

I. Introduction
   A. History of Use
   B. Chemical Information
   C. Metabolism

II. Current Regulatory Status
   A. Current Regulatory Status, EPA
   B. Other sections as applicable

III. Summary on Evidence of Overall Carcinogenicity (Non-Breast Sites)
   A. Human Studies
   B. Animal Studies
   C. Current Classification of Carcinogenicity by other Agencies
      1. IARC (International Agency for Research on Cancer)
      2. NTP (National Toxicology Program)
      3. EPA (Environmental Protection Agency)

IV. Critical Evaluation of the Scientific Evidence for Breast Carcinogenicity
   A. Human Studies will include:
      1. Case-Studies
      2. Human Epidemiological Cohort Studies
      3. Human Epidemiological Case-Control Studies
   B. Experimental Animal Studies
   C. Other Relevant Information, including mechanisms by which exposure may affect breast cancer risk (examples: co-
      carcinogenicity, estrogenicity, endocrine disruptor, mutagenicity, tumor promotion, cell proliferation, oncogene/tumor
      suppressor gene expression, immune function, etc.)

V. Other Relevant Information
   A. Specific for the pesticide (i.e. may include information on environmental fate)
   B. When available will summarize information on detection /accumulation in human tissues / and validation of biomarkers

VI. Summary, Conclusions, Recommendation for Classification

VII. Identification of Research Gaps, and Other Recommendations

VIII. Brief Summaries of New Human Studies Currently Being Conducted

IX. Bibliography

X. Appendix A. Common Abbreviations, Acronyms and Symbols

XI. Appendix B. Critical Evaluations of Breast Cancer Risk

XII. Appendix C. Trade Names

XIII. Appendix D. Public Comments Received
BCERF Breast Cancer Risk Classification Scheme (adapted from the IARC Preamble by S.M. Snedeker)

Group 1: **Human breast carcinogen**: sufficient evidence of carcinogenicity to humans is necessary. Sufficient evidence is considered to be evidence that a causal relationship has been established between exposure to the agent and human breast cancer.

Group 2A: **Probable breast carcinogen**: this category generally includes agents for which there is 1) limited evidence of breast carcinogenicity in humans and sufficient evidence of mammary carcinogenicity in experimental animals. The classification may also be used when there is 2) limited evidence of breast carcinogenicity in humans and strong supporting evidence from other relevant data, or when there is 3) sufficient evidence of mammary carcinogenicity in experimental animals and strong supporting evidence from other relevant data.

Group 2B: **Possible breast carcinogen**: this category generally includes agents for which there is 1) limited evidence in humans in the absence of sufficient evidence in experimental animals; 2) inadequate evidence of carcinogenicity in humans or when human data is nonexistent but there is sufficient evidence of carcinogenicity in experimental animals, 3) inadequate evidence or no data in humans but with limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data.

Group 2C: **Potential to affect breast cancer risk**: this category includes agents for which there is inadequate or nonexistent human and animal data, but there is supporting evidence from other relevant data that identifies a mechanism by which the agent may affect breast cancer risk. Examples are, but are not limited to: evidence of agent’s estrogenicity, disruption of estrogen metabolism resulting in potential to affect exposure to estrogen; evidence of breast tumor promotion, progression or co-carcinogenicity; increased expression of proto-oncogenes or oncogenes; evidence of inactivation of tumor suppressor gene associated with breast cancer; evidence of adverse effect on immune function; or evidence of a structural similarity to a known breast carcinogen (structure-activity relationship).

Group 3: **Not classifiable** as to its breast carcinogenicity to humans. Agents are placed in this category when they do not fall into any other group.

Group 4: **Probably not a breast carcinogen in humans**: This category is used for agents for which there is evidence suggesting a lack of breast carcinogenicity in human studies and in animal studies, together with a lack of related evidence which may predict breast cancer risk. The absence of studies does not constitute evidence for a lack of breast carcinogenicity.

**Brief Definitions of Sufficient, Limited, and Inadequate Evidence**: (adapted for breast carcinogenicity from the IARC Preamble by S.M. Snedeker)

**Human Studies**

**Sufficient evidence of carcinogenicity in humans**: Must have established evidence between exposure to the agent and human breast cancer. Case-reports are given the least weight in considering carcinogenicity data in humans—they are suggestive of a relationship, but by themselves cannot demonstrate causality. Consistent, case-control studies which have controlled for confounding factors and have found high relative risks of developing breast cancer in relation to an identified exposure are given the most weight in determining a causal relationship.

**Limited evidence of breast carcinogenicity in humans**: A positive association has been observed between exposure to the agent and breast cancer, but chance, bias or confounding factors could not be ruled out.

**Inadequate evidence of breast carcinogenicity in humans**: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association.

**Experimental Animal Studies**

**Sufficient evidence of breast carcinogenicity in animals**: Evidence of malignant tumors or combination of benign and malignant tumors in (a) two or more species of animals, (b) or two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

**Limited evidence of breast carcinogenicity in animals**: The studies suggest a carcinogenic effect, but are limited for making a definitive evaluation because: (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent increases the incidence of only benign neoplasms of lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains of animals.

**Inadequate evidence of breast carcinogenicity in animals**: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations.
**XII. Appendix C: Trade Names of Phosmet and Phosmet Pre-Mixes**

Table 3. Trade names and producers of phosmet-containing products

<table>
<thead>
<tr>
<th>Trade names</th>
<th>Producer/formulator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosmedan®</td>
<td>Papaeconomou Agrochemicals S.A.</td>
</tr>
<tr>
<td>Cekumet®</td>
<td>Cequisa</td>
</tr>
<tr>
<td>Fosdan®</td>
<td>General Quimica</td>
</tr>
<tr>
<td>Imidan®</td>
<td>Gowan Co.</td>
</tr>
<tr>
<td>Prolate®</td>
<td>ZENECA Ag Products</td>
</tr>
<tr>
<td>Inovat®</td>
<td>Productos OSA S.A. C.I.F.A.</td>
</tr>
<tr>
<td>Inovitan®</td>
<td>Efthymiadis S.A.</td>
</tr>
<tr>
<td>Appa®</td>
<td></td>
</tr>
<tr>
<td>Kemolate®</td>
<td></td>
</tr>
<tr>
<td>Siguro®</td>
<td>Vector Argo S.A.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trade names</th>
<th>Other pesticides in pre-mix</th>
<th>Producer/formulator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clatar®</td>
<td>chlorpyrifos</td>
<td>Lainco, s.a.</td>
</tr>
</tbody>
</table>

References: (Meister, 1999; Tomlin, 1994)

*Trade names are used herein for convenience and informational purposes only. No endorsements of products is intended and no criticism of unnamed products is implied.*
XIII. Appendix D. Public Comments Received

After technical internal and external peer-review, the Critical Evaluation will be posted on the BCERF web site for 30 days. If any public comments are received, they will be scanned as submitted, and become a part of Appendix D.