September 1992

DATA DEFICIENCIES, PROBLEM AREAS, AND RECOMMENDATIONS FOR ADDITIONAL DATABASE DEVELOPMENT FOR *p*-CHLOROPHENYL METHYL SULFIDE, -SULFOXIDE, AND -SULFONE (PCPMS, PCPMSO, AND $PCPMSO_2$)

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PREFACE

This report was prepared in accordance with the Memorandum of Understanding between the Department of the Army, Deputy for Environmental Safety and Occupational Health (OASA (IL&E)), and the U.S. Environmental Protection Agency (EPA), Office of Water (OW), Office of Science and Technology (OST) for the purpose of developing drinking water Health Advisories (HAs) for selected environmental contaminants, as requested by the Army.

Health Advisories provide specific advice on the levels of contaminants in drinking water at which adverse health effects would not be anticipated and which include a margin of safety so as to protect the most sensitive members of the population at risk. These advisories normally are prepared for One-day, Ten-day, Longer-term, and Lifetime exposure periods where available toxicological data permit.

This report is the product of the foregoing process. Available toxicological data, including that provided by the Army, on the chemical analogs *p*-chlorophenyl methyl sulfide, -sulfoxide, and -sulfone (PCPMS, PCPMSO, and $PCPMSO_2$) have been reviewed, and relevant findings are presented in a manner that allows for an evaluation of the data without continued reference to the primary documents.

The available data are not sufficient to develop a HA; therefore, this report identifies deficiencies and recommends research that will enhance and optimize the database. When the recommended research has been conducted, it is expected that the data will allow the development of a drinking water HA for PCPMS, PCPMSO, and $PCPMSO_2$.

I would like to thank the authors, Dr. Margaret E. Brower, Dr. Mary B. Deardorff, and Dr. Welford C. Roberts, who provided the extensive technical skills required for the preparation of this report. I am grateful to the members of the EPA Tox-Review Panel who took time to review this report and to provide their invaluable input, and I would like to thank Dr. Edward Ohanian, Chief, Human Risk Assessment Branch, and Ms. Margaret J. Stasikowski, Director, Health and Ecological Criteria Division for providing me with the opportunity and encouragement to be a part of this project.

The preparation of this Health Advisory was funded in part by Interagency Agreement (IAG) between the U.S. EPA and the U.S. Army Medical Research and Development Command (USAMRDC). This IAG was conducted with the technical support of the U.S. Army Biomedical Research and Development Laboratory (USABRDL), Dr. Howard T. Bausum, Project Manager.

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EXECUTIVE SUMMARY

p-Chlorophenyl methyl sulfide (PCPMS) is described as a colorless liquid; *p*-chlorophenyl methyl sulfoxide (PCPMSO) is described as a waxlike solid; and *p*-chlorophenyl methyl sulfone ($PCPMSO_2$) is described as a white crystalline solid. The three compounds are intermediates in the manufacture of the herbicide Planavin.®

p-Chlorophenyl methyl sulfide, PCPMSO, and $PCPMSO_2$ are readily and almost completely absorbed when administered orally to rats or monkeys. Elimination is primarily in the urine. Clearance from blood in rats follows first-order kinetics with an initial half-life of about 12 hours for all three analogs. However, in monkeys, clearance from blood follows zero-order kinetics with a constant half-life of about 7 days, indicating that renal clearance in monkeys is saturable. In rats, urinary excretion of a single dose is rapid, up to 65% of a 2.5 mg/kg dose by 24 hours and 95% by 48 hours. In monkeys, urinary excretion is slow, and measurable quantities of about a 6 mg/kg dose are retained in the body for up to 14 days in males and 28 days in females. Less than 5% of an orally administered dose is eliminated in the feces of rats or monkeys for all three compounds. Kinetics of repeated dosing have not been studied, nor has tissue distribution been examined.

p-Chlorophenyl methyl sulfide is converted to PCPMSO and then to $PCPMSO_2$ in rats and monkeys. A large part of the urinary metabolites are conjugated to water-soluble compounds. Conjugation of metabolites is slower in monkeys than in rats. The $PCPMSO_2$ is poorly conjugated in monkeys. Metabolism probably proceeds by sulfoxidation, hydroxylation of a ring carbon, and conjugation to form glucuronic acid or sulfate. Toxicity in monkeys may correlate with the slower excretion time compared with rats. Hexobarbital "sleep-time" experiments with male rats indicate that all three compounds induce microsomal enzymes.

The health effects of PCPMS, PCPMSO, and $PCPMSO_2$ have not been studied in humans. Acute oral toxicity studies indicate that PCPMS and PCPMSO are equally toxic to rats, and $PCPMSO_2$ is slightly more toxic than the other compounds. Male rats are more resistant than females to the adverse effects as evidenced by their higher LD_{50} values. In mice, $PCPMSO_2$ is moderately less toxic than PCPMSO to males and females and moderately more toxic than PCPMS to males. The PCPMSO is significantly more toxic than either $PCPMSO_2$ or PCPMS to male and female mice. The oral LD_{50} values range from 400 to 619 mg/kg in rats and from 328 to 877 mg/kg

in mice. At doses of 5,630 mg/kg PCPMS applied in a single 24-hour dermal exposure, rats exhibited decreases in motor activity, prostration, lack of coordination, coma, and death.

Twenty-eight-day range-finding studies, conducted in mice (feeding study) and rats (gavage and feeding studies) to determine dosage levels for subchronic 91-day studies, showed that these compounds increase mortality and depress motor activity. Approximately five animals/sex/dose were used in each study. In the gavage study in rats, mortality occurred in 60% of the animals dosed with 50 mg/kg $PCPMSO_2$ and in 100% of the animals dosed at levels greater than 50 mg/kg. No animals survived at doses of 220 mg/kg PCPMS and above, or at 400 mg/kg PCPMSO. Rats treated with more than 50 mg/kg of each of the three compounds exhibited marked depression of motor activity. Eleven percent of the mice fed 4,500 ppm PCPMS (corresponding to 675 mg/kg/day), and 22% of the mice and 70% of the rats fed 5,200 ppm PCPMSO (corresponding to 780 mg/kg/day in mice, 520 mg/kg/day in rats) died during the study. No other deaths occurred. Both body weights and food consumption appeared depressed as a result of dosing, but data were inadequate to draw conclusions.

In 13-week feeding studies with all three compounds, mice and rats exhibited hepatotoxicity, mortality, weight loss, and slight anemia. Sixteen animals/sex/dose plus controls groups of 24 rats/sex or 33 mice/sex were used in these studies. Mortality occurred prior to study termination in 38% of male rats fed 3,000 ppm (corresponding to 246 mg/kg/day) PCPMSO. In mice, mortality occurred in 100% of males and females fed 6,000 ppm PCPMS or $PCPMSO_2$ (corresponding to 840 mg/kg/day in males, 517 mg/kg/day in females for PCPMS; 890 mg/kg/day in males, 680 mg/kg/day in females for $PCPMSO_2$) or 5,000 ppm PCPMSO (corresponding to 628 mg/kg/day in males, 530 mg/kg/day in females for PCPMSO), 31% of males and 75% of females fed 3,000 ppm PCPMS (corresponding to 182 mg/kg/day and 180 mg/kg/day in males and females, respectively), and 6% of males and 44% of females fed 3,000 ppm PCPMSO (corresponding to 224 and 235 mg/kg/day in males and females, respectively). Body weights, body weight gains, and food consumption of rats and mice fed the three test compounds at all dose levels were significantly depressed. Erythrocyte parameters and serum alkaline phosphatase (except low-dose PCPMS females) in all dosed rats were significantly depressed compared with controls, and serum potassium and calcium levels in rats were elevated for all compounds. Hematology and clinical chemistry were not evaluated in mice. Liver weights were increased in all dosed rats and in PCPMS and PCPMSO treated mice at 3,000 ppm (corresponding to 426 mg/kg/day in male mice, 259 mg/kg/day in female mice for PCPMS; 377 mg/

kg/day in male mice, 318 mg/kg/day in female mice for PCPMSO). The most predominant hepatic lesions included megalocytosis, necrosis, and vacuolar cytoplasmic change in rats and mice. The highest incidences of hepatic lesions were exhibited in PCPMS treated rats and PCPMS and PCPMSO treated mice. No renal lesions were found. Based on depressed body weights, hematologic and serum chemistry changes, increased liver weights, and hepatic pathologic changes, the Lowest-Observed-Adverse-Effect Level (LOAEL) for rats (all three compounds) is 750 ppm (corresponding to 60 mg/kg/day in males and 57 mg/kg/day in females for PCPMS; 61 mg/kg/day in males and 67 mg/kg/day in females for PCPMSO; and 57 mg/kg/day in males and 54 mg/kg/day in females for $PCPMSO_2$). Based on hepatic pathology, the LOAEL for mice (all three compounds) is 750 ppm (corresponding to 108 mg/kg/day in males and 109 mg/kg/day in females for PCPMS; 112 mg/kg/day in males and 70 mg/kg/day in females for PCPMSO; and 106 mg/kg/day in males and 86 mg/kg/day in females $PCPMSO_2$). No No-Observed-Adverse-Effect Levels (NOAELs) could be determined because the lowest dose tested caused adverse effects.

Toxicity was assessed in 68 male and female monkeys administered PCPMS, PCPMSO, or $PCPMSO_2$ via gavage for 14 days. The dose levels were 0, 5, 10, 20, 30, 40, or 80 mg/kg/day for PCPMS; 0, 5, 10, or 20 mg/kg/day for PCPMSO; and 0, 2.5, 5, 10, 15, 20, or 30 mg/kg/day for $PCPMSO_2$. During the treatment period, mortality occurred in 17% of the six monkeys dosed with 20 mg/kg/day PCPMS and 33% of the six animals dosed with the same amount of $PCPMSO_2$. Fifty percent mortality occurred in PCPMS animals dosed at 40 or 80 mg/kg/day (two animals/dose). In addition, 100% of the two animals dosed with 30 mg/kg/day $PCPMSO_2$ were moribund by day 10 and sacrificed. No other deaths occurred during the treatment period. Monkeys treated with PCPMS or $PCPMSO_2$ at all dose levels exhibited anorexia. Weakness and depression also occurred at all PCPMS dose levels. The PCPMSO treated monkeys did not manifest anorexia and depression below 10 mg/kg/day. Reticulocyte counts were significantly depressed at 10 mg/kg/day or greater PCPMSO. Blood urea nitrogen was increased over pretreatment levels in animals receiving PCPMSO at 10 mg/kg/day and in $PCPMSO_2$ animals at 20 mg/kg/day or greater. Alkaline phosphatase and blood glucose levels also were depressed in some animals. Organ weight data were inconclusive. Pathologic liver lesions, observed in monkeys treated with all three compounds, were most severe in PCPMSO and PCPMS treated monkeys. Pathologic lesions also occurred in the lymphoid system of animals treated with all three compounds. Based on the incidence of anorexia, depression, and weakness at the lowest dose, the LOAEL for PCPMS is 5 mg/kg/day. Based on the incidence of liver and lymphoid system lesions at the lowest dose, the LOAEL for PCPMSO is

5 mg/kg/day. Based on the clinical observation of anorexia at the lowest dose, the LOAEL for $PCPMSO_2$ is 2.5 mg/kg/day.

No reproductive or developmental toxicity studies have been conducted with PCPMS, PCPMSO, or $PCPMSO_2$.

No conclusions can be reached regarding the potential genotoxicity of the three compounds. The findings from *Salmonella typhimurium* gene mutation assays indicated that PCPMS, PCPMSO, and $PCPMSO_2$ were not mutagenic in the absence or presence of S9 metabolic activator of either Aroclor 1254 or phenobarbital-induced rat liver microsomes. However, the individual assays were considered to be either incomplete (an unstable form of the PCPMS was tested with Aroclor 1254 S9) or inadequate to conclude a valid negative response (PCPMSO and $PCPMSO_2$ were not assayed to an appropriately high concentration). No other genetic toxicology studies were found in the available literature.

p-Chlorophenyl methyl sulfide, -sulfoxide, and -sulfone each are classified as Group D: not classifiable as to human carcinogenicity.

The health effects data for PCPMS, PCPMSO, and $PCPMSO_2$ were reviewed by the U.S. EPA Reference Dose/Reference Concentration (RfD/RfC) Work Group and were determined to be inadequate for the derivation of an oral RfD. Thus, the current verification status of the chemical is classified as "not verifiable." Apparent liver changes observed in rats treated subchronically with each analog were potential endpoints for establishing RfDs. However, comparisons between gross, histologic and clinical chemical parameters were not consistent. Additionally, subacute effects observed in monkeys treated for 14 days were more severe (*e.g.*, neurotoxicity and lethality) and developed in a period of time that was much shorter than in rodents. These observations suggest that primates, including humans, may be more sensitive than rodents to the effects of PCPMS, PCPMSO, and $PCPMSO_2$. The 14-day exposure period to monkeys is not a sufficient duration to derive an RfD, which is protective for lifetime exposure.

I. OBJECTIVE

The objective of this document is to provide an evaluation of data deficiencies and problem areas encountered after a careful review of the literature on *p*-chlorophenyl methyl sulfide, -sulfoxide, and -sulfone (PCPMS, PCPMSO, and $PCPMSO_2$) and to make recommendations for additional database development. This document is presented as an independent analysis of the current data related to PCPMS, PCPMSO, and $PCPMSO_2$ in drinking water, and it includes a summary of the background information that was considered for the development of a Health Advisory (HA). For greater detail on the toxicology of PCPMS, PCPMSO, and $PCPMSO_2$, the *Review of Health Effects and Other Data: p-Chlorophenyl methyl sulfide, -sulfoxide, and -sulfone (PCPMS, PCPMSO, and $PCPMSO_2$)* (Appendix A) should be consulted.

II. BACKGROUND

p-Chlorophenyl methyl sulfide (PCPMS) is described as a colorless liquid; *p*-chlorophenyl methyl sulfoxide (PCPMSO) is described as a waxlike solid; and *p*-chlorophenyl methyl sulfone ($PCPMSO_2$) is described as a white crystalline solid (Fairfield Chemical, 1985). The three compounds are intermediates in the manufacture of the herbicide Planavin® and are degradation products of sulfide-containing pesticides (Tetrasul®, Ovex®, and carbophenolthion). *p*-Chlorophenyl methyl sulfide, -sulfoxide, and -sulfone have been found in groundwaters of an Army arsenal (Burrows, 1978). Concentrations in groundwater at the Rocky Mountain Arsenal, reported as an organosulfur composite (summed concentration of the analogs), were measured in the fall of 1989 and ranged from 2.62 µg/L to 7,950 µg/L (PMRMA, 1991). These compounds are taken up by plants, and the sulfide form readily evaporates from the soil (Guenzi *et al.*, 1981; Miller *et al.*, 1976). An increase in the concentrations of the compounds follows a linear relationship in both the plant tissues and soil; however, an inverse linear relationship was found between soil compound concentration and plant growth. The compounds bioconcentrate more in plant tops than in plant roots. Damage to plant tissues depends on the method of compound application; the foliage method was reported to cause no damage. The PCPMS moiety was shown to undergo aerobic sulfoxidation to PCPMSO in plant cell cultures (Blair *et al.*, 1982, 1984). This finding indicated the presence of sulfide oxidase in these cell cultures. The PCPMSO and $PCPMSO_2$ analogs tend to persist in soil more than the does PCPMS (Guenzi and Beard, 1981). Gas chromatography (GC) with a sulfur-specific flame photometric detector is the most sensitive method used to detect and quantify the three sulfur compounds (Miller *et al.*, 1976). Other methods include GC with an electron capture detector and GC/mass spectrometry.

p-Chlorophenyl methyl sulfide, PCPMSO, and $PCPMSO_2$ are readily and almost completely absorbed when administered orally to rats or monkeys (Thake *et al.*, 1979). Elimination is primarily in the urine. Clearance from blood in rats follows first-order kinetics with an initial half-life of about 12 hours for all three analogs. However, in monkeys, clearance from blood follows zero-order kinetics with a constant half-life of about 7 days, indicating that renal clearance in monkeys is saturable. In rats, urinary excretion of a single dose is rapid, up to 65% of a 2.5 mg/kg dose by 24 hours and 95% by 48 hours. In monkeys, urinary excretion is slow, and measurable quantities of about a 6 mg/kg dose are retained in the body for up to 14 days in males and 28 days in females. Less than 5% of an orally administered dose is eliminated in the feces of rats or monkeys for all

three compounds. The kinetics of repeated dosing have not been studied. Tissue distribution studies in very small numbers of cattle and sheep indicate that PCPMS and $PCPMSO_2$ (the only analogs tested) are widely distributed but favor fat and liver tissues (Oehler and Ivie, 1983). No distribution studies are available in rats and monkeys.

The PCPMS is converted to PCPMSO and to $PCPMSO_2$ in rats and monkeys (Thake *et al.*, 1979). A large part of the urinary metabolites are conjugated, producing water-soluble compounds. Conjugation of metabolites is slower in monkeys than in rats. The $PCPMSO_2$ is particularly slow to conjugate in monkeys. Metabolism probably proceeds by sulfoxidation, hydroxylation of a ring carbon, and conjugation with glucuronic acid or sulfate (Dacre *et al.*, 1980). Toxicity in monkeys may correlate with the slower excretion time compared with rats. Hexobarbital "sleep-time" experiments with male rats indicate that PCPMS, PCPMSO, and $PCPMSO_2$ each have an inductive effect on microsomal enzymes.

The health effects of PCPMS, PCPMSO, and $PCPMSO_2$ have not been studied in humans. Acute oral toxicity studies by Thake *et al.* (1979) indicate that PCPMS and PCPMSO are equally toxic to rats, and $PCPMSO_2$ is slightly more toxic than either of the other compounds. The LD_{50} values for male rats are 619, 611, and 529 mg/kg for PCPMS, PCPMSO, and $PCPMSO_2$, respectively. For female rats, the LD_{50} values are 479, 463, and 400 mg/kg for PCPMS, PCPMSO, and $PCPMSO_2$, respectively. Male rats are more resistant than females to adverse effects as evidenced by their higher LD_{50} values. Rats exhibited decreases in motor activity, prostration, lack of coordination, coma, and death at PCPMS doses of 5,630 mg/kg applied in a single 24-hour dermal exposure (Thake *et al.*, 1979). The LD_{50} values for male mice are 877, 328, and 600 mg/kg for PCPMS, PCPMSO, and $PCPMSO_2$, respectively (Thake *et al.*, 1979). For female mice, the LD_{50} values are 672, 440, and 606 mg/kg for PCPMS, PCPMSO, and $PCPMSO_2$, respectively. In mice, the $PCPMSO_2$ analog is moderately less toxic than PCPMSO to males and females and moderately more toxic than PCPMS to males. The PCPMSO is significantly more toxic than either $PCPMSO_2$ or PCPMS to male and female mice.

In a 28-day range finding study, rats (feeding and gavage studies) and mice (feeding study) showed increased mortality and depressed motor activity in response to all three analogs (Thake *et al.*, 1979). Data were inadequate to compare body weight gain and food consumption. Approximately five animals/sex/dose were used in each study. In rats fed PCPMS at 9,000 ppm (corres-

ponding to 900 mg/kg/day; highest dose), deaths were not attributed directly to the compound, but rats fed PCPMSO at 5,200 ppm (corresponding to 520 mg/kg/day; highest dose) exhibited 80% mortality in males and 60% mortality in females. No mortality occurred in rats fed $PCPMSO_2$ (highest dose given was 2,250 ppm [corresponding to 225 mg/kg/day]). In the mouse feeding study, 11% of the mice died taking 4,500 ppm PCPMS (corresponding to 675 mg/kg/day, highest dose) and 22% died taking 5,200 ppm PCPMSO (corresponding to 780 mg/kg/day, highest dose). Mice exhibited depression prior to death. No deaths were reported in $PCPMSO_2$ mice (highest dose, 675 mg/kg/day).

Rats appear more sensitive to all three compounds when administered by gavage rather than by feeding (Thake *et al.*, 1979). The $PCPMSO_2$ produced 60% mortality in males and females at the 50 mg/kg/day dose (the lowest dose at which deaths occurred), indicating that the rats were less resistent to $PCPMSO_2$ than to PCPMS or PCPMSO. Mortality from $PCPMSO_2$ increased to 100% at higher doses. Mortality from PCPMS was 100% in females at 330 mg/kg/day (highest female dose) and in males at 220 mg/kg/day or greater. The PCPMSO gavaged rats exhibited 100% mortality at 400 mg/kg/day (highest dose tested) in both sexes. Decreased motor activity was observed at 50 mg/kg/day or greater for all three compounds.

In a 14-day gavage study, monkeys exhibited compound-related effects at the lowest doses tested (5 mg/kg/day for PCPMS and PCPMSO, and 2.5 mg/kg/day for $PCPMSO_2$) (Thake *et al.*, 1979). Sixty-eight monkeys were used in this study. The dose levels were 0, 5, 10, 20, 30, 40, or 80 mg/kg/day for PCPMS; 0, 5, 10, or 20 mg/kg/day for PCPMSO; and 0, 2.5, 5, 10, 15, 20, or 30 mg/kg/day for $PCPMSO_2$. Groups ranged in size from one animal/sex to three/sex for each analog. The lowest dose at which deaths occurred during the treatment period was 20 mg/kg/day for PCPMS and $PCPMSO_2$. No deaths occurred in monkeys treated with PCPMSO. However, animals at 20 mg PCPMSO/kg/day (highest dose tested) were depressed, one severely. Monkeys treated with PCPMS or $PCPMSO_2$ at all dose levels exhibited anorexia. Weakness and depression also occurred at all PCPMS dose levels. The PCPMSO treated monkeys did not manifest anorexia and depression below 10 mg/kg/day. Blood urea nitrogen showed a significant increase over pretreatment levels in PCPMSO treated males and females (combined data) at 10 mg/kg/day or greater and in PCPMS and $PCPMSO_2$ animals at 20 mg/kg/day or greater. Alkaline phosphatase was significantly depressed at 10 mg/kg/day or greater in PCPMS and PCPMSO monkeys. No effect was observed in $PCPMSO_2$ rats for this parameter. Glucose levels were significantly depressed in PCPMS and $PCPMSO_2$

treated monkeys at 20 mg/kg/day but not in PCPMSO monkeys. The PCPMSO analog produced the only significant hematological change, a depressed reticulocyte count at 10 mg/kg/day or greater.

Although the organ weight data were difficult to assess in the monkeys, PCPMS and PCPMSO were associated with a significant increase in relative liver and kidney weights over controls, and $PCPMSO_2$ with increased adrenal weights. The PCPMS analog also significantly increased adrenal weights but only at higher doses than for $PCPMSO_2$. Pathologic changes were observed in the livers of PCPMSO monkeys at all doses and in PCPMS monkeys at 10 mg/kg/day or greater. Only minor liver pathology occurred in $PCPMSO_2$ animals at 15-30 mg/kg/day (pooled data). Significant pathologic lesions also occurred in the lymphoid system in monkeys treated with all three analogs. Lymphoid lesions were most prominent at the higher doses but did occur in PCPMSO and $PCPMSO_2$ treated rats at 5 mg/kg/day. The LOAEL for PCPMS is 5 mg/kg/day based on the incidence of anorexia, depression, and weakness at the lowest dose. The LOAEL for PCPMSO is 5 mg/kg/day based on the incidence of liver and lymphoid system lesions at the lowest dose. The LOAEL for $PCPMSO_2$ is 2.5 mg/kg/day based on the incidence of anorexia at the lowest dose. A NOAEL could not be determined for any of the compounds because adverse effects occurred at the lowest dose tested.

In 13-week feeding studies with all three compounds, mice and rats exhibited hepatotoxicity, mortality, weight loss, and slight anemia. Sixteen animals/sex/dose plus control groups of 24 rats/sex or 33 mice/sex were used in these studies. Mortality occurred prior to study termination in 38% of male rats fed 3,000 ppm (corresponding to 246 mg/kg/day) PCPMSO. In mice, mortality occurred in 100% of males and females fed 6,000 ppm PCPMS or $PCPMSO_2$ (corresponding to 840 mg/kg/day in males, 517 mg/kg/day in females for PCPMS; 890 mg/kg/day in males, 680 mg/kg/day in females for $PCPMSO_2$) or 5,000 ppm PCPMSO (corresponding to 628 mg/kg/day in males, 530 mg/kg/day in females for PCPMSO), 31% of males and 75% of females fed 3,000 ppm PCPMS (corresponding to 182 mg/kg/day and 180 mg/kg/day in males and females, respectively), and 6% of males and 44% of females fed 3,000 ppm PCPMSO (corresponding to 224 and 235 mg/kg/day in males and females, respectively). Body weights, body weight gains, and food consumption of rats and mice fed the three test compounds at all dose levels were significantly depressed. Erythrocyte parameters and serum alkaline phosphatase (except low-dose PCPMS females) in all dosed rats were significantly depressed compared with controls, and serum potassium and calcium levels in rats were elevated for all compounds. Hematology and clinical chemistry were not evaluated in mice. Liver

weights were increased in all dosed rats and in PCPMS and PCPMSO treated mice at 3,000 ppm (corresponding to 426 mg/kg/day in male mice, 259 mg/kg/day in female mice for PCPMS; 377 mg/kg/day in male mice, 318 mg/kg/day in female mice for PCPMSO). The most predominant hepatic lesions included megalocytosis, necrosis, and vacuolar cytoplasmic change in rats and mice. The highest incidences of hepatic lesions were exhibited in PCPMS treated rats and PCPMS and PCPMSO treated mice. No renal lesions were found. Based on depressed body weights, hematologic and serum chemistry changes, increased liver weights, and hepatic pathologic changes, the Lowest-Observed-Adverse-Effect Level (LOAEL) for rats (all three compounds) is 750 ppm (corresponding to 60 mg/kg/day in males and 57 mg/kg/day in females for PCPMS; 61 mg/kg/day in males and 67 mg/kg/day in females for PCPMSO; and 57 mg/kg/day in males and 54 mg/kg/day in females for $PCPMSO_2$). Based on hepatic pathology, the LOAEL for mice (all three compounds) is 750 ppm (corresponding to 108 mg/kg/day in males and 109 mg/kg/day in females for PCPMS; 112 mg/kg/day in males and 70 mg/kg/day in females for PCPMSO; and 106 mg/kg/day in males and 86 mg/kg/day in females $PCPMSO_2$). No-Observed-Adverse-Effect Levels (NOAELs) could be determined for any of the compounds because adverse effects occurred at the lowest dose tested..

No reproductive or developmental toxicity studies have been conducted with PCPMS, PCPMSO, or $PCPMSO_2$. Data regarding treatment technologies are lacking.

No conclusions can be reached regarding the potential genotoxicity of the three compounds. The findings from *Salmonella typhimurium* gene mutation assays with PCPMS, PCPMSO, and $PCPMSO_2$ indicated that the three compounds were not mutagenic in the absence or presence of S9 metabolic activator of either Aroclor 1254 or phenobarbital-induced rat liver microsomes (Thake *et al.*, 1979). However, the individual assays were considered to be either incomplete (an unstable form of the sulfide was tested with Aroclor 1254 S9) or inadequate to conclude a valid negative response (PCPMSO and $PCPMSO_2$ were not assayed to an appropriately high concentration). No other genetic toxicology studies were found in the available literature.

p-Chlorophenyl methyl sulfide, -sulfoxide, and -sulfone each are classified as Group D: not classifiable as to human carcinogenicity.

The health effects data for PCPMS, PCPMSO, and $PCPMSO_2$ were reviewed by the U.S. EPA Reference Dose/Reference Concentration (RfD/RfC) Work Group and were determined to be inade-

quate for the derivation of an oral RfD. Thus, the current verification status of the chemical is classified as "not verifiable." Apparent liver changes observed in rats treated subchronically with each analog were potential endpoints for establishing RfDs. However, comparisons between gross, histologic, and clinical chemical parameters were not consistent. Additionally, subacute effects observed in monkeys treated for 14 days were more severe (*e.g.*, neurotoxicity and lethality) and developed in a period of time that was much shorter than in rodents. These observations suggest that primates, including humans, may be more sensitive than rodents to the effects of PCPMS, PCPMSO, and $PCPMSO_2$. The 14-day exposure period to monkeys is not a sufficient duration to derive an RfD, which is protective for lifetime exposure.

III. DISCUSSION

In reviewing the available data on exposure, toxicokinetics, health effects, analytical methods, and treatment of *p*-chlorophenyl methyl sulfide, -sulfoxide, and -sulfone (PCPMS, PCPMSO, and $PCPMSO_2$), it is evident that some important data deficiencies exist. All toxicity studies to date have been conducted by the same investigators.

The toxicokinetic studies of PCPMS, PCPMSO, and $PCPMSO_2$ in rats and monkeys provide some useful data regarding the rate and speed of absorption of these compounds and their conjugation and elimination in urine and feces. However, the toxicokinetics were evaluated only for a single dose, and the monkey study was limited by the small number of animals of a single sex. Also, lacking in these studies is the tissue distribution of the compounds and the kinetics of repeated dosing, which is useful in supporting Health Advisory determinations.

The only acute toxicity studies are oral LD_{50} studies in mice and rats. Subacute studies in these same species (28-day) reveal mortality and depressed motor activity for all three compounds, but they provide essentially no other useful data for deriving a Health Advisory. The body weight and food consumption data from these studies were difficult to interpret or not completely reliable, owing to the use of control data extracted from other studies, divergent initial body weights, or decreased food consumption in control animals. A NOAEL could not be determined.

Thake *et al.* (1979) conducted pathologic examinations, blood and clinical chemistry assays, and organ weight measures on monkeys following 14 days of oral dosing with PCPMS, PCPMSO, and $PCPMSO_2$. Small numbers of animals were used for some dose groups, and male and female data for relative organ weights and clinical chemistry and hematological parameters were combined. Also, body weights and absolute organ weights were not measured, making it difficult to assess the importance of the relative organ weight data. Further, the 2-week exposure period is inadequate for deriving an RfD and most HAs. However, lymphoid system and liver pathology and possible central nervous system effects at doses as low as 5 mg/kg/day in some animals suggest that the monkey may be sensitive to these compounds and should be studied further.

The 13-week studies of rats and mice included evaluations of body weight, body weight gain, food consumption, absolute organ weights, and pathology. The rat study also included an evaluation

of hematologic and clinical chemistry. However, lower dose levels could have been tested to achieve a NOAEL for these studies. Also, the 750 ppm PCPMSO low-dose mouse group (corresponding to 112 mg/kg/day males, 70 mg/kg/day females) was placed into the study owing to high mortality at 5,000 ppm PCPMSO (corresponding to 628 mg/kg/day in males, 530 mg/kg/day in females); no date of study initiation for this group was reported.

Several other areas lack sufficient data to support development of a Health Advisory. No lifetime toxicity or carcinogenicity studies on PCPMS, PCPMSO, or $PCPMSO_2$ are available. Study deficiencies in existing genotoxicity data on PCPMS, PCPMSO, or $PCPMSO_2$ require that further study of all major genotoxic endpoints be conducted prior to a final assessment of the genotoxic potential of these compounds. No studies on the reproductive or developmental effects of PCPMS, PCPMSO, or $PCPMSO_2$ are available. No data treatment technologies for PCPMS, PCPMSO, and $PCPMSO_2$ are available. Although PCPMS, PCPMSO, and $PCPMSO_2$ are manufactured and used in various forms in this country, measures of its presence in the environment are lacking, and no occupational studies currently are available.

IV. CONCLUSIONS AND RECOMMENDATIONS

The following conclusions and recommendations are based upon the preceeding discussion:

- The available studies on PCPMS, PCPMSO, and $PCPMSO_2$ toxicity are inadequate for development of Health Advisories to deal with potential contamination of drinking water.

- It is recommended that the kinetics of repeated dosing with all three compounds and tissue distribution be examined in rats and in monkeys, which appears to be the more sensitive specie.

- It is recommended that additional subacute and subchronic studies be performed in rats and subchronic studies be performed in monkeys.

- It is recommended that chronic toxicity/carcinogenicity studies be performed in rats, mice, and preferably monkeys.

- It is recommended that adequate reproductive toxicity studies be performed in at least one rodent species and developmental toxicity studies in two species.

- It is recommended that adequate genotoxicity studies be performed in microbial and nonmicrobial cell systems.

The recommended order of completion for these studies is as follows: chronic toxicity/carcinogenicity (preferably in monkeys), subchronic monkey, subacute and subchronic rat, pharmacokinetics, genotoxicity, and reproductive/developmental toxicity.

It is recommended that the human health effects of these compounds be studied. Potential study groups are people occupationally exposed and people ingesting water containing measurable quantities of PCPMS, PCPMSO, or $PCPMSO_2$. Investigation of the potential existence of these compounds in the environment also is needed.

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APPENDIX A

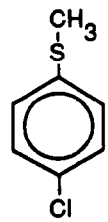
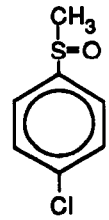
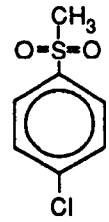
REVIEW OF HEALTH EFFECTS AND OTHER DATA: *p*-CHLOROPHENYL METHYL SULFIDE, -SULFOXIDE, AND -SULFONE (PCPMS, PCPMSO, AND $PCPMSO_2$)

I. GENERAL INFORMATION

p-Chlorophenyl methyl sulfide (PCPMS), *p*-chlorophenyl methyl sulfoxide (PCPMSO), and *p*-chlorophenyl methyl sulfone ($PCPMSO_2$) are three distinct chemical species with differences in appearance, boiling point, and other physical properties. *p*-Chlorophenyl methyl sulfide appears as a colorless liquid at room temperature, PCPMSO as a waxlike solid, and $PCPMSO_2$ as a white crystalline solid (Fairfield Chemical Co., 1985). All three are combustible compounds, decomposing upon combustion to release toxic and hazardous vapors. The general physical and chemical properties of PCPMS (CAS No. 123-09-1), PCPMSO (CAS No. 934-73-6), and $PCPMSO_2$ (CAS No. 98-57-1), are presented in Table I-1.

All three compounds are intermediates in the manufacture of the herbicide Planavin®, but they are also produced by other means. *p*-Chlorophenyl methyl sulfide is synthesized via two processes: (1) methylation of the *p*-chlorobenzenethiol with either chloromethane or dimethyl sulfate in the presence of alkali; and (2) pyrolysis of S-*p*-chlorophenyl-O-methyl dithiocarbonate. *p*-Chlorophenyl methyl sulfoxide is found in trace amounts in $PCPMSO_2$. It arises from incomplete oxidation of the sulfide with hydrogen peroxide. It can be manufactured by a variety of methods; however, industrial production utilizes a mixture of oxygen and nitrogen dioxide in the oxidation process. The PCPMSO analog can be produced in the environment via oxidation of PCPMS in air following discharge of the sulfide (Miller *et al.*, 1976). The $PCPMSO_2$ analog can be synthesized via vigorous oxidation of either PCPMS or PCPMSO; however, oxidation of PCPMS is 50 times faster than oxidation of PCPMSO. The $PCPMSO_2$ can also be made from chloroaniline via substitution of the amino group with sulfur dioxide followed by methylation. Friedel-Crafts acylation of chlorobenzene with methanesulfonyl chloride followed by recrystallization can also be used. Only a few domestic companies produce these three chemicals (Table I-2).

Table I-1. Chemical and Physical Properties of *p*-Chlorophenyl Methyl Sulfide, -Sulfoxide, -Sulfone (PCPMS, PCPMSO, and $PCPMSO_2$)

Property	Sulfide	Sulfoxide	Sulfone	Reference
CAS No.	123-09-1	934-73-6	98-57-7	Miller *et al.* (1976)
Synonyms	*p*-Chlorothioanisole, 4-chlorothioanisole, methyl-*p*-chlorophenyl sulfide, methyl-4-chlorophenyl sulfide	4-Chlorophenyl sulfoxide, methyl-4-chlorophenyl sulfoxide, methyl-4-chlorophenyl sulfoxide	4-Chlorophenyl methyl sulfone, methyl-4-chlorophenyl sulfone	Sax (1984)
Empirical formula	C_7H_7ClS	C_7H_7ClSO	$C_7H_7ClSO_2$	Sax (1984)
Structure				Miller *et al.* (1976)
Molecular weight	158.65	174.65	190.65	Miller *et al.* (1976)
Melting point	17-19°C	37-48°C	92-99°C	Miller *et al.* (1976), Fairfield Chemical (1985)
Boiling point (at 760 mm)	220-224°C	—	—	—
Density	1.202 g/mL (at 49°C)	—	—	Miller *et al.* (1976)
Solubility water, mg/L	Insoluble	Insoluble	Insoluble	Fairfield Chemical (1985)
Conversion factors (in air):				
ppm (v/v)* to mg/m^3 (20°C)	1 ppm ≈ 6.5 mg/m^3	1 ppm ≈ 7.1 mg/m^3	1 ppm ≈ 7.8 mg/m^3	
mg/m^3 to ppm (v/v)*	1 mg/m^3 ≈ 0.15 ppm	1 mg/m^3 ≈ 0.14 ppm	1 mg/m^3 ≈ 0.13 ppm	

*Calculated using the following formulas: $1 \text{ ppm} = \frac{MW}{24.5} \times mg/m^3$ $1\ mg/m^3 = \frac{24.5}{MW} \times \text{ppm}$

SOURCE: Adapted from Sax (1984), Miller *et al.* (1976), Fairfield Chemical (1985)

Table I-2. Manufacturers of *p*-Chlorophenyl Methyl Sulfide, -Sulfoxide, -Sulfone

Analog	Manufacturer	Location
Sulfide	American Tokyo Kasei, Inc.	Portland, OR
	Lancaster Synthesis Ltd.	Windham, NH
	Fairfield Chemical Company	Blythewood, SC
	Alfa Products	Danvers, MA
	Aldrich Chemical Co., Inc.	Milwaukee, WI
Sulfoxide	Fairfield Chemical Company	Blythewood, SC
Sulfone	Chem Service, Inc.	West Chester, PA
	Lancaster Synthesis Ltd.	Windham, NH
	Fairfield Chemical Company	Blythewood, SC
	Aldrich Chemical Company, Inc.	Milwaukee, WI

II. SOURCES OF EXPOSURE

Information concerning occupational and environmental exposure is limited. Occupational exposure to *p*-chlorophenyl methyl sulfide (PCPMS), *p*-chlorophenyl methyl sulfoxide (PCPMSO), and *p*-chlorophenyl methyl sulfone ($PCPMSO_2$) may occur during manufacturing and munitions incorporation. The wastewaters could contaminate groundwater, soil used for agriculture, and public drinking water supplies. However, quantitative data are not available.

The analogs PCPMS, PCPMSO, $PCPMSO_2$ are degradation products of sulfide-containing pesticides (Tetrasul,® Ovex,® and carbophenothion) and are intermediates in the synthesis of the herbicide Planavin.® These pesticides are applied to crop plants or natural flora. If wastewaters resulting from the manufacture or use of PCPMS, PCPMSO, or $PCPMSO_2$ were discharged into the environment, they could present a potential for aquatic pollution. Seepage into groundwater may occur from sediment deposits generated in Army ammunition plants (Burrows, 1978; Miller *et al.*, 1976). Concentrations in groundwater at the Rocky Mountain Arsenal, reported as an organosulfur composite (summed concentration of the analogs), were measured in the fall of 1989 and ranged from 2.62 µg/L to 7,950 µg/L (PMRMA, 1991).

III. ENVIRONMENTAL FATE

A. PHOTOLYSIS

There is little information to indicate that *p*-chlorophenyl methyl sulfide, -sulfoxide, -sulfone (PCPMS, PCPMSO, and $PCPMSO_2$) undergo photolysis (Miller *et al.*, 1976). If such a reaction occurs, it is most likely to be air oxidation of PCPMS to PCPMSO and, consequently, to $PCPMSO_2$.

B. LEACHING

No information was reported on the leaching of PCPMS, PCPMSO, or $PCPMSO_2$.

C. HYDROLYSIS

No information was reported on the hydrolysis of PCPMS, PCPMSO, or $PCPMSO_2$.

D. PLANT UPTAKE AND DEGRADATION

The pesticides Tetrasul®, Ovex®, and carbophenothion are reported to degrade forming PCPMS, PCPMSO, or $PCPMSO_2$ (Guenzi *et al.*, 1981). Guenzi *et al.* (1981) investigated the effects of [^{14}C]-ring-labeled PCPMS, PCPMSO, or $PCPMSO_2$ on seedling growth and uptake by alfalfa, corn, tall fescue, sugarbeet, and spring wheat. Each crop was tested separately at concentrations of 0.5, 5, and 25 ppm (dry soil weight basis) for 3 months in sandy loam soil. The results for each of the three compounds were, in general, comparable for the five plant species. The increases in the concentration of the compounds followed a linear relationship in both the plant tissues and soil; the r values were 0.894 for plant tops and 0.942 for plant roots. There was an inverse linear relationship ($p < 0.01$) between soil compound concentration and plant growth (r = -0.46 to -0.96 for tops and -0.76 to -0.92 for roots). The root growth was generally affected to a greater degree than was the top growth at a given soil compound concentration. The mean soil compound concentrations that caused 20% reduction in top growth were 4.7, 6.3, 7.3, and 15.5 µg/g for alfalfa, fescue, sugarbeet, and wheat, respectively; the top growth in corn was depressed only at 25 ppm $PCPMSO_2$. The mean plant top compound concentrations that caused 20% reduction in top growth were 216, 250, 379, 559, and 1,320 µg/g for alfalfa, fescue, sugarbeet, wheat, and corn (sulfone only), respectively. No

data were reported for root growth. Bioconcentration of the compounds was, on the average, eight times greater in plant tops than in plant roots. The mean bioconcentration values for the tops of corn, alfalfa, wheat, fescue, and sugarbeet were 28, 34, 37, 44, and 62, respectively; the corresponding values in roots were 6, 5, 8, 3, and 5, respectively.

Knaus (as cited in Miller *et al.*, 1976) applied these three compounds to six grass and herb species at two dosages using three methods of application (foliage, soil, and solution). Minor to severe plant damage was observed using the soil and solution application methods; however, no damage was observed using the foliage application of all three compounds.

Guenzi and Beard (1981) evaluated degradation and residue of [^{14}C]-ring-labeled PCPMS, PCPMSO, and PCPMSO$_2$ in soil. They measured total CO_2, [^{14}C]-O_2, and residual [^{14}C] in soil incubated for 160 days with 0.5, 5.0, and 50 ppm of each compound at 30°C. Total CO_2 production from PCPMS in soils treated with 50 ppm of the compound was significantly higher ($p < 0.05$) at 160 days than from the PCPMSO and PCPMSO$_2$. All three compounds at the 50-ppm soil treatment level showed a significant ($p < 0.05$) reduction in total CO_2 production compared with the untreated control soil. However, total CO_2 production was not affected by soil compound concentrations of 0.5 and 5.0 ppm. Production of [^{14}C]-O_2, an indicator of ring cleavage and oxidation, decreased as concentration increased and was lowest ($p < 0.05$) for the sulfone when the three compounds were compared. Residual [^{14}C] activity accounted for the total activity in the 0.5- and 5.0-ppm treatments of the PCPMSO and PCPMSO$_2$ (91-97%), but not from the 50 ppm treatment (83%) for these compounds. Recovery from the PCPMS decreased as the concentration increased and ranged from 51 to 82%. Degradation of chemicals was significantly correlated with degradation of soil organic carbon at the two low concentrations ($r = 0.928$ and 0.813 for 0.5 and 5.0 ppm, respectively).

Blair *et al.* (1984) reported that PCPMS was enzymatically sulfoxidized to PCPMSO under aerobic conditions in cotton, carrot, and tobacco cell suspension cultures. The PCPMSO$_2$ was not produced in any of the three species. Rates of sulfoxidation were linearly related to PCPMS concentrations. The rates of PCPMS sulfoxidation were cotton>carrot>tobacco. The apparent Michaelis-Menten constant (K_m) value for carrot cells was 88 µM PCPMS (14 µg/mL), and the apparent maximum rate (V_{max}) was 7 nmol PCPMSO/mg whole-cell protein/hr. The study concluded that PCPMS-sulfide-oxidase was present in cell cultures prior to exposure to PCPMS.

E. VAPORIZATION

The PCPMS compound readily evaporated following application to soil, and losses of up to 58% were reported (Guenzi *et al.*, 1981; Guenzi and Beard, 1981).

IV. TOXICOKINETICS

Based on toxicokinetic and metabolic studies of *p*-chlorophenyl methyl sulfide, -sulfoxide, and -sulfone (PCPMS, PCPMSO, and $PCPMSO_2$) in rats and monkeys, there may be species differences in absorption, excretion, and metabolism (Thake *et al.*, 1979). Monkeys appear to absorb and excrete PCPMS, PCPMSO, and $PCPMSO_2$ (and metabolites) slower than rodents. Because the dose given to monkeys was approximately double that of rats, dose-related kinetics might have influenced experimental results. The metabolism of the unmethylated *p*-chlorophenyl sulfide, which is the proximal metabolic product of several thioaryl organophosphorus pesticides, has also been studied in rats and is discussed below. Toxicokinetics of PCPMS and $PCPMSO_2$ have also been investigated in cattle and sheep. These studies provide some information on tissue distribution and are included even though ruminant metabolism is not expected to be similar to human metabolism.

A. ABSORPTION

1. PCPMS

Thake *et al.* (1979) administered a single dose (2.5 mg/kg) of 20 µCi [^{14}C]-benzene-labeled PCPMS by gavage (in corn oil) to groups of 48 rats of each sex. Blood samples were collected from groups of six/sex at 0.5, 1, 2, 6, 12, and 24 hours and at 3 and 7 days post-treatment. The groups bled at 7 days were housed individually in glass metabolism cages, and urine and feces were collected daily. Excretion was primarily in urine with less than 5% eliminated in feces, indicating nearly complete absorption. Excretion data from this study are described in paragraph IV.D of this review. Blood levels of radioactivity peaked rapidly (probably within 2 hours) indicating rapid absorption of the analog.

In another study, Thake *et al.* (1979) administered PCPMS (in corn oil) by gavage to groups of four male and an unspecified number of female Rhesus monkeys fasted overnight. No control animals were reported. Each animal received one 25 mg dose of the analog, which included 100 µCi of [^{14}C]-labeled analog. This corresponded to a dose of about 6 mg/kg. Post-treatment blood samples were collected at 0.5, 1, 2, 6, 12, and 24 hours and at 3, 7, 14, and 28 days. The monkeys were kept in restraint chairs for 7 days, and urine and feces samples were collected at 24-hour intervals. Blood levels of radioactivity peaked at about 24 hours suggesting slower absorption of the

analog than that observed in rats. However, like the rat, excretion was primarily in urine with less than 5% eliminated in feces (see paragraph IV.D of this review), which suggests that oral doses of PCPMS are nearly completely absorbed.

2. PCPMSO

The Thake *et al.* (1979) studies in rats and monkeys (described above for PCPMS) were repeated for PCPMSO, and the peak blood levels for each species occurred at approximately the same time as the other analogs. Excretion data (see paragraph IV.D of this review) suggest that oral doses of PCPMSO are nearly completely absorbed.

3. $PCPMSO_2$

The Thake *et al.* (1979) studies in rats and monkeys (described above for PCPMS) were repeated for $PCPMSO_2$, and the peak blood levels for each species occurred at approximately the same time as the other analogs. Excretion data (see paragraph IV.D of this review) suggest that oral doses of $PCPMSO_2$ are nearly completely absorbed.

4. Comparison between PCPMS, PCPMSO, and $PCPMSO_2$

All three analogs (PCPMS, PCPMSO, and $PCPMSO_2$) showed essentially the same absorption patterns (Thake *et al.*, 1979). Blood levels peaked in rats within 2 hours following a 2.5 mg/kg dose and in monkeys at about 24 hours following about a 6 mg/kg dose. Absorption of all three analogs appeared to be nearly complete by the end of 7 days observation in both species.

B. DISTRIBUTION

Tissue distribution for PCPMS, PCPMSO, and $PCPMSO_2$ was not determined for rats and monkeys.

1. PCPMS

In two lactating cattle, 4 days after receiving six consecutive doses of PCPMS and one dose of [^{14}C]-PCPMS by gavage at 10 mg/kg/day (total 7 days dosing with compound), [^{14}C]-labeled residues were equally distributed throughout the body with the highest levels generally in fat and liver tissues (Oehler and Ivie, 1983).

2. PCPMSO

No data are available in the literature.

3. $PCPMSO_2$

In two lactating cattle, 4 days after receiving six consecutive doses of $PCPMSO_2$ and one dose of [^{14}C]-$PCPMSO_2$ by gavage at 10 mg/kg/day (total 7 days dosing with compound), [^{14}C]-labeled residues were equally distributed throughout the body with the highest levels generally in fat and liver tissues (Oehler and Ivie, 1983).

In two adult sheep treated orally with unlabeled $PCPMSO_2$ at 0.022 or 22 mg/kg/day via gelatin capsule for 5 days followed by a single dose of [^{14}C]-$PCPMSO_2$, [^{14}C]-labeled residues were equally distributed throughout the body with the highest levels generally in fat and liver tissues, especially at the highest dose (Oehler and Ivie, 1983).

4. Comparison between PCPMS, PCPMSO, and $PCPMSO_2$

Distribution studies in very small numbers of cattle and sheep (Oehler and Ivie, 1983) indicate that PCPMS and $PCPMSO_2$ (the only analogs tested) show similar tissue distribution patterns, which favor fat and liver tissues.

C. METABOLISM

1. PCPMS

For identification of urinary metabolites, Thake *et al.* (1979) pooled urine samples (0-24 hours) from Fischer 344 rats (48/sex) that had received 2.5 mg/kg of 20 µCi[^{14}C]-benzene-labeled PCPMS by gavage. Pooled samples were acidified and extracted with chloroform prior to or after hydrolysis with glusulase/sulfatase. Extracts were subjected to gas chromatography (GC), and peaks were analyzed for radioactivity. Urine samples were not pooled from Rhesus monkeys, but the samples were analyzed similarly. Four males and an unspecified number female monkeys were given 25 mg PCPMS including 100 µCi of [^{14}C]-labeled compound by gavage for 7 days.

Only 5 to 6% of the [^{14}C] in rat urine was extracted by chloroform, whereas for monkeys, about 24% of the urinary [^{14}C] was extracted after treatment (Thake *et al.*, 1979). Rats converted PCPMS to water-soluble compounds (conjugates) more readily than monkeys. After enzymatic hydrolysis in monkeys, an additional 45 to 55% of the [^{14}C] in urine became extractable with chloroform. In the PCPMS treated rats, PCPMS and PCPMSO were found in all urine samples; $PCPMSO_2$ presence was uncertain. Smaller amounts of free PCPMS were found in monkey urine, and $PCPMSO_2$ was found prior to hydrolysis. The presence of PCPMSO in monkey urine was inconclusive. From the GC data, it can be concluded that PCPMS is converted to the PCPMSO and further metabolized to $PCPMSO_2$. There is some interconversion of PCPMS to PCPMSO and PCPMSO to $PCPMSO_2$ when urine samples of undosed rats are spiked with test compound and kept at room temperature for 24 hours, but interconversion of PCPMS and PCPMSO to $PCPMSO_2$ occurs much more rapidly and completely *in vivo*. This was tested by mass spectral analysis of chloroform extracts of urine of undosed rats or rats dosed with 50 mg/kg unlabeled compound. It does not take into account the conjugated metabolites in dosed rats.

Thake *et al.* (1979) conducted a hexobarbital "sleep-time" experiment in male Fischer 344 rats to determine whether hepatic microsomal enzymes are induced by treatment with PCPMS. Rats (ten/group), weighing 150-180 g, received an oral dose of 50 mg PCPMS/kg in corn oil or 5 mL/kg corn oil (vehicle control) for 3 consecutive days. An additional (positive control) group of ten rats received an intraperitoneal injection of 175 mg hexobarbital/kg in distilled water. On day 4, treated rats were given a single intraperitoneal injection of 175 mg hexobarbital/kg and observed for time to

loss of righting reflex and duration of loss of the righting reflex. When group means were compared to vehicle controls, significant differences ($p < 0.001$) were found in animals treated with PCPMS and hexobarbital. The investigators concluded that PCPMS has an inductive effect on microsomal enzymes in male rats.

2. PCPMSO

Following the protocol for PCPMS (see paragraph IV.C.1 of this review), Thake *et al.* (1979) extracted only 5 to 6% of the [^{14}C] in rat urine following treatment with PCPMSO, whereas for monkeys, about 16% of the urinary [^{14}C] was extracted after treatment with PCPMSO (Thake *et al.*, 1979). Rats converted PCPMS to water-soluble compounds (conjugates) more readily than monkeys. After enzymatic hydrolysis in monkeys, an additional 45 to 55% of the [^{14}C] in urine became extractable with chloroform. There is some interconversion of PCPMSO to $PCPMSO_2$ when urine samples of undosed rats are spiked with test compound and kept at room temperature for 24 hours, but interconversion is much more rapid *in vivo*. This was tested by mass spectral analysis of chloroform extracts of urine of undosed rats or rats dosed with 50 mg/kg unlabeled compound. It does not take into account the conjugated metabolites in dosed rats.

Thake *et al.* (1979) conducted a hexobarbital "sleep-time" experiment in male Fischer 344 rats to determine whether hepatic microsomal enzymes are induced by oral treatment with 50 mg PCPMSO/kg in corn oil (see paragraph IV.C.1 of this review for experimental details). Significant differences ($p < 0.001$) were found in animals treated with PCPMSO and hexobarbital when compared with vehicle controls, indicating that PCPMSO has an inductive effect on microsomal enzymes in male rats.

3. $PCPMSO_2$

Following the protocol for PCPMS (see paragraph IV.C.1 of this review), Thake *et al.* (1979) extracted only 5 to 6% of the [^{14}C] in rat urine following treatment with $PCPMSO_2$, whereas for monkeys, about 59% of the urinary [^{14}C] was extracted after administration of $PCPMSO_2$ (Thake *et al.*, 1979). Rats converted the chemicals to water-soluble compounds (conjugates) more readily than monkeys. After enzymatic hydrolysis in monkeys, an additional 45 to 55% of the [^{14}C] in urine became extractable with chloroform.

Thake *et al.* (1979) conducted a hexobarbital "sleep-time" experiment in male Fischer 344 rats to determine whether hepatic microsomal enzymes are induced by oral treatment with 50 mg $PCPMSO_2$/kg in corn oil (see paragraph IV.C.1 of this review for experimental details). Significant differences ($p < 0.001$) were found in animals treated with $PCPMSO_2$ and hexobarbital when compared with vehicle controls, indicating that $PCPMSO_2$ has an inductive effect on microsomal enzymes in male rats.

4. Comparison between PCPMS, PCPMSO, and $PCPMSO_2$

Metabolites extracted from rat and monkey urines indicate that PCPMS is converted to PCPMSO and to $PCPMSO_2$. Rats convert all three analogs to water soluble conjugates more rapidly than monkeys. The $PCPMSO_2$ analog is the most poorly conjugated of the three compounds in monkeys. Metabolism probably proceeds by sulfoxidation, hydroxylation of a ring compound, and conjugation with glucuronic acid or sulfate. Hexobarbital "sleep-time" experiments with male rats indicate that all three compounds induce microsomal enzymes.

5. Metabolism of Chlorothiophenol

Menn *et al.* (1975) examined the urinary metabolites of [^{14}C]-4-chlorothiophenol 144 hours after administration of 8.3 mg/kg to rats. About 70% of the administered radioactivity was excreted in the urine and 30% in the feces. Seven metabolites were separated by thin-layer chromatography of urine and were identified: *p*-chlorophenyl methyl sulfone (8.1%), 4-chlorobenzene sulfonic acid (4%), *p*-chloro-3-hydroxy phenyl methyl sulfone (15.4%), the glucuronide conjugate (16%) and O-sulfate conjugate (21%) of the above 3-hydroxy compound, and 4-chlorophenyl thio-S-glucosiduronic acid (27%). The glucosiduronic acid conjugate was refractory to enzyme hydrolysis and was found in the free acid and lactone forms. Chlorothiophenol is the primary cleavage product of the thioarylorganophosphorous insecticides (*e.g.*, Dyphonate® and trithion), and earlier studies indicated that in plants and animals, metabolism of these insecticides proceeded by cleavage of the thiophenol and chlorothiophenol moiety, methylation to chloromethylphenyl sulfide or methylphenyl sulfide, sulfoxidation, ring hydroxylation, and conjugation. It is reasonable to expect that metabolism of the *p*-chlorophenyl methyl sulfide, -sulfoxide, and -sulfone would follow a pathway similar to that of chlorothiophenol.

D. EXCRETION

1. PCPMS

Thake *et al.* (1979) administered a single dose (2.5 mg/kg) of 20 µCi [^{14}C]-benzene-labeled PCPMS by gavage (in corn oil) to groups of 48 rats of each sex (see paragraph IV.A. for experimental details). Disappearance of [^{14}C] from blood followed first-order kinetics for both sexes; the alpha phase had a half-life of 9.5 to 12 hours, and the half-life for the second (beta) phase was 3.1 and 3.4 days in males and females, respectively. Excretion was primarily in the urine. Rats excreted 35 to 65% of the dose in urine by 24 hours and 50 to 90% by 48 hours, with less than 5% eliminated in feces. Half-lives of urinary excretion were not reported.

Thake *et al.* (1979) administered PCPMS (in corn oil) by gavage to groups of four male and an unspecified number of female Rhesus monkeys fasted overnight (see paragraph IV.A. for experimental details). Blood levels appeared to follow zero-order kinetics with a half-life of approximately 7 days, and the rate of decline was much slower than in rats. Blood clearance was somewhat slower in females than in males, with detectable levels of radioactivity still present in the blood of females at 28 days. Excretion was primarily in the urine with constant amounts excreted daily for 7 days. Elimination in feces was less than 5% of the total dose administered.

Oehler and Ivie (1983) gave PCPMS orally in a gelatin capsule to two lactating cattle at 10 mg/kg/day for six consecutive days before administering a single oral dose of the [^{14}C] radiolabeled analog. *p*-Chlorophenyl methyl sulfide was rapidly metabolized to $PCPMSO_2$ and slowly excreted in the urine. After 4 days, 22% of the [^{14}C]-PCPMS had been recovered in the urine. Also, within 4 days post-treatment, 1 to 3% of the dose had been secreted in milk, nearly all of it as $PCPMSO_2$.

2. PCPMSO

Thake *et al.* (1979) administered a single dose (2.5 mg/kg) of 20 µCi [^{14}C]-benzene-labeled PCPMSO by gavage (in corn oil) to groups of 48 rats of each sex (see paragraph IV.A. for experimental details). Disappearance of [^{14}C] from the blood followed first-order kinetics for both sexes; the alpha phase had a half-life of 9.5 to 12 hours, and the half-life for the second (beta) phase was

2.5 and 2.1 days in males and females, respectively. Elimination in feces was less than 5% of total dose.

Thake *et al.* (1979) administered PCPMSO (in corn oil) by gavage to groups of four male and an unspecified number of female Rhesus monkeys fasted overnight (see paragraph IV.A. for experimental details). Blood levels appeared to follow zero-order kinetics with a half-life of approximately 7 days, and the rate of decline was much slower than in rats. Blood clearance was somewhat slower in females than in males, with detectable levels of radioactivity still present in the blood of females at 28 days. Excretion was primarily in the urine with constant amounts excreted daily for 7 days. Elimination in feces less than 5% of the total dose administered.

3. PCPMSO$_2$

Thake *et al.* (1979) administered a single dose (2.5 mg/kg) of 20 µCi [^{14}C]-benzene-labeled PCPMSO$_2$ by gavage (in corn oil) to groups of 48 rats of each sex (see paragraph IV.A. for experimental details). Disappearance of [^{14}C] from blood followed first-order kinetics for both sexes; the alpha phase had a half-life of 9.5 to 12 hours, and the half-life for the second (beta) phase was 1.6 and 2.8 days in males and females, respectively. Elimination in feces was less than 5% of total dose.

Thake *et al.* (1979) administered PCPMSO$_2$ (in corn oil) by gavage to groups of four male and an unspecified number of female Rhesus monkeys fasted overnight (see paragraph IV.A. for experimental details). Blood levels appeared to follow zero-order kinetics with a half-life of approximately 7 days, and the rate of decline was much slower than in rats. Blood clearance was somewhat slower in females than in males, with detectable levels of radioactivity still present in the blood of females at 28 days. Excretion was primarily in the urine with constant amounts excreted daily for 7 days. Elimination in feces was less than 5% of the total dose administered.

Oehler and Ivie (1983) gave PCPMSO$_2$ orally in a gelatin capsule to two lactating cattle at 10 mg/kg/day for 5 consecutive days before administering a single oral dose of the [^{14}C] radiolabeled analog at the same dose. *p*-Chlorophenyl methyl sulfone, which appeared quite resistant to further metabolism, was slowly excreted in the urine. After 4 days, 13% of the [^{14}C]-PCPMSO$_2$ had been

recovered in the urine. Also, within 4 days post-treatment, 1 to 3% of the dose had been secreted in milk, nearly all of it as $PCPMSO_2$.

Oehler and Ivie (1983) similarly dosed two adult sheep with unlabeled $PCPMSO_2$ for 5 days (0.022 or 22 mg/kg) followed by a single [^{14}C]-$PCPMSO_2$ dose at the same dose levels. At the low dose, there was complete urinary excretion in 14 days. At the high dose by day 14, 35% and 23% of the radioactivity had been eliminated in the urine and feces, respectively.

4. Comparison between PCPMS, PCPMSO, and $PCPMSO_2$

In the rat study, in which Thake *et al.* (1979) administered a single dose (2.5 mg/kg) of 20 µCi [^{14}C]-benzene-labeled PCPMS by gavage (in corn oil) to groups of 48 rats of each sex, blood levels of radioactivity peaked rapidly (probably within 2 hours), and disappearance of [^{14}C] from blood followed first-order kinetics. The alpha phase had a half-life of 9.5 to 12 hours for both sexes for all three analogs. The alpha half-lives for $PCPMSO_2$ were slightly slower than for PCPMS. The half-life for the second (beta) phase for PCPMS was 3.1 and 3.4 days in males and females, respectively; for PCPMSO, the half-lives were 2.5 and 2.1 days in males and females respectively; and for $PCPMSO_2$, the half-lives were 1.6 and 2.8 days in males and females, respectively. Elimination in feces was less than 5% of total dose.

In the Thake *et al.* (1979) gavage study with Rhesus monkeys that received one 25 mg dose of each analog (corresponding to a dose of about 6 mg/kg), blood levels for all three analogs peaked at about 24 hours. Excretion was primarily in the urine with constant amounts excreted daily for 7 days. Elimination from the blood appeared to follow zero-order kinetics indicating saturability for all three analogs. Although PCPMSO cleared more slowly from the blood than PCPMS or $PCPMS_2$, there were no significant differences reported for the blood levels of the different analogs. Recovery of radioactivity in 7 days was somewhat less with the sulfide (26%) than with the sulfoxide (50%) or sulfone (42%). Elimination in feces was less than 5% of the total dose administered for all analogs.

V. HEALTH EFFECTS

A. HUMANS

No studies on the health effects of *p*-chlorophenyl methyl sulfide (PCPMS), -sulfoxide (PCPMSO), and -sulfone ($PCPMSO_2$) in humans were found in the literature.

B. ANIMAL EXPERIMENTS

1. Short-term Exposure

a. Acute

(1) PCPMS

In an acute, oral toxicity study, Thake *et al.* (1979) gavaged Fischer 344 rats with a single dose of PCPMS dissolved in corn oil and observed the animals twice daily for mortality and toxic symptoms. Ten rats/sex/dose, except two female dose groups, each with 20 rats, were treated with the compound. Ten rats/sex served as controls. The dose levels, which ranged from 398 to 708 mg/kg in males and 355 to 794 mg/kg in females, had been established to cover a range of 0-100% mortality. At all treatment levels in both sexes, there was an immediate decrease in locomotor activity. At the higher doses, this was followed by a loss of coordination, prostration, loss of consciousness, severe lacrimation, labored respiration, and death. The investigators indicated that dehydration and starvation in prostrate animals may have contributed to the deaths of treated animals, although death occurred within 4 hours in some rats at the highest dose. No toxicity or mortality was observed in controls. Table V-1 presents the LD_{50}s for PCPMS, which were higher for males (619 mg/kg) than for females (479 mg/kg).

In a similar, acute gavage study with $B_6C_3F_1$ mice (10/sex/dose, except one male treatment group with 20 mice), Thake *et al.* (1979) administered PCPMS dissolved in corn oil and observed the mice twice daily for mortality and toxic symptoms. The dose levels, established to induce 0-100% mortality, ranged from 501 to 1,122 mg/kg in males and 631 to 1,000 mg/kg in females. Ten mice/sex served as controls. At all treatment levels in both sexes, there was an immediate decrease

Table V-1. Acute Oral LD_{50} Values for *p*-Chlorophenyl Methyl Sulfide, -Sulfoxide, -Sulfone (PCPMS, PCPMSO, and $PCPMSO_2$)

Chemical	Species/Strain	LD_{50} (mg/kg)		Effects
		Male	Female	
PCPMS	Mouse/$B_6C_3F_1$	877	672	Toxic signs included an immediate decrease in locomotor activity, prostration, loss of consciousness, labored respiration, and death. Severe lacrimation was characteristic of animals treated with sulfide and sulfoxide analogs.
	Rat/F344	619	479	
PCPMSO	Mouse/$B_6C_3F_1$	328	440	
	Rat/F344	611	463	
$PCPMSO_2$	Mouse/$B_6C_3F_1$	600	606	
	Rat/F344	529	400	

SOURCE: Adapted from Thake *et al.* (1979)

in locomotor activity. At the higher doses, this was followed by a loss of coordination, prostration, loss of consciousness, severe lacrimation, labored respiration, and death. The investigators indicated that dehydration and starvation in prostrate animals may have contributed to the deaths of treated animals, although death occurred within hours in some mice at the highest dose. No toxicity or mortality was observed in controls. Table V-1 presents the LD_{50}s for PCPMS, which were higher for males (877 mg/kg) than for males (672 mg/kg).

In an acute dermal toxicity study, Thake *et al.* (1979) applied gauze sponges with PCPMS in acetone to the shaved backs of Fischer 344 rats (2/sex/dose) for 24 hours and observed the animals daily for 14 days. The dose levels were 0, 1,000, 2,190, or 5,630 mg/kg. All animals at the highest dose died within 24 hours following removal of the gauze. Also, at the highest dose, locomotor activity immediately decreased, followed by a loss of coordination, prostration, severe lacrimation, diarrhea, loss of consciousness, labored respiration, and death. Similar, but less severe, toxic symptoms occurred in the 2,190 mg/kg treatment group and were noted for 7 days. Rats in the 1,000 mg/kg group showed decreased locomotion for approximately 24 hours following removal of the gauze.

(2) PCPMSO

In an acute, oral toxicity study, Thake *et al.* (1979) gavaged Fischer 344 rats (10/sex/dose, except two male dose groups with 20 rats) with PCPMSO dissolved in corn oil and observed the animals twice daily for mortality and toxic symptoms. The dose levels, which ranged from 398 to 794 mg/kg in males and 316 to 631 mg/kg in females, had been established to produce 0-100% mortality. Ten rats/sex served as controls. The results were the same as those for PCPMS (see paragraph V.B.1.a.(1) of this review). Table V-1 presents the LD_{50}s for PCPMSO, which were higher for males (611 mg/kg) than for females (463 mg/kg).

In a similar, acute gavage study with $B_6C_3F_1$ mice (10/sex/dose, except one female treatment group with 20 mice), Thake *et al.* (1979) gave PCPMSO dissolved in corn oil and observed the mice twice daily for mortality and toxic symptoms. The dose levels, which had been established to produce 0-100% mortality, ranged from 158 to 501 mg/kg in males and 251 to 631 mg/kg in

females. Ten mice/sex served as controls. The results were essentially the same as those for PCPMS (see paragraph V.B.1.a.(1) of this review). Table V-1 presents the LD_{50}s for PCPMSO, which were higher for females (440 mg/kg) than for males (328 mg/kg).

In an acute dermal toxicity study, Thake *et al.* (1979) applied gauze sponges with PCPMSO in acetone to the shaved backs of Fischer 344 rats (2/sex/dose) for 24 hours and observed the animals daily for 14 days. The dose levels were 0, 1,000, 2,190, or 5,630 mg/kg. No deaths occurred with this analog. However, at the highest dose, locomotor activity immediately decreased, followed by a loss of coordination, prostration, severe lacrimation, diarrhea, loss of consciousness, and labored respiration. A gradual recovery followed. Similar, but less severe, toxic symptoms occurred in the 2,190 mg/kg treatment group, but animals were normal within 24 hours following removal of the gauze.

(3) PCPMSO$_2$

In an acute, oral toxicity study, Thake *et al.* (1979) gavaged Fischer 344 rats (10/sex/dose, except one male and four female dose groups with 20 rats) with PCPMSO$_2$ dissolved in corn oil and observed the animals twice daily for mortality and toxic symptoms. The dose levels, which ranged from 464 to 708 mg/kg in males and 282 to 473 mg/kg in females, had been established to produce 0-100% mortality. Ten rats/sex served as controls. At all treatment levels in both sexes, there was an immediate decrease in locomotor activity. This was followed, at the higher doses, with a loss of coordination, prostration, diarrhea, loss of consciousness, labored respiration, and death. The investigators indicated that dehydration and starvation in prostrate animals may have contributed to the deaths of treated animals, although death occurred within 4 hours in some rats at the highest dose. No toxicity or mortality was observed in controls. Table V-1 presents the LD_{50}s for PCPMSO$_2$, which were higher for males (529 mg/kg) than for females (400 mg/kg).

In a similar, acute gavage study with $B_6C_3F_1$ mice (10/sex/dose, except one female treatment group with 9 mice), Thake *et al.* (1979) administered PCPMSO$_2$ dissolved in corn oil and observed the mice twice daily for mortality and toxic symptoms. The dose levels, which had been established to produce 0-100% mortality, ranged from 562 to 794 mg/kg for both sexes. Ten mice/sex served as controls. At all treatment levels in both sexes, there was an immediate decrease in locomotor activity. This was followed at the higher doses with a loss of coordination, prostration, loss of

consciousness, diarrhea, labored respiration, and death. The investigators indicated that dehydration and starvation in prostrate animals may have contributed to the deaths of treated animals, although death occurred within hours in some mice at the highest dose. No toxicity or mortality was observed in controls. Table V-1 presents the LD_{50}s for $PCPMSO_2$, which were 600 mg/kg for males and 606 mg/kg for females.

In an acute dermal toxicity study, Thake *et al.* (1979) applied gauze sponges with $PCPMSO_2$ in acetone to the shaved backs of Fischer 344 rats (2/sex/dose) for 24 hours and observed the animals daily for 14 days. The dose levels were 0, 1,000, 2,190, or 5,630 mg/kg. No deaths and no toxic symptoms occurred with this analog.

(4) Comparison between PCPMS, PCPMSO, and $PCPMSO_2$

Acute oral doses of PCPMS and PCPMSO were equally toxic to male and female Fischer 344 rats and slightly less toxic than $PCPMSO_2$ to this strain (Thake *et al.*, 1979). However, the investigators reported that while PCPMS and PCPMSO were readily soluble in corn oil, $PCPMSO_2$ was not, and, thus, required higher vehicle volumes, which could have enhanced compound absorption. This effect, however, was not observed in similar experiments with mice. Thake *et al.* (1979) observed in $B_6C_3F_1$ mice that while oral $PCPMSO_2$ was more toxic than PCPMS to male mice, PCPMSO was far more lethal than either $PCPMSO_2$ or PCPMS to both sexes. Thus, while $PCPMSO_2$ was slightly more toxic than PCPMS or PCPMSO when administered orally in rats, mice were more sensitive to the lethal effects of PCPMSO. Severe lacrimation was observed in rats and mice given PCPMS or PCPMSO but not in $PCPMSO_2$ treated animals.

The types of toxic symptoms observed in rats following oral exposure to all three analogs were similar to those observed following dermal applications of PCPMS or PCPMSO. Dermal application of $PCPMSO_2$, however, had no effect. The investigators did not indicate whether $PCPMSO_2$ had been absorbed through the skin.

b. Primary Irritation, Dermal Sensitization, and Ophthalmologic Effects

Thake *et al.* (1979) conducted skin irritation studies of PCPMS, PCPMSO, and $PCPMSO_2$ on 18 male and female New Zealand albino rabbits. Three animals/sex/compound were treated with

slurries or solutions of the compounds at 50% (w/v) concentrations in corn oil according to the Modified Draize Procedure. The animals' skin was graded and evaluated at 24, 48, and 72 hours post-treatment. The PCPMS analog did not produce irritation in any of the treated rabbits. The $PCPMSO_2$ analog produced a mild irritation in one male and one female, and PCPMSO produced a mild irritation in two males and two females and a severe reaction in one female rabbit.

In an eye irritation study, liquid PCPMS (0.1 mL), solid PCPMSO (100 mg), and solid $PCPMSO_2$ (100 mg) were tested in groups of five male New Zealand albino rabbits according to the Modified Draize Procedure (Thake *et al.*, 1979). Eye examinations were conducted at 24, 48, and 72 hours, and at 7 days post-treatment. The PCPMS produced positive corneal responses in four of five animals; eyes were normal by day 7. The PCPMSO produced positive responses in all treated animals for the cornea, iris, and conjunctivae. Lesions of the iris and conjunctivae were completely reversible by day 7; however, the corneal lesions were considered to be irreversible. The $PCPMSO_2$ did not produce a positive response in any of the treated animals.

Thake *et al.* (1979) studied skin sensitization of PCPMS, PCPMSO, and $PCPMSO_2$ in female Hartley albino guinea pigs. Groups of eight guinea pigs were induced by a two-stage operation: first, with an intradermal injection of the compounds in Freund's adjuvant and then, after 1 week, with topical application of the compounds in petrolatum. The animals received a topical challenge 2 weeks later and were examined 24 and 48 hours post-treatment. Animals treated with PCPMS showed no adverse effects. Animals treated with PCPMSO exhibited minimal focal intracellular vacuolation (2/8) and mild multifocal papillar dermatitis (1/8). Animals treated with $PCPMSO_2$ exhibited minimal focal acantholysis (one of eight, 1/8) and minimal focal intracellular vacuolation (2/8). The changes observed with PCPMSO and $PCPMSO_2$ were considered to represent background changes, not the result of dosing.

c. Subacute

Because PCPMS, PCPMSO, and $PCPMSO_2$ were expected to be unpalatable at high doses, Thake *et al.* (1979) conducted parallel 28-day feeding and gavage studies (range finding studies) in rats to determine dietary dosages for a 91-day rat study (paragraph V.B.2 of this review). They also conducted a 28-day feeding study in mice to determine appropriate dosages for a 91-day mouse

study (paragraph V.2 of this review). Thake *et al.* (1979) conducted an additional gavage study with Rhesus monkeys.

(1) PCPMS

Thake *et al.* (1979) fed Fischer 344 rats (five/sex/dose) diets containing PCPMS for 28 days at levels of 0, 281, 562, 2,250, or 9,000 ppm, which correspond to calculated doses of 0, 28.1, 56.2, 225, and 900 mg/kg/day, respectively (Lehman, 1959). Mortality, body weight, and food consumption were observed throughout the study. All rats at the 9,000 ppm dose died within the first week, but the investigators attributed these deaths to starvation rather than to the test compound. No mortality occurred at lower dietary levels. Although, it appeared that body weights and food consumption decreased in a dose-related manner throughout the study, body weight and food consumption recordings were compared to control data conducted on another chemical (not specified); for this reason, initial body weights of the animals differed and interpretation of these data is not completely reliable.

In the mouse feeding study, $B_6C_3F_1$ mice (five/sex/dose, except highest male dose group with four mice) were given diets containing PCPMS at levels of 0, 281, 562, 2,750, or 4,500 ppm for 28 days (Thake *et al.*, 1979). These levels correspond to calculated doses of 0, 42.2, 84.3, 412.5, and 675 mg/kg/day, respectively (Lehman, 1959). Except for one female in the highest treatment group, no mortalities were observed. Death was preceded by a marked depression in motor activity. Food consumption data showed no consistent trends, and the investigators could not adequately interpret the body weight gain data.

In the gavage study, Fischer 344 rats (five/sex/dose) received PCPMS in corn oil for 28 days at dose levels of 0, 18.8, 37.5, 75, 150, 180, 220, 265, or 530 mg/kg/day for males and 0, 9.4, 18.8, 37.5, 75, 150, or 330 mg/kg/day for females (Thake *et al.*, 1979). Mortality was 100% in males at 220, 265, or 530 mg/kg/day levels and in females at the 330 mg/kg/day dose. Below these levels, mortality decreased in a dose-related manner, though females exhibited a higher rate of mortality. The investigators reported difficulty in interpreting body weight and food consumption data, noting that most treated animals consumed greater amounts of feed than controls. Generally, at doses greater than 50 mg/kg/day, the rats showed an immediate decrease in motor activity after each daily

treatment. Rats that died became progressively depressed with each subsequent dose. Signs of depression completely disappeared before termination of the study in all surviving rats.

In a 14-day gavage study, Thake *et al.* (1979) administered PCPMS to male and female Rhesus monkeys at dose levels of 0, 5, 10, 20, 30, 40, or 80 mg/kg/day. The control group and the 5, 10, and 20 mg/kg/day treatment groups each contained six animals (three/sex). The remaining groups each contained two animals (one/sex). Twenty-four hours after the final treatment, half of the animals in each group were randomized for immediate sacrifice and necropsy while the other half were observed throughout a 14-day recovery period. The animals were observed for mortality, toxic symptoms, clinical chemistry, and hematological parameters before treatment began and on days 7 and 14 (as well as on days 21 and 29 during recovery). Statistical analyses for hematology and clinical chemistry parameters were done only for days 7 and 14; thus, no conclusions for these parameters can be drawn for the recovery period. The clinical chemistry parameters were compared statistically with pretreatment levels, the hematology parameters with controls. Clinical chemistry and hematology parameters, pathologic data, and relative organ weights were combined for males and females. Body weights and absolute organ weights were not measured.

Three deaths occurred during the treatment period; one at the highest dose (80 mg/kg/day) on day 6, one at the 40 mg/kg/day dose on day 9, and one at the 20 mg/kg/day dose on day 12. One death occurred 2 days into the recovery period at the 20 mg/kg/day level. In the 20 mg/kg/day group one monkey that survived to the end of the recovery period appeared normal at necropsy, two monkeys were moribund by the 13 or 14 day of treatment, and one was depressed when sacrificed post-treatment. At doses greater than 20 mg/kg/day, all animals were dead or moribund at necropsy. Anorexia, weakness, and depression were observed in all treatment groups. Adipsia was observed at the 40 and 80 mg/kg/day levels. Hypothermia occurred in the 10, 20 and 30 mg/kg/day groups. Thake *et al.* (1979) attributed the diarrhea and emesis exhibited in control animals and sporadically in treated animals to the corn oil vehicle. No statistically significant changes in hematologic parameters were reported. In the 20-80 mg/kg/day (pooled data) groups, blood urea nitrogen (BUN) increased significantly over pretreatment levels on days 7 and 14, and total bilirubin significantly increased on day 7 and remained at that level through the treatment period. Blood glucose levels decreased significantly over pretreatment levels on day 14 in the 20-80 mg/kg/day (pooled) dose group. Serum alkaline phosphatase levels significantly decreased at dose levels of 10 mg/kg/day and higher on day 14. Although hematology and clinical chemistry parameters fluctuated in control

animals, all parameters (with the exception of one male) were back within pretreatment limits by necropsy at either day 15 or 29.

A statistically significant increase in the relative liver and kidney weights (compared with controls) were observed in the monkeys receiving 10 mg/kg/day or greater PCPMS. Animals receiving 20 mg/kg/day or greater doses also exhibited increased relative brain, adrenal, and atrial (weights of other heart sections not reported) weights. The investigators did not indicate whether the comparisons of organ weight included animals necropsied at the end of the recovery period. Further, without body weights or absolute organ weights, these data are difficult to assess.

Treated monkeys that died or were sacrificed at the end of the treatment period exhibited compound-related pathologic changes in liver, kidney, adrenal and thyroid glands, lymphoid system, and intestine. Thake *et al.* (1979) pooled the pathology data for treatment groups 20, 30, 40, and 80 mg/kg/day and combined the results for males and females. Hepatocyte vacuolization, vacuolar degeneration, and hepatocyte necrosis occurred primarily in the 20-80 mg/kg/day dose groups and far less frequently at the 10 mg/kg/day level. Vacuolization and pigmentation of renal tubular epithelium was observed at 10 mg/kg/day or greater dose levels. Animals mainly at the 20-80 mg/kg/day levels exhibited adrenal cortex hyperplasia, hemorrhage, and congestion; follicular cell hyperplasia and degeneration of the thyroid, vacuolization and degeneration of gastric and intestinal epithelium with cell cycle alterations; and lymphoreticular proliferative lesions in lymph nodes, spleen, and bone marrow and lymphoid depletion. None of the monkeys exhibited ophthalmic lesions. A few recovery group animals at all dose levels exhibited hepatic, renal, and adrenal pathologic changes. Based on symptoms of anorexia, depression, and weakness, the Lowest-Observed-Adverse-Effect Level (LOAEL) for PCPMS is 5 mg/kg/day, which was the lowest dose tested. A NOAEL could not be determined.

(2) <u>PCPMSO</u>

In the 28-day feeding study, Thake *et al.* (1979) fed Fischer 344 rats (five/sex/dose except the control group of 10 rats/sex) diets containing 0, 162, 325, 650, 1,300, 2,600, or 5,200 ppm PCPMSO, which corresponds to calculated doses of 0, 16.2, 32.5, 65, 130, 260, 520 mg/kg/day, respectively (Lehman, 1959). Mortality, body weight, and food consumption were recorded throughout the study. At the highest dose, four males (80%) and three females (60%) died. No other

mortalities occurred. Food consumption was depressed throughout the study in rats fed 5,200 or 2,600 ppm PCPMSO. Rats receiving 1,300 ppm or less returned to near control levels of food consumption during weeks 2, 3, and 4 for males and weeks 3 and 4 for females. Except at the highest dose, body weight gain decreased as the study progressed.

In the mouse feeding study, $B_6C_3F_1$ mice (five/sex/dose, except highest male dose with four mice) were given diets containing PCPMSO at levels of 0, 188, 375, 750, 1,300, 2,600, or 5,200 ppm for 28 days (Thake *et al.*, 1979). These levels correspond to calculated doses of 0, 28.2, 56.3, 112.5, 195, 390, and 780 mg/kg/day, respectively (Lehman, 1959). Two females died during the first week in the 5,200 ppm group. Death was preceded by a marked depression in motor activity. No other mortalities occurred. Food consumption data showed no consistent trends, and the investigators could not adequately interpret the body weight gain data, though they reported that the 750 ppm or higher dose groups showed decrements in body weights.

In the gavage study, Fischer 344 rats (five/sex/dose) received PCPMSO in corn oil for 28 days at dose levels of 0, 6.25, 12.5, 25, 50, 100, 200, 400 mg/kg/day (Thake *et al.*, 1979). Mortality was 100% at the highest dose in both sexes. No other deaths occurred among the males. One death occurred in the 200 mg/kg/day female group and three deaths in the female control group. Body weight gain showed a dose-related decrease in both sexes. However, during the final week of the study, weight gain approached that of controls. The investigators attributed this finding to an increased tolerance to treatment. Weekly food consumption for several treatment groups often exceeded that for controls. Generally, at doses greater than 50 mg/kg/day, the rats showed an immediate decrease in motor activity after each daily treatment. Rats that died became progressively depressed with each subsequent dose. Signs of depression completely disappeared before termination of the study in all surviving rats.

In a 14-day gavage study, Thake *et al.* (1979) administered PCPMSO to male and female Rhesus monkeys at dose levels of 0, 5, 10, or 20 mg/kg/day. The control group, which also served as the PCPMS and $PCPMSO_2$ controls, and the 10 and 20 mg/kg/day treatment groups each contained six animals (three/sex). Seven animals (three females, four males) were given the lowest dose. The remaining experimental details are the same as those for PCPMS (see paragraph V.B.1.c.(1) of this review).

There were no mortalities. At post-treatment necropsy (day 15), three monkeys at the highest dose were depressed, one severely. Another high dose monkey sacrificed after 14 days of recovery also was depressed. All other animals appeared normal at necropsy on day 15 or 29. Anorexia, weakness, depression, and hypothermia were observed at the 20 mg/kg/day dose, and the same symptoms except weakness were observed at 10 mg/kg/day. Thake *et al.* (1979) attributed the diarrhea exhibited in some treated animals at the 5 and 10 mg/kg/day dose levels as well as in controls to the corn oil vehicle. Monkeys treated at 10 or 20 mg/kg/day exhibited a statistically significant decrease in the reticulocyte count compared with controls on day 14, and no recovery occurred by day 29. Monkeys at the highest dose (20 mg/kg/day) on day 7 and at the intermediate or highest dose on day 14 exhibited significantly elevated BUN levels compared to pretreatment levels. Only 25% of monkeys at the highest dose recovered to pretreatment BUN levels by the end of the recovery period. Alkaline phosphatase was significantly decreased from pretreatment levels on day 14 at the 10 and 20 mg/kg/day doses. Sporadic, moderate to marked elevations of serum glutamate oxalate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), and calcium levels also occurred but were not statistically significant. Although hematology and clinical chemistry parameters fluctuated in control animals, all parameters (with the exception of one male) were back within pretreatment limits by necropsy at either day 15 or 29.

A statistically significant increase in the relative liver and kidney weights (compared with controls) were observed in the monkeys receiving 10 or 20 mg/kg/day PCPMSO. The investigators did not indicate whether the comparisons of organ weight included animals necropsied at the end of the recovery period. Further, without body weights or absolute organ weights, these data are difficult to assess.

Treated monkeys that died or were sacrificed at the end of the treatment period exhibited compound-related pathologic changes in liver, kidney, adrenal and thyroid glands, lymphoid system, and intestine. Thake *et al.* (1979) combined the results for males and females. Lymphoreticular proliferative lesions in lymph nodes, spleen, and bone marrow were most severe in the highest dosed animals, but occurred in one animal at 5 mg/kg/day. Also, at the 5 mg/kg/day dose, hepatocyte vacuolization, vacuolar degeneration, and hepatocyte necrosis occurred in two monkeys during the treatment period. Liver lesions were also observed at the high dose. Other lesions, which occurred most frequently at the highest dose, included vacuolization and pigmentation of renal tubular epithelium; adrenal cortex hyperplasia, hemorrhage, and congestion; follicular cell hyperplasia and

degeneration of the thyroid, vacuolization and degeneration of gastric and intestinal epithelium with cell cycle alterations. None of the monkeys exhibited ophthalmic lesions. A few recovery group animals at all dose levels exhibited hepatic, renal, and adrenal pathologic changes. Based on the incidence of hepatic and lymphoreticular proliferative lesions, the LOAEL is 5 mg/kg/day, the lowest dose tested. A NOAEL could not be determined.

(3) PCPMSO$_2$

In the 28-day feeding study, Thake *et al.* (1979) fed Fischer 344 rats (five/sex/dose) diets containing 0, 281, 562, or 2,250 ppm PCPMSO$_2$, which corresponds to calculated doses of 0, 42.2, 84.3, 337.5, and 675 mg/kg/day, respectively (Lehman, 1959). Mortality, body weight, and food consumption were recorded throughout the study. No mortalities occurred during the study. Generally, body weight and food consumption decreased in a dose-related manner; however, these parameters were compared to a control group of Fischer 344 rats used in another feeding study. For this reason, initial body weights of the animals differed and interpretation of the data is not completely reliable.

In the mouse feeding study, $B_6C_3F_1$ mice (five/sex/dose, except highest male dose with four mice) were given diets containing PCPMSO$_2$ at levels of 0, 281, 562, 2,250, or 4,500 ppm for 28 days (Thake *et al.*, 1979). These levels correspond to calculated doses of 0, 28.1, 56.2, 225, and 450 mg/kg/day, respectively (Lehman, 1959). No deaths occurred. Food consumption data showed no consistent trends, and the investigators could not adequately interpret the body weight gain data.

In the gavage study, Fischer 344 rats (five/sex/dose) received PCPMSO$_2$ in corn oil for 28 days at dose levels of 0, 50, 100, 200, 460 mg/kg/day in 28 mL/kg and 3.12, 6.25, 12.5, 25, 50, or 100 mg/kg/day in 5 mL/kg volumes (Thake *et al.*, 1979). Both sexes exhibited high mortality at 50 mg/kg/day (60%) and greater dose levels (100%). The investigators reported difficulty in interpreting body weight and food consumption data, noting that most treated animals consumed greater amounts of feed than controls. At doses greater than 50 mg/kg/day, the rats showed an immediate decrease in motor activity after each daily treatment. Rats that died became progressively depressed with each subsequent dose. Signs of depression completely disappeared before termination of the study in all surviving rats.

In a 14-day gavage study, Thake *et al.* (1979) administered $PCPMSO_2$ to male and female Rhesus monkeys at dose levels of 0, 2.5, 5, 10, 15, 20, or 30 mg/kg/day. The control group, which served for the PCPMS and PCPMSO controls as well, and the 10 mg/kg/day treatment group each contained six animals (three/sex). The 2.5 mg/kg/day group contained four animals (two/sex), the 20 mg/kg/day group contained three animals (two females, one male), and the remaining groups each contained two animals (one/sex). Animals from the three highest dose levels were grouped together for statistical purposes. The 2.5 and 5 mg/kg/day groups were combined for statistical purposes. Otherwise, the experimental protocol was the same as that for PCPMS (see paragraph V.B.1.c.(1) of this review).

One female died on day 9 in the 20 mg/kg/day group and another animal at this dose was moribund at necropsy on day 15. Both animals at the highest dose (30 mg/kg/day) were moribund by day 10 and were sacrificed. All other animals appeared normal at necropsy on either day 15 or 29. Anorexia was observed at all dose levels, and depression, weakness, hypothermia, and adipsia at the 20 and 30 mg/kg/day levels. Thake *et al.* (1979) attributed the diarrhea and emesis exhibited in control animals and sporadically in treated animals to the corn oil vehicle. No statistically significant differences in hematologic parameters were reported. Significantly elevated BUN levels over pretreatment values were observed on day 7 at 20-30 mg/kg/day (pooled data). This effect persisted until termination on day 15. At 20-30 mg/kg/day (pooled data), monkeys exhibited a significant decrease in blood glucose levels, which remained depressed through termination on day 15. Several other clinical parameters tended to fluctuate in treated as well as control animals.

A statistically significant increase in relative adrenal weights (compared with controls) was observed in the 20 and 30 mg/kg/day dose groups (pooled data). The investigators did not indicate whether the comparisons of organ weight were limited to animals sacrificed on or before the end of the treatment period or included animals necropsied at the end of the recovery period as well. Further, without body weights or absolute organ weights, these data are difficult to assess.

Treated monkeys that died or were sacrificed at the end of the treatment period exhibited compound-related pathologic changes in the lymphoid system, kidney, adrenal and thyroid glands, liver, and intestine. Lymphoreticular proliferative lesions in lymph nodes, spleen, and bone marrow and lymphoid depletion were more severe in animals dosed with 15 mg/kg/day or greater (pooled data), but occurred in one animal at 5 mg/kg/day. Animals at 10 mg/kg/day or greater dose levels

exhibited adrenal cortex hyperplasia and hemorrhage. Minor hepatocyte vacuolization occurred in one animal in the pooled 15-30 mg/kg/day groups. Other lesions, observed mainly at doses of 10 mg/kg/day or higher, included vacuolization and pigmentation of renal tubular epithelium; follicular cell hyperplasia and degeneration of the thyroid; and vacuolization and degeneration of gastric and intestinal epithelium with cell cycle alterations. None of the monkeys exhibited ophthalmic lesions. A few recovery group animals at all dose levels exhibited lymphoid, renal, adrenal, and liver pathologic changes. Based on clinical observations of anorexia, the LOAEL is 2.5 mg/kg/day, the lowest dose tested. A NOAEL could not be determined.

(4) Comparison between PCPMS, PCPMSO, and $PCPMSO_2$

The 28-day range finding studies in rats (feeding and gavage studies) and mice (feeding study) showed increased mortality and depressed motor activity in response to all three analogs (Thake *et al.*, 1979). Data were inadequate to compare body weight gain and food consumption. In rats fed PCPMS at 9,000 ppm (corresponding to 900 mg/kg/day; highest dose), deaths were not attributed directly to the compound, but rats fed PCPMSO at 5,200 ppm (corresponding to 520 mg/kg/day; highest dose) exhibited 80% mortality in males and 60% mortality in females. No mortality occurred in rats fed $PCPMSO_2$ (highest dose given was 2,250 ppm [corresponding to 250 mg/kg/day]).

Rats appeared more sensitive to all three compounds when administered by gavage rather than by feeding (Thake *et al.*, 1979). The $PCPMSO_2$ analog produced 60% mortality in males and females at the 50 mg/kg/day dose (the lowest dose at which deaths occurred), indicating that the rats were less resistent to $PCPMSO_2$ than to PCPMS or PCPMSO. Mortality from $PCPMSO_2$ increased to 100% at higher doses. Mortality from PCPMS was 100% in females at 330 mg/kg/day (highest female dose) and in males at 220 mg/kg/day or greater. The PCPMSO gavaged rats exhibited 100% mortality at 400 mg/kg/day (highest dose tested) in both sexes. Decreased motor activity was observed at 50 mg/kg/day or greater for all three compounds.

In the mouse feeding study, 11% of the mice died taking PCPMS at 675 mg/kg/day (highest dose) and 22% died taking PCPMSO at 780 mg/kg/day (highest dose). Mice exhibited depression prior to death. No deaths were reported in $PCPMSO_2$ mice (highest dose, 675 mg/kg/day).

In the 14-day gavage study, monkeys exhibited compound-related effects at the lowest doses tested (5 mg/kg/day for PCPMS and PCPMSO, and 2.5 mg/kg/day for $PCPMSO_2$). The lowest dose at which deaths occurred during the treatment period was 20 mg/kg/day for PCPMS and $PCPMSO_2$. No deaths occurred in monkeys treated with PCPMSO. However, animals at 20 mg PCPMSO/kg/day (highest dose tested) were depressed, one severely. Monkeys treated with PCPMS or $PCPMSO_2$ at all dose levels exhibited anorexia. Weakness and depression also occurred at all PCPMS dose levels. The PCPMSO treated monkeys did not manifest anorexia and depression below 10 mg/kg/day. Blood urea nitrogen showed a significant increase over pretreatment levels in PCPMSO treated males and females combined at 10 mg/kg/day or greater and in PCPMS and $PCPMSO_2$ animals at 20 mg/kg/day or greater. Alkaline phosphatase was significantly depressed at 10 mg/kg/day or greater in PCPMS and PCPMSO monkeys. No effect was observed in $PCPMSO_2$ rats for this parameter. Glucose levels were significantly depressed in PCPMS and $PCPMSO_2$ treated monkeys at 20 mg/kg/day but not in PCPMSO monkeys. The PCPMSO analog produced the only significant hematological change, a depressed reticulocyte count at 10 mg/kg/day or greater.

Although the organ weight data were difficult to assess in the monkeys, PCPMS and PCPMSO were associated with a significant increase in relative liver and kidney weights over controls, and $PCPMSO_2$ with increased adrenal weights. The PCPMS analog also significantly increased adrenal weights but only at higher doses than for $PCPMSO_2$. Pathologic changes were observed in the livers of PCPMSO monkeys at all doses and in PCPMS monkeys at 10 mg/kg/day or greater. Only minor liver pathology occurred in $PCPMSO_2$ animals at 15-30 mg/kg/day (pooled data). Significant pathologic lesions also occurred in the lymphoid system in monkeys treated with all three analogs. Lymphoid lesions were most prominent at the higher doses but did occur in PCPMSO and $PCPMSO_2$ treated rats at 5 mg/kg/day. The LOAEL for PCPMS is 5 mg/kg/day based on the incidence of anorexia, depression, and weakness at the lowest dose. The LOAEL for PCPMSO is 5 mg/kg/day based on liver and lymphoid system lesions at the lowest dose. The LOAEL for $PCPMSO_2$ is 2.5 mg/kg/day based on the incidence of anorexia at the lowest dose. A NOAEL could not be determined for any of the compounds.

2. Longer-term Exposure

(1) PCPMS

Thake *et al.* (1979) studied the effects of PCPMS on Fischer 344 rats (16/sex/dose plus 24 controls/sex) fed the compound in the diet for 13 weeks. Rats were fed diets containing 0, 750, 1,500, or 3,000 ppm PCPMS, which based on reported body weight and food consumption data correspond to calculated doses of 0, 60, 113, and 223 mg/kg/day, respectively, for males and 0, 57, 111, or 211 mg/kg/day, respectively, for females. Interim sacrifices at week 4 and 8 and after a 14-day recovery group were conducted at all dose levels. The number of rats sacrificed at each interim period was not specified. Clinical observations were not reported. Body weight, food consumption, and hematology and clinical chemistry parameters were evaluated in rats sacrificed at 4, 8, and 13 weeks. All tissues from high-dose and control animals sacrificed at 4 and 13 weeks were examined histopathologically. If lesions were present in these animals, the tissues that contained the lesions were examined at succeedingly lower doses until a level was reached where the lesions were not apparent.

All rats survived the study period. Body weights and body weight gains of all treated males and females were significantly ($p < 0.05$) depressed throughout the dosing period when compared with concurrent controls, and the body weights of these animals remained depressed following the 14 days of recovery even though there was increased growth during this time, especially in animals at the highest dose. Food consumption was significantly depressed in animals at 3,000 ppm and was depressed in 1,500 ppm dosed animals at weeks 4 and 8. Total food consumption was significantly less for males and females in the mid- and high-dose groups. Depressed food and water consumption in the initial stages of treatment was attributed to poor palatability, especially at the highest dose, as well as to toxicity. Also at the highest dose, animals exhibited ocular and nasal discharges, similar to those observed following acute exposure (see paragraph V.B.1.a), and inactivity was common.

Hemoglobin, hematocrit, and erythrocyte counts for male and female rats at 13 weeks were significantly ($p < 0.05$) depressed compared with controls at all dose levels, and among females at the highest dose these parameters remained depressed following the recovery period. Because these changes were beyond the normal range for this species, they were considered biologically important.

Small but statistically significant changes in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were not considered biologically significant. Significant differences in the clinical chemistry of treated animals compared with controls were observed, but most of the differences were small and not considered biologically important (Thake *et al.*, 1979). Serum potassium and calcium levels in both sexes at all treatment levels were significantly elevated, and potassium and alkaline phosphatase levels were significantly depressed at all dose levels in males and at the mid- and high-dose levels in females. Males at all treatment levels and females at the high dose exhibited significantly depressed SGOT values. Clinical chemistry parameters for recovery group rats were not compared to rats sacrificed at 13 weeks.

In female rats at all dose levels, significant decreases between treated animals and controls occurred in the absolute weights of uterus, spleen, pituitary, and heart, and significant increases occurred in the kidney and liver weights. Also in females, brain weights at the mid- and high-dose levels were significantly decreased and adrenal weights were significantly decreased at the 3,000 ppm (high) dose. Males in all dose groups exhibited a significant decrease in brain and seminal vesicle weights and an increase in adrenal and liver weights. Also in males, heart and testicle weights were decreased significantly at the high dose; at the mid- and high-dose, spleen weight was decreased. Lower heart, pituitary, thyroid, brain, spleen, testicle, and ovary weights in treated rats were approximately proportional to decreases in body weight.

The principal pathological changes included hepatic megalocytosis of centrilobular hepatocytes with syncytial cell formation, multifocal coagulative hepatic necrosis, and hepatic vacuolar cytoplasmic change in males and females. The incidence of these findings for both sexes is presented in Tables V-2 and V-3, respectively. The incidence of hepatic megalocytosis, the most prevalent finding, occurred in 100% of the animals examined at each dose level. The incidence of hepatic lesions in high-dose male and female rats following the 14-day recovery period is presented in Table V-4. Generally, the incidence of hepatic lesions decreased following recovery but remained prevalent in male rats. Based on depression of body weights, hematologic and serum chemistry changes, increased liver weights, and hepatic pathology, the LOAEL is 750 ppm (calculated to be 60 mg/kg/day in males and 57 mg/kg/day in females). The NOAEL cannot be determined.

Table V-2. Incidence of Compound-Related Hepatic Lesions in Male Rats Fed *p*-Chlorophenyl Methyl Sulfide, -Sulfoxide, -Sulfone (PCPMS, PCPMSO, and $PCPMSO_2$)

Chemical	Dose (ppm)	Number Animals Examined	Findings		
			Necrosis	Megalocytosis	Vacuolar Cyto-plasmic Change
PCPMS	3,000	10	0	10	0
	1,500	10	0	10	0
	750	10	2	10	1
PCPMSO	3,000	10	3	7	0
	1,500	10	1	10	0
	750	10	0	10	0
$PCPMSO_2$	3,000	10	0	9	0
	1,500	10	0	10	1
	750	10	0	9	0
Control	0	24	0	0	0

SOURCE: Adapted from Thake *et al.* (1979)

Table V-3. Incidence of Compound-Related Hepatic Lesions in Female Rats Fed *p*-Chlorophenyl Methyl Sulfide, -Sulfoxide, -Sulfone (PCPMS, PCPMSO, and $PCPMSO_2$)

Chemical	Dose (ppm)	Number Animals Examined	Findings			
			Necrosis	Megalocytosis	Vacuolar Cyto-plasmic Change	Sinusoidal Ectasia
PCPMS	3,000	10	1	9	0	0
	1,500	10	0	10	5	0
	750	10	0	10	5	0
PCPMSO	3,000	10	0	9	2	0
	1,500	10	0	10	8	0
	750	10	0	10	0	0
$PCPMSO_2$	3,000	10	0	10	0	0
	1,500	10	1	10	5	0
	750	10	0	10	10	1
Control	0	24	0	0	0	0

SOURCE: Adapted from Thake *et al.* (1979)

Table V-4. Incidence of Hepatic Lesions in Rats Fed 3,000 ppm *p*-Chlorophenyl Methyl Sulfide, -Sulfoxide, -Sulfone (PCPMS, PCPMSO, and $PCPMSO_2$) Following a 14-Day Recovery Period

Hepatic Lesion	PCPMS		PCPMSO		$PCPMSO_2$	
	Males (3)*	Females (3)	Males (5)	Females (3)	Males (3)	Females (3)
Necrosis	1	0	0	0	0	0
Megalocytosis	3	0	3	0	2	0
Vacuolar Cyto-plasmic Change	0	0	2	1	0	1

*Number of animals examined

SOURCE: Adapted from Thake *et al.* (1979)

Thake *et al.* (1979) studied the effects of PCPMS on $B_6C_3F_1$ mice (16/sex/dose plus 33 male and 34 female controls) fed the compound in the diet for 13 weeks. Mice were fed diets containing 0, 750, 1,500, 3,000, or 6,000 ppm PCPMS, which based on reported body weight and food consumption data correspond to calculated doses of 0, 108, 182, 426, and 840 mg/kg/day, respectively, for males and 0, 109, 180, 259, and 517 mg/kg/day, respectively, for females. Body weight and food consumption data were not reported for the 6,000 ppm PCPMS group, which died early in the study. Interim sacrifices at week 4 and 8 and after a 14-day recovery group were conducted at all dose levels. The exact number of mice sacrificed at each interim period was not specified. Body and absolute organ weights and food consumption were evaluated. Clinical observations and hematology and clinical chemistry parameters were not measured. All tissues from high dose and control animals sacrificed at 4 and 13 weeks were examined histopathologically. If lesions were present in these animals, the tissues that contained the lesions were examined at succeedingly lower doses until a level was reached where the lesions were not apparent.

All mice dosed with 6,000 ppm PCPMS died within the first two weeks. Twelve females and five males at the 3,000 ppm dose died during the first week of treatment (Table V-5). One male and one female control mouse died as a result of wounds received during group housing or handling. Weekly body weights were significantly depressed compared with controls throughout the study in male mice at all treatment levels. Weekly body weights and total body weight gains for female mice were statistically equivalent to control mice. Food consumption, though highly variable, was generally depressed in treated mice compared with controls. Both sexes at the 3,000 ppm dose exhibited a significant increase in absolute liver weights compared to controls. Absolute kidney weights in all treated males were significantly less than those of controls. Males also exhibited significantly decreased brain weights at the 1,500 and 3,000 ppm dose levels and decreased seminal vesicle weight at the 3,000 ppm dose. Dose-related hepatic lesions, similar to those described in the rat 13-week study (Thake *et al.*, 1979), were observed in both sexes but more frequently in males (Table V-6). Pulmonary lesions, characterized by bronchial and bronchiolar epithelial degeneration, were observed in females at the 3,000 ppm dose. Based on hepatic lesions at the low dose, the LOAEL is 108 mg/kg/day for males and 109 mg/kg/day for females. A NOAEL could not be determined.

Table V-5. Cumulative Mortality at Selected Intervals for Mice Fed *p*-Chlorophenyl Methyl Sulfide, -Sulfoxide, -Sulfone (PCPMS, PCPMSO, and $PCPMSO_2$) for 13 weeks[a]

Chemical/ Dose (ppm)	Week 1		Week 2		Week 7		Week 13	
	Males	Females	Males	Females	Males	Females	Males	Females
PCPMS								
6,000	—[b]	—	—	—	—	—	—	—
3,000	5	12	5	12	5	12	5	12
1,500	0	0	0	0	0	0	0	0
750	0	0	0	0	0	0	0	0
PCPMSO								
5,000	16	16	16	16	16	16	16	16
3,000	1	4	1	7	3[c]	7	3	7
1,500	0	0	0	0	3[c]	2[c]	3	2
750	0	0	0	0	0	0	0	0
$PCPMSO_2$								
6,000	12	10	16	15	16	15	16	15
3,000	0	0	0	0	0	0	0	0
1,500	0	0	0	0	0	0	0	0
750	0	0	0	0	0	0	0	0
Control	0	0	0	0	1[c]	1	1	1

[a]Based on 33 male and 34 female controls and 16 mice/sex/compound
[b]All animals died before week 2; specific mortality data were not reported
[c]Deaths of animals attributed to trauma from fighting, which occurred during weeks 4 and 5 from a 24-hour period of multiple housing (with the exception of one male dosed with 3,000 ppm $PCPMSO_2$ that died during week 2)

SOURCE: Adapted from Thake *et al.* (1979)

Table V-6. Incidence of Hepatic and Pulmonary Lesions in Mice Fed *p*-Chlorophenyl Methyl Sulfide, -Sulfoxide, -Sulfone (PCPMS, PCPMSO, and $PCPMSO_2$) for 13 weeks

	Organ Lesions				
	Liver			Lung	
Chemical/ Dose (ppm)/ Sex	**Necrosis**	**Megalocytosis**	**Vascular Cytoplasmic change**	**Bronchial and Bronchiolar Epithelial Degeneration**	**Bronchiolar Papillary Hyperplasia**
PCPMS					
3,000 M (10)[a]	3	6	0	0	0
F (10)	1	4	1	3	0
1,500 M (10)	0	3	0	0	0
F (9)	0	0	0	0	0
750 M (9)	0	1	0	0	0
F (11)	0	0	0	0	0
PCPMSO					
3,000 M (10)	7	8	0	2	1
F (10)	3	7	0	0	0
1,500 M (10)	0	3	0	0	0
F (10)	0	0	0	0	0
750 M (10)	0	1	0	0	0
F (10)	0	1	0	0	0
$PCPMSO_2$					
3,000 M (10)	2	4	3	10	0
F (10)	0	4	2	10	0
1,500 M (10)	0	4	0	0	0
F (9)	0	0	0	0	0
750 M (10)	0	1	0	0	0
F (10)	0	1	0	0	0
Control M (24)	0	0	3	0	0
F (22)	0	0	0	0	0

[a]Numbers in parentheses indicate the number of animals examined

SOURCE: Adapted from Thake *et al.* (1979)

(2) PCPMSO

Thake *et al.* (1979) studied the effects of PCPMSO on Fischer 344 rats (16/sex/dose plus 24 controls/sex) fed the compound in the diet for 13 weeks. Rats were fed diets containing 0, 750, 1,500, or 3,000 ppm PCPMSO, which based on reported body weight and food consumption data correspond to a calculated doses of 0, 61, 123, and 246 mg/kg/day, respectively, for males and 0, 67, 127, and 234 mg/kg/day, respectively, for females. For further experimental details, see PCPMS (paragraph V.B.2.(1) of this review).

Deaths, considered compound related by the investigators, occurred at the 3,000 ppm level in six male rats, which like most male rats at this level were severely emaciated throughout the study. Body weights and body weight gains of all treated males and females were significantly ($p < 0.05$) depressed throughout the dosing period when compared with concurrent controls, and the body weights of these animals remained depressed following the 14 days of recovery even though there was increased growth during this time, especially in animals at the highest dose. Food consumption decreased in a dose-related manner. Significant decreases in food consumption occurred during week 8 in males and females at the 3,000 ppm level. Depressed food and water consumption in the initial stages of treatment was attributed to poor palatability, especially at the highest dose, as well as to toxicity. At the highest dose, animals exhibited ocular and nasal discharges, similar to those observed following acute exposure (see V.B.1.a), and inactivity was common.

Hematocrit and erythrocyte count in males and hemoglobin and hematocrit in female rats at 13 weeks were significantly depressed at all dose levels compared with controls, and among females at the highest dose these parameters remained depressed following the recovery period. The investigators considered these changes to be beyond the normal range for this species, and thus biologically important (Thake *et al.*, 1979). Small but statistically significant changes in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were not considered biologically significant. Significant differences in the clinical chemistry of treated animals compared with controls were observed, but most of the differences were small and probably not biologically important. SGOT and alkaline phosphatase were significantly depressed, and potassium and calcium levels significantly elevated in males at all dose levels. Sodium was significantly depressed in males at the high dose. In females, alkaline phosphatase and sodium were significantly depressed in all dose groups. Other significant changes in females included a depressed

SGOT and elevated calcium levels at the mid- and high-doses, and depressed SGPT at the high dose. Clinical chemistry parameters for recovery group rats were not compared with rats sacrificed at 13-weeks.

In all dose groups of both sexes, significant decreases between treated animals and controls occurred in the absolute weights of the pituitary, and significant increases occurred in the liver. In addition, males exhibited a significant decrease in the heart and adrenal gland weights at all dose levels and in brain, testicles, and seminal vesicles at mid- or high-doses. Significant decreases in females occurred in spleen, ovaries, and uterus at all dose levels and in brain and heart at the high dose. Kidney weights significantly increased in females at all doses. Decrements in heart, pituitary, thyroid, brain, spleen, testicle, and ovary weights in treated rats were approximately proportional to decreases in body weight.

The principal pathological changes included hepatic megalocytosis of centrilobular hepatocytes with syncytial cell formation, multifocal coagulative hepatic necrosis, and hepatic vacuolar cytoplasmic change. The incidence of these findings for male and female rats is presented in Tables V-2 and V-3, respectively. The incidence of hepatic megalocytosis, the most prevalent finding, occurred in 70 to 100% of the animals examined at each dose level. The incidence of hepatic lesions in high-dose male and female rats following the 14-day recovery period is presented in Table V-4. Generally, the incidence of hepatic lesions decreased following recovery but remained prevalent in male rats. Based on depression of body weights, hematologic and serum chemistry changes, increased liver weights, and hepatic pathology, the LOAEL is 750 ppm (calculated to be 61 mg/kg/day in males and 67 mg/kg/day in females). The NOAEL could not be determined.

Thake *et al.* (1979) studied the effects of PCPMSO on $B_6C_3F_1$ mice (16/sex/dose plus 33 male and 34 female controls) fed the compound in the diet for 13 weeks. Mice were fed diets containing 0, 750, 1,500, 3,000, or 5,000 ppm PCPMSO, which based on reported body weight and food consumption data correspond to calculated doses of 0, 112, 224, 377, and 628 mg/kg/day, respectively, for males and 0, 70, 235, 318, and 530 mg/kg/day, respectively, for females. Body weight and food consumption data were not reported for the 5,000 ppm PCPMSO group, though the investigators noted that marked decreases in these measures occurred prior to death, which occurred in all animals at this dose during the first week of treatment. See PCPMS (paragraph V.B.2.(1) of this review) for experimental details.

Seven female mice and one male at the 3,000 ppm dose died by the end of week 2 (Table V-5). Seven other deaths occurred at the 1,500 or 3,000 ppm dose levels, but these deaths were attributed to trauma from fighting when multiple housed for 24 hours during week 4, rather than treatment. Weekly body weights were significantly depressed compared with controls throughout the study in male mice at the 1,500 and 3,000 ppm dose levels. At week 13, females also showed a significant decrease in body weight compared to controls at the 1,500 and 3,000 ppm levels. Food consumption, though highly variable, was significantly depressed at week 13 in males at the 1,500 and 3,000 ppm dose levels. Both sexes at the 3,000 ppm dose exhibited a significant increase in absolute liver weights compared to controls, and both sexes had decreased spleen weights at the 1,500 and 3,000 ppm level at week 13. Ovaries in females and adrenals in males also were significantly decreased at the 1,500 and 3,000 ppm dose levels. Dose-related hepatic lesions, similar to those described in the rat 13-week study (Thake *et al.*, 1979), were observed in both sexes (Table V-6). Two males at the 3,000 ppm dose exhibited bronchial and bronchiolar epithelial degeneration. Based on hepatic lesions at the low dose, the LOAEL is 112 mg/kg/day for males and 70 mg/kg/day for females. The NOAEL could not be determined.

(3) PCPMSO$_2$

Thake *et al.* (1979) studied the effects of PCPMSO$_2$ on Fischer 344 rats (16/sex/dose plus 24 controls/sex) fed the compound in the diet for 13 weeks. Rats were fed diets containing 0, 750, 1,500, or 3,000 ppm PCPMSO$_2$, which based on reported body weight and food consumption data correspond to a calculated doses of 0, 57, 115, and 240 mg/kg/day, respectively, for males and 0, 54, 122, or 220 mg/kg/day, respectively, for females. See experimental details for PCPMS (paragraph V.B.2.(1) of this review).

All rats survived the study period with the exception of one male that died spontaneously during week 4 at the 750 ppm dose level. The investigators did not consider this death to be compound related. Body weights and body weight gains of all treated males and females (except in 750 ppm females at week 4) were significantly ($p < 0.05$) depressed throughout the dosing period when compared with concurrent controls. The body weights of these animals remained depressed following the 14 days of recovery even though there was increased growth during this time, especially in animals at the highest dose. Total food consumption for the 13 week treatment period was decreased in a dose-related manner for both males and females. Statistically significant dose-

related decreases in food consumption occurred in week 4 for both males and females at the mid- and high-dose levels. However, by week 8 and 13, food consumption in some groups exceeded that of the controls. Depressed food and water consumption in the initial stages of treatment was attributed to poor palatability, especially at the highest dose, as well as to toxicity. Also at the highest dose, animals exhibited ocular and nasal discharges, similar to those observed following acute exposure (see paragraph V.B.1.a), and inactivity was common.

Hematocrit and erythrocyte count in both sexes and hemoglobin in females at 13 weeks were significantly depressed ($p < 0.05$) at all dose levels compared with controls, and among females at the highest dose these parameters remained depressed following the recovery period. Because these changes were beyond the normal range for this species, they were considered biologically important (Thake *et al.*, 1979). Small but statistically significant changes in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were not considered biologically significant. Significant differences in the clinical chemistry of treated animals compared with controls were observed, but the investigators considered most of these differences small and not biologically important. Blood urea nitrogen in males and potassium in both sexes were significantly elevated in all dose groups at 13 weeks. Sodium in females and alkaline phosphatase in both sexes was significantly depressed at all dose levels. Clinical chemistry parameters for recovery group rats were not compared to rats dosed for 13 weeks.

In all dose groups of both sexes, the absolute weights of liver and kidney increased significantly over controls by week 13, and spleen weights decreased. In males, brain weights decreased and adrenal weights increased significantly in all dose groups. Also, heart weights decreased significantly at the high dose. In females at the mid- and high-dose levels, heart and pituitary weights generally decreased. Lower heart, pituitary, thyroid, brain, spleen, testicle, and ovary weights in treated rats were approximately proportional to decreases in body weight.

The principal pathological changes included hepatic megalocytosis of centrilobular hepatocytes with syncytial cell formation, multifocal coagulative hepatic necrosis, and hepatic vacuolar cytoplasmic change. The incidence of these findings for males and females is presented in Tables V-2 and V-3, respectively. The incidence of megalocytosis, the most prevalent finding, occurred in 90 to 100% of the animals examined at each dose level. The incidence of hepatic lesions in high-dose male and female rats following the 14-day recovery period is presented in Table V-4. Generally, the

incidence of hepatic lesions decreased following recovery but remained prevalent in male rats. Based on depression of body weights, hematologic and serum chemistry changes, increased liver weights, and hepatic pathology, the LOAEL is 750 ppm (calculated to be 57 mg/kg/day in males and 54 mg/kg/day in females). The NOAEL could not be determined.

Thake *et al.* (1979) studied the effects of $PCPMSO_2$ on $B_6C_3F_1$ mice (16/sex/dose plus 33 male and 34 female controls) fed the compound in the diet for 13 weeks. Mice were fed diets containing 0, 750, 1,500, 3,000, or 6,000 ppm $PCPMSO_2$, which based on reported body weight and food consumption data correspond to calculated doses of 0, 106, 183, 445, and 890 mg/kg/day, respectively, for males and 0, 86, 204, 340, and 680 mg/kg/day, respectively, for females. Body weight and food consumption data were not reported for the 6,000 ppm $PCPMSO_2$ group, though the investigators noted that marked decreases in these measures occurred prior to death, which occurred in all but one animal at this dose within the first 2 weeks of treatment. See experimental details for PCPMS (paragraph V.B.2.(1) of this review).

No deaths, other than those that occurred in the 6,000 ppm dose groups, were observed (Table V-5). Weekly body weights were significantly depressed compared with controls throughout the study in male and female mice at all treatment levels. Dose-related decreases in food consumption occurred at all dose levels in both sexes. Absolute kidney weights in males showed a significant decrease at the 3,000 ppm dose and significant increases at the lower doses. Significant decreases in males were observed in adrenal, brain, and testicle weights at all treatment levels and in seminal vesicles at the 1,500 and 3,000 ppm dose levels. Females at all dose levels exhibited a significant decrease in spleen weight and a significant increase in heart weight. Brain weight was also decreased at the highest dose in females. Dose-related hepatic lesions, similar to those described in the rat 13-week study (Thake *et al.*, 1979), were observed in both sexes (Table V-6). All animals examined (10/sex) at the 3,000 ppm dose exhibited bronchial and bronchiolar epithelial degeneration. Based on hepatic lesions at the low dose, the LOAEL is 750 ppm (106 mg/kg/day for males and 86 mg/kg/day for females). The NOAEL could not be determined.

(4) Comparison between PCPMS, PCPMSO, and $PCPMSO_2$

In the Thake *et al.* (1979) 13-week rat study, PCPMS and $PCPMSO_2$ caused no compound-related deaths at dose levels up to 3,000 ppm (the highest dose tested). This corresponds to 223 mg/

kg/day in males and 211 mg/kg/day in females for PCPMS and 240 and 220 mg/kg/day in males and females, respectively for $PCPMSO_2$. However, a 38% mortality occurred among male rats fed PCPMSO at the 3,000 ppm level (246 mg/kg/day). All three compounds caused significant reductions in body weight, body weight gain, and food consumption compared with controls. The only toxicological symptoms reported were ocular and nasal discharges in rats treated at the high dose with each compound.

All compounds at all dose levels significantly depressed hematocrit and erythrocyte counts compared with controls. The PCPMS treated rats also exhibited reduced hemoglobin at all dose levels. All three compounds significantly depressed serum alkaline phosphatase levels in both sexes at all dose levels except females at the low PCPMS dose. Also, all three compounds significantly increased serum potassium and calcium levels at all dose levels. Only PCPMS and PCPMSO significantly reduced SGOT levels at all doses in males and at the highest dose levels in females. The $PCPMSO_2$ analog significantly depressed BUN levels in both sexes at all doses, an effect not observed with the other compounds. Thus, in general, all three compounds had similar effects on the hematology and clinical chemistry parameters tested. The most notable exceptions were the absence of SGOT effects in $PCPMSO_2$ treated rats and the absence of elevated BUN levels in PCPMS and PCPMSO treated rats.

Absolute liver weights in rats treated with all three compounds were significantly elevated compared with controls in both sexes at all dose levels. In addition, significantly reduced spleen weights were found in rats treated at some or all dose levels with all three compounds. Kidney weights were increased and pituitary weights were decreased in PCPMSO and $PCPMSO_2$ rats, but not in PCPMS rats. The most prevalent pathologic lesions were hepatic megalocytosis in 100% of the rats treated with PCPMS, 70-100% of rats treated with PCPMSO, and 90-100% treated with $PCPMSO_2$. Based on increased liver weights, hepatic pathology, hematologic and serum chemistry changes, and depressed body weight, the lowest dose tested was the LOAEL for each compound. A NOAEL could not be determined.

The mouse 13-week feeding study revealed mortality, significant reductions in body weight and food consumption, changes in absolute organ weights, and hepatic and pulmonary pathology for all three compounds (Thake *et al.*, 1979). At the 6,000 ppm PCPMS or $PCPMSO_2$ dose and the 5,000 ppm PCPMSO dose, all but one $PCPMSO_2$ animal died before the end of week 2 of the study. In

addition, mortality was 53% in PCPMS treated mice at 3,000 ppm (182 mg/kg/day and 180 mg/kg/day in males and females, respectively) and 25% in PCPMSO treated mice at 3,000 ppm (224 mg/kg/day and 235 mg/kg/day in males and females, respectively. Except for the deaths at the 6,000 ppm dose, $PCPMSO_2$ produced no other compound-related deaths. All three analogs caused significant reductions in body weight, body weight gain, and food consumption compared with controls. The PCPMSO and $PCPMSO_2$ analogs significantly reduced spleen weights compared with controls, and PCPMS and $PCPMSO_2$ significantly changed kidney weights. Both PCPMS and PCPMSO increased liver weights at the 3,000 ppm dose in both sexes. All three compounds were associated with lesions, mainly hepatic megalocytosis at all dose levels. Based on the hepatic lesions, the lowest dose tested was the LOAEL for each compound. A NOAEL could not be determined for any of the compounds.

3. Reproductive Effects

(1) PCPMS

No studies on the reproductive effects of PCPMS were found in the literature.

(2) PCPMSO

No studies on the reproductive effects of PCPMSO were found in the literature.

(3) $PCPMSO_2$

No studies on the reproductive effects of $PCPMSO_2$ were found in the literature.

(4) Comparison between PCPMS, PCPMSO, and $PCPMSO_2$

No studies on the reproductive effects of PCPMS, PCPMSO, or $PCPMSO_2$ were found in the literature.

4. Developmental Toxicity

(1) PCPMS

No studies on the developmental effects of PCPMS were found in the literature.

(2) PCPMSO

No studies on the developmental effects of PCPMSO were found in the literature.

(3) $PCPMSO_2$

No studies on the developmental effects of $PCPMSO_2$ were found in the literature.

(4) Comparison between PCPMS, PCPMSO, and $PCPMSO_2$

No studies on the developmental effects of PCPMS, PCPMSO, or $PCPMSO_2$ were found in the literature.

5. Carcinogenicity

(1) PCPMS

No studies on the carcinogenic effects of PCPMS were found in the literature.

(2) PCPMSO

No studies on the carcinogenic effects of PCPMSO were found in the literature.

(3) $PCPMSO_2$

No studies on the carcinogenic effects of $PCPMSO_2$ were found in the literature.

(4) Comparison between PCPMS, PCPMSO, and $PCPMSO_2$

No studies on the carcinogenic effects of PCPMS, PCPMSO, or $PCPMSO_2$ were found in the literature.

6. Genotoxicity

(1) PCPMS

Samples of >99% pure PCPMS were evaluated for the potential to induce gene mutations in *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, and TA100 (Thake *et al.*, 1979). At least two independent experiments, which included a nonactivated and an S9-activated phase with either Aroclor 1254- or phenobarbital-induced rat liver microsomes, were performed. Summarized results are presented in Table VI-7.

Five nonactivated and five Aroclor 1254 S9-activated doses ranging from 0.01 to 100 µL/plate were not mutagenic in any test strain. Cytotoxicity was, however, apparent for all strains at the two highest doses (10 and 100 µL/plate +/-S9).

The independent trial was performed with a lower dose range (0.01 to 0.3 µL/plate) in both the absence and presence of phenobarbital-induced S9. The study authors stated that the lower dose range was necessary because PCPMS was found to be unstable in the solvent, dimethylsulfoxide (DMSO). The sample assayed in the repeat trial was used within 3 hours of preparation, and the sample evaluated in the initial trial was prepared in DMSO and stored for "longer periods of time." The test material was not mutagenic in the repeat assay, and cytotoxicity was achieved at 0.3 µL/plate +/-S9. However, the overall study with PCPMS should be considered incomplete. Conditions were not optimum for the detection of potential mutagenesis induced by a "biologically active" form of the test material in the presence of the Aroclor S9 fraction.

Table V-7. Ames Bacterial Mutagenicity Assays of *p*-Chlorophenyl Methyl Sulfide, -Sulfoxide, -Sulfone (PCPMS, PCPMSO, and $PCPMSO_2$)

Strain	Activation	Dose/ Concentration	Toxic Effect	Independent Evaluation[a]
		PCPMS		
Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100	± S9 Aroclor 1254 induction	100, 10, 1, 0.1, 0.01, 0.0 µL/plate	Cytotoxic ± S9 at doses ≥10 µL/plate all strains; no mutagenicity	Invalid; unstable form of test material assayed
	± S9 Phenobarbital induction	0.3, 0.1, 0.05, 0.03, 0.01, 0.0 µL/plate	Cytotoxic ± S9 at 0.3 µL/plate all strains; no mutagenicity	Acceptable evidence of a negative response, but overall study is incomplete because it lacks acceptable Aroclor 1254 S9 activation assay
		PCPMSO		
Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100	± S9 Aroclor 1254 induction	500, 100, 10, 1, 0.1, 0.0 µL/plate	No cytotoxicity; no mutagenicity	Unacceptable; inadequate high dose
	± S9 Phenobarbital induction	1,000, 300, 100, 30, 10, 0.0 µL/plate	No cytotoxicity; no mutagenicity	Unacceptable; inadequate high dose
		$PCPMSO_2$		
Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100	± S9 Aroclor 1254 induction	500, 100, 10, 1, 0.1, 0.0 µg/plate	No cytotoxicity; no mutagenicity	Unacceptable; inadequate high dose
	± S9 Phenobarbital induction	1,000, 300, 100, 30, 10, 0.0 µg/plate	No cytotoxicity; no mutagenicity	Unacceptable; inadequate high dose

[a]Independent evaluation by the authors of this review document

SOURCE: Adapted from Thake *et al.* (1979)

(2) PCPMSO

Samples of >99% pure PCPMSO were evaluated for the potential to induce gene mutations in *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, and TA100 (Thake *et al.*, 1979). At least two independent experiments, which included a nonactivated and an S9-activated phase with either Aroclor 1254- or phenobarbital-induced rat liver microsomes, were performed. Summarized results are presented in Table VI-7.

Dose ranges evaluated were 0.1 to 500 µL/plate -/+ Aroclor S9 and 10 to 1,000 µL/plate -/+ phenobarbital S9. Under both nonactivated and S9-activated conditions, the test material was neither cytotoxic nor mutagenic in any test strain. The lack of a cytotoxic response at the highest assayed level renders the study invalid. Without some evidence that the test material was assayed to either a cytotoxic level, the limit of solubility, or the recommended high dose (5,000 µg PCPMSO/plate), the findings should not be considered acceptable evidence of a negative response in this test system.

(3) $PCPMSO_2$

Samples of >99% pure $PCPMSO_2$ were evaluated for the potential to induce gene mutations in *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, and TA100 (Thake *et al.*, 1979). At least two independent experiments, which included a nonactivated and an S9-activated phase with either Aroclor 1254- or phenobarbital-induced rat liver microsomes, were performed. Summarized results are presented in Table VI-7.

Five doses of $PCPMSO_2$ ranging from 0.1 to 500 µg/plate -/+ Aroclor 1254 S9 or from 10 to 1,000 µg/plate -/+ phenobarbital S9 failed to induce a cytotoxic or mutagenic response in any of the tester strains. For the reasons given above, these findings are considered inadequate evidence of a valid negative response in this test system.

(4) Comparison between PCPMS, PCPMSO, and $PCPMSO_2$

The overall findings of this study indicate that without S9 and with phenobarbital-induced S9 activation, PCPMS is not mutagenic in *S. typhimurium*. No conclusions can be drawn from the studies performed with PCPMSO or $PCPMSO_2$. With the exception of this bacterial gene mutation

assay, no other genetic toxicology studies with any of the three compounds were found in the available literature.

C. CARCINOGENIC POTENTIAL

Applying the criteria described in EPA's guidelines for assessment of Carcinogenic Risk (U.S. EPA, 1986), PCPMS, PCPMSO, and $PCPMSO_2$ are classified in Group D: not classifiable as to human carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE, AND STANDARDS

No information has been reported on the criteria and standards of *p*-chlorophenyl methyl sulfide (PCPMS), *p*-chlorophenyl methyl sulfoxide (PCPMSO), and *p*-chlorophenyl methyl sulfone ($PCPMSO_2$).

VII. ANALYTICAL METHODS

Gas chromatography (GC) with sulfur-specific flame photometric detection is the most sensitive method to detect and quantify the three sulfur compounds, *p*-chlorophenyl methyl sulfide (PCPMS), *p*-chlorophenyl methyl sulfoxide (PCPMSO), and *p*-chlorophenyl methyl sulfone ($PCPMSO_2$) (Miller *et al.*, 1976). Elution times were 14.1 minutes for PCPMS, 21.5 minutes for PCPMSO, and 27.1 minutes for $PCPMSO_2$. The extraction efficiencies were 90, 90, and 98%, respectively, for the three compounds. The detection limit was approximately 10 ppb.

Other analytical methods include gas chromatography/mass spectroscopy (GC/MS), and electron capture/GC (Miller *et al.*, 1976; Blair *et al.*, 1982). Detection methods include infrared and Raman spectroscopy, ultraviolet spectroscopy, and proton magnetic resonance (Miller *et al.*, 1976).

VIII. TREATMENT TECHNOLOGIES

No information was reported on the treatment technology of *p*-chlorophenyl methyl sulfide (PCPMS), *p*-chlorophenyl methyl sulfoxide (PCPMSO), and *p*-chlorophenyl methyl sulfone ($PCPMSO_2$).

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