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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Transmittal of Chlordane Standard

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Attached please find the Toxicology Chapter for the Registration Standard on Chlordane.

cc: Coberly
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Summary

Chlordane is one of the group of chlorinated cyclodiene hydrocarbons. Chlordane has been in use for approximately 40 years. Following its evaluation for continued use and registration in 1972 and subsequent food use cancellations in 1979, its major use has been in the treatment of structures for the control of subterranean termites.

Toxicology data on chlordane have been developed over a long period of time from the 1950's through the 1980's. This has resulted in a data base using chemicals from manufacturing processes which may have changed over a period of 30 to 40 years. Early chronic feeding studies in rats have shown dietary NOEL's as high as 5 ppm, while later studies using more contemporary test material have indicated much lower NOEL's. Most studies however, do not display a NOEL for liver effects. Recent testing has not established a NOEL for chlordane-effected liver changes and the absence of this NOEL is considered a data gap.

Carcinogenicity testing in older studies has been limited to mice with positive results. More recent and longer exposure studies conducted in rats have shown a minimal though significant increase in liver tumors.

Studies evaluating the acute toxicity of technical chlordane are generally inadequate to provide proper labeling for the chemical.

In most cases, the chronic studies carried out on chlordane have shown that the liver is a major target organ.

The Cancer Assessment Group (CAG) has determined that chlordane, through its activity in multiple strains of mice and additional effects reported in a recent rat study, is a B_2 carcinogen with a Q^* of 1.3.

Both teratology information and reproductive study information are quite limited on chlordane. The data which are available are inadequate as reported to satisfy registration requirements and are data gaps.

Mutagenicity studies are currently under review and results of these reviews will be submitted as an addendum to this chapter.

A two year dog study had shown only increases in body weight ratios. Additional histopathology did not support this effect as a toxic reaction. Even though the effect occurred at the lowest dose of 0.3 ppm in the diet, and was an effect, it was not considered to be a significant effect on which a toxicity LEL should be established. This is a data gap.

An acceptable daily intake/provisional acceptable daily intake (ADI/PADI) has been established for chlordane although food uses of chlordane are no longer registered. A 30-month chronic feeding study in rats provided an LEL at 1 ppm in the diet (0.05 mg/kg/day). Due to data gaps in other study areas, a thousandfold safety factor (SF) was used in establishing a PADI or reference dose (Rfd); e.g., 0.05 mg/kg/day x 1000 SF = PADI (0.00005 mg/kg/day).

Studies in exposure from termiticidal treatment of dwellings have not been completed and will not be addressed in this chapter. Therefore, cancer risk perceived from air exposure in the home will be evaluated when the studies are submitted and reviewed.

The use of chlordane over long periods of time has produced a number of health complaints and are addressed in the text.

Acute Toxicity

Summary

Toxicity data previously submitted to the Agency were on studies conducted in the early part of the 1950's. Those data were produced on the then current technical chlordane. However, the more recent tests have been carried out using a current product. The current test results will be represented where possible to more accurately reflect the current toxicity picture for chlordane.

81:1 - Acute Oral Toxicity

Technical chlordane was tested by Gaines (1969) in Sherman rats for its lethal dose 50 (LD_{50}) for that species. The methodology was the same as one reported earlier by Gaines (1960) also using a technical chlordane. Male rats in the earlier study exhibited an LD_{50} of 335 mg/kg and female rats showed an LD_{50} of 430 mg/kg. The study (MRID 05000974) was only supplementary since insufficient information on the methodology and results were presented.

A data gap for this area of toxicity testing exists for the technical and end-use formulation.

81:2 - Acute Dermal Toxicity

Data determining the dermal lethal dose 50 (LD_{50}) of technical chlordane was submitted to the Agency (MRID 05000974). The most recent studies on dermal toxicity indicate that the dermal LD_{50} value found for technical chlordane using an undiluted technical formulation on the backs of female rats was 530 mg/kg. However, when the chemical was administered in peanut oil, the LD_{50} value determined for the female rats was 690 mg/kg and for male rats was 840 mg/kg. These study results were inadequately reported as a summary in table form and are therefore considered as supplementary information. The values derived from chlordane technical as tested place the chemical in Toxicity Category II.

A recent study (TBS-20) was submitted on Chlordane 4 EC formulation using rabbits and the occluded skin exposure method. The dermal LD_{50} for the 4 EC formulation was reported as greater than 2 g/kg. The data are sufficient to place the 4 EC formulation into Toxicity Category III. The 4E formulation was tested as a limit-dose, which is sufficient for regulatory purposes for the 4E formulation.

The technical chlordane study is, however, insufficient for regulatory requirements and is considered a data gap.

81:3 - Acute Inhalation Toxicity

Several studies on the toxicity of chlordane and formulations by the inhalation route have been submitted to the Agency. A study using only male rats exposed to an analytical reference standard of technical chlordane for 4 hours (MRID 00097911) was evaluated and found that the LC_{50} was greater than 200 mg/L (Toxicity Category IV) based on the nominal exposure from spraying a corn oil suspension of test material. Though toxicity was seen in the study, no deaths occurred in the test subjects. The study is classified as supplementary because of the use of a questionably absorbable carrier and calculations only for nominal exposure, and is considered a data gap.

A study using an undetermined purity of a reference technical chlordane in corn oil suggested that toxicity of technical chlordane following a 4-hour exposure to five animals/sex was moderate. An LC_{50} of 746 mg/L for males and an LC_{50} value of greater than 800 mg/L for female rats was reported. Exposure levels in the study ranged from 12.5 mg/L to 800 mg/L in the highest dose (MRID 00066861). This study was considered to be invalid due to the variability of mortality effects at different dosage levels. This study does not satisfy registration requirements.

A chlordane inhalation study using rats in which a 4 EC formulation was tested for 4 hours and 11 minutes was submitted to the Agency (MRID 00103124; TBS0020). Analytically, the levels tested were 0, 0.171, 0.54, 0.58, 1.5, or 3.2 mg/L of chlordane in the test chamber. Ten animals of each sex were exposed to each dosage level. The livers of survivors above 0.171 mg/L exhibited mild to moderately severe fatty changes. Generally toxic effects were not observed in those animals exposed to 0.171 mg/L. The 4-hour LC_{50} for males was 0.914 mg/L and for females was 0.561 mg/L.

The data are sufficient to tentatively place the 4 EC formulation in Toxicity Category II.

These data are not sufficient to fulfill the registration requirements for acute inhalation toxicity of the technical chemical. In addition, the data provide indications that the solvents in the EC formulation enhance the toxicity of chlordane.

81:4 - Primary Eye Irritation

A study using a 72% technical chlordane was submitted to the Agency in which white rabbits were exposed to Chlordane 8 EC (TBS-0021). Washing the eyes prevented corneal opacity while animals without eye wash exhibited corneal opacity in two of five subjects on day 21. The data are sufficient for registration requirements for a formulation of 8 EC as a Toxicity Category I substance. A second study in rabbits using a lower concentration

of technical chlordane did not indicate corneal involvement (TBS 0020). These data are sufficient to delineate the formulation toxicity to the eyes to be in Category III. No further studies are required to support the registration of these formulations with respect to eye irritation properties. The viscosity of pure technical chlordane without a solvent does not preclude the requirement for primary eye irritation studies using a pure technical chlordane.

81:5 - Primary Dermal Irritation

No data have been reviewed for the dermal irritative capabilities of chlordane. This area of toxicity testing is a data gap for both the formulation and technical chlordane, even though the technical chlordane is not marketed to the public.

81:6 - Dermal Sensitization

A dermal sensitization study using white guinea pigs (MRID 00103884) was submitted to the Agency. The study utilized the occluded patch method of exposure for three times per week for a period of 3 weeks. After challenging the treated animals twice, readings of the irritative and sensitization effects did not support technical chlordane as a skin sensitizer. No further data are required for this area of testing.

81:7 - Acute Delayed Neurotoxicity

The chemical is dissimilar to known delayed neurotoxic agents (organophosphates). Although chlorinated hydrocarbon pesticides provide CNS effects following heavy exposure, neurotoxicity of the delayed type has not been reported in the large number of chemical plant intoxications encountered. This area of delayed neurotoxicity testing is not a data gap.

82:1 - 90-Day-Feeding - Rodent

A study was reviewed by the Agency (TBS-0022) in which small groups (6/sex/dose) of rats were fed either 2.5 or 25 ppm of a technical chlordane for up to 9 months. The technical chlordane contained from 60 to 75% chlordane with up to 40 percent related products. Effects noted at the 2.5 ppm dosage level were the usual liver effects noted as "CHIRL" (chlorinated hydrocarbon insecticide rodent liver). The effects of hypertrophy of centrolobular cells, peripheral migration of cytoplasmic granules and cytoplasmic bodies were noted only in males. An LEL of 2.5 ppm was established for the CHIRL effect.

A 90-day study on oxychlordane using rats was submitted to the Agency. Oxychlordane is the oxidative metabolite and one of the most prevalent storage metabolites in mammals following the ingestion of chlordane. Groups of 20 males and 20 females were fed 5, 25, or 50 ppm of oxychlordane in the diets. Results of the study indicate that: 1) oxychlordane is more acutely toxic

than the parent, chlordane, 2) unlike chlordane, oxychlordane produces adverse effects (spongiosis) in the white matter of spinal cord and brain of both sexes at dosage levels of 25 ppm and above, 3) only an LEL was determined for the study for histologic effects in the livers of male rats. A NOEL for the study could not be established at 5 ppm (TBS 0023). The Agency does not consider a data gap for oxychlordane to exist for this short-term exposure testing.

82:1 - 90-Feeding - Nonrodent

Nonrodent studies of 3 months' duration have not been submitted to the Agency. However, the need for subchronic studies in nonrodents is not considered to be required since longer term studies in dogs preclude their need.

82:2 - 21-Day Dermal Toxicity

No data were submitted for this area of toxicity testing. Since technical chlordane is not used in treating subterranean termites and sufficient information exists of certain chlordane formulations, the Toxicology Branch does not consider that the need exists for the 21-day dermal study using technical chlordane.

82:3 - 90-Day Dermal Toxicity

No data were submitted to the Agency in this area of toxicity testing. The Agency recognizes that chlordane may be absorbed dermally and toxicity may ensue from that exposure. However, target organs have been well-defined from other routes of exposure.

No further data are required for this area of toxicity.

82:4 - 90-Day Inhalation

A 90-day inhalation study using rats and monkeys was evaluated by the Agency (TBS-0024).

Analytical values for diameters of test particles were less than 5.5 micrometers in over 80 percent of the particles examined at exposures of 1 and 10 mg/m^3. A low dose of 0.1 mg/m^3 was also tested in the animals. Results for rats included liver lesions, increased serum calcium, cholesterol, glutamic dehyrogenase and liver cytochrome p450 levels. The systemic LEL was considered to be 1.0 mg/m^3 or 1000 micrograms/m^3. Cytochrome p450 level was increased in rats at the lowest dose level of 0.1 mg/m^3, but was not considered to be more than a reversible tissue reaction since the rat liver was not significantly increased at that dosage. The NOEL for liver lesions was 0.1 mg or 100 micrograms/m^3. The LEL for monkeys is based on increased liver to body weight ratios for females at 10 mg/m^3 whereas 1 mg/m^3 was a NOEL.

This study with two different species was submitted by the registrant to fulfill a Data Call-In (DCI) Notice of 1984. The DCI Notice required that testing of animals be carried out to determine a NOEL using the National Academy of Sciences (NAS) recommended permissible air levels of chlordane.*

An additional inhalation study of relatively short duration (1-2 weeks) using rats or guinea pigs is required to further delineate the toxicity of chlordane, the solvent, or the combination of chlordane and solvent with respect to irritative toxicity to the upper respiratory tract. This is needed because of the report of human cases purported to result from exposure to chlordane (MRID 00057151).

82:5 - 90-Day Neurotoxicity - Hen or Mammal

The Agency considers the available chronic feeding studies to have adequately covered the experimentation phase of a 90-day mammal study. However, in view of the neurotoxicity information found in the 90-day oxychlordane study (TBS 0023) the Agency considers that further examination by specialists in nerve pathology of the already existing treated brain and spinal cord tissues should be carried out in an expeditious manner. Examination of optic nerves is by necessity to be included in further examinations.

This further examination is considered a data gap.

83:1 - Chronic Feeding - Rodent

Several chronic rodent studies have been reviewed by the Agency. These include four mouse and four rat studies. Generally the chronic studies pertained to examinations for chlordane's oncogenic potential and they did not provide dosage levels low enough to determine a NOEL for systemic toxicity.

A recent chronic feeding study using mice was submitted to the Agency (TBS 0025).

Groups of 80 male and 80 female ICR mice were fed diets containing 1, 5, or 12.5 ppm of a technical chlordane for 2 years. Results of the study indicated that no unusual clinical signs were noted during the treatment. Clinical chemistry values of liver enzymes that were increased were correlated with histologic examination and increased liver weights of individual animals. Increased liver to body weight ratios were significantly increased in all treated groups of male mice at 1 year. Liver effects noted in male mice at 2 years included hepatocellular

* The 90 day inhalation study does not fulfill the DCI, 1984 requirements since NAS air levels were not tested.

swelling and degeneration, necrosis and fatty degeneration. Effects were not significantly increased at 1 ppm in males except at 1 year. A NOEL for other than increased liver to body weight ratios (which reversed by 2 years in males) was 1 ppm with an LEL of 5 ppm.

A second chronic feeding study in the rat was also recently reviewed for the Agency (TBS 0026). The study used Fischer 344 rats which were dosed with 1, 5, or 25 ppm of technical chlordane for a period of 30 months. Each test group contained 80 male and 80 female rats. Male rats fed 25 ppm exhibited a significantly increased number of hepatocellular adenomas compared to controls. The male rats exhibited liver effects attributable to chlordane ingestion at all treatment levels. The effects included hepatocellular swelling; liver necrosis, and fatty degeneration.

An LEL for the male rat was for liver effects at 1 ppm (0.025 mg/kg) after 130 weeks treatment without a NOEL being established in the study.

This rat study does not fulfill registration requirements in efforts to determine a NOEL in the study.

83:2 - Chronic Feeding - Nonrodent

A 2-year feeding study using dogs was completed by Wazeter (1967) (in TBS-0022) in which dosages of chlordane in the diet varied from 0.3 ppm to 30 ppm. Toxic changes reported in the study included liver function tests at 15 ppm and above. Only liver to body weight changes in both males and females at 3 ppm were reported. Female dogs also exhibited an increased liver to body weight ratio at the 0.3 ppm dosage level. Strictly speaking, a NOEL was not determined for the study at 0.3 ppm in female dogs.

The chronic feeding nonrodent testing is a data gap.

83:3 - Oncogenicity Studies - Rat and Mouse

Mice

The following four studies on chlordane in mice have been submitted to the Agency. Two of the studies were carried out with either technical chlordane containing heptachlor or analytical grade chlordane.

The studies are summarized as follows: from the Cancer Assessment Group Document (TBS 0028).

Becker and Sell (1979)

A 90:10 mixture of chlordane/heptachlor was fed to an unspecified number of male C57Bl/6N mice at concentrations of 25 to 50 ppm for 18 months. The C57Bl/6N mice rarely develop spontaneous liver lesions and in a group of 200 control mice no liver tumors or nodular lesions were found in over 18 months of observation. In mice receiving the chlordane/heptachlor diet, many liver lesions were seen, including both benign proliferative lesions and hepatocellular carcinomas. Specific information as to treatment, observation periods, time of death or data relating tumor incidence to dose were not available. Of the treated mice surviving to the end of the experiment, 27 percent (16 mice) had primary hepatocellular carcimonas, with the first tumor appearing at 36 weeks.

This study is considered to be supplementary at best because of the lack of specific data necessary to adequately evaluate the entire study.

The International Research and Development Corporation (IRDC, 1973)

Analytical grade chlordane at concentrations of 0, 5, 25, or 50 ppm was administered in the diet to groups of 100 male and 100 female CD-1 mice for 18 months. A 6-month interim sacrifice of 10 mice/sex/group did not reveal compound-related lesions. Survival was greatly reduced at the high-dose levels. A large number of animals was also lost due to autolysis. Only about one-half of the mice were histologically examined. A significant increase in liver nodules/hepatocellular carcinomas were observed in the 25 and 50 ppm groups.

This study is considered to be minimum data.

National Cancer Institute Bioassay (NCI, 1977)

Analytical grade chlordane was administered in the diet to groups of 50 B6C3F1 mice of each sex/treatment level for 80 weeks, then observed for 10 weeks. Doses were reduced for females during the test and increased for males. The time weighted average doses used for the male mice were 29.9 and 56.2 ppm; for the females, 30.1 and 63.8 ppm. Controls consisted of 20 matched control mice of each sex and 100 and 80 male and female control mice, respectively.

The effects of chlordane on body weights and other clinical signs indicated that the dosages used were near the maximum permissible. Hepatocellular carcinomas showed a highly significant

($p < 0.001$) dose-related incidence in both male and female mice when compared to either the matched or pooled controls.

The study is considered to be minimum data for oncogenicity evaluation in the mouse.

Research Institute for Animal Science in Biochemistry and Toxicology, Japan (1983)

In this study, technical grade chlordane was fed to groups of 80 male and 80 female ICR mice at levels of 0, 1, 5, or 12.5 ppm for a period of 24 months. An interim sacrifice of eight animals/sex/dose was made at 52 weeks. A significant increase ($p < 0.001$) in the incidence of hepatocellular adenoma and hemamgioma of the liver was found in the 12.5 ppm male group in animals dying between 19 and 24 months or at terminal sacrifice. Nontumor liver lesions were present in males fed 5 ppm and females fed 5 or 12.5 ppm.

This study is considered minimum data for technical chlordane oncogenicity testing in mice and fulfills the registration requirement.

Rats

Ambrose et al., (1953)

Technical grade chlordane was fed to groups of three to five male and female albino rats for 400 days at dietary levels of 0, 10, 20, 40, 80, 160, 320, 640, or 1280 ppm. Although, no treatment-related increase in tumors was found, the study duration (400 days) is considered too short and number of animals too few for this to be a valid carcinogenicity study.

Ingle (1952)

Six groups of 20 male and 20 female Osborne-Mendel rats were fed chlordane diets at 0, 5, 10, 20, 150, or 300 ppm for up to 2 years. Marked toxicity was encountered at 300 ppm in both sexes. This included high mortality, reduced growth rates, eye, and nose hemorrhaging and severe histopathologic damage to the liver, kidneys, heart, adrenals, lungs, myocardium, and spleen. No symptoms of toxicity, gross or histopathologic changes were noted at 5 ppm. No treatment-related tumor incidences was found.

This study is supplementary for oncogenicity or systemic testing in rat due to the small numbers or animals and the date of technical chlordane used in the study.

National Cancer Institute Bioassay (1977a)

Analytical-grade chlordane was administered to groups of 50 Osborne-Mendel rats of each sex for 80 weeks, then observed for 29 weeks. Because of toxic effects, doses were reduced during the tests. Time-weighted average doses used for the male rats were 203.5 and 407 ppm; for females 120.8 and 241.5 ppm. Matched controls consisted of groups of 10 untreated rats of each sex; pooled controls consisted of matched-controls plus 50 untreated animals of each sex from similar bioassays of five other compounds. All surviving rats were killed at 109 weeks.

There was significant statistical evidence in the treated male rats of proliferative lesions of follicular cells of the thyroid and of malignant fibrous histiocytoma, but NCI discounted these findings. These lesions had occurred spontaneously throughout the bioassay program. All other tumors were common for this strain of rat and were not treatment related.

This study is considered supplementary data because of the inadequate use of controls for the particular study.

The Research Institute for Animal Science in Biochemistry and Toxicology, Japan (1983)

In this study, technical grade chlordane was fed to groups of 80 Fischer 344 rats of each sex at levels of 0, 1, 5, or 25 ppm for a period of 130 weeks. Interim sacrifices of 8 animals/sex/dose were made at 26 and 52 weeks.

There was a significant ($p < 0.001$) increase in adenomas of the liver in males receiving 25 ppm as compared to controls but no corresponding effect in females. All of these tumors were found after 104 weeks (mean time to tumor death was 121.8 weeks).

This study is minimum data and fulfills the registration requirements for oncogenicity testing.

83:4 - Teratogenicity - Two Species

Data have not been submitted to the Agency concerning this area of toxicity testing. This area of testing is considered to be a data gap.

83-4: - Reproduction - Two-Generation

A review by the Agency in July 1972 (TBS 0022) of several studies relating to reproduction is excerpted in the following paragraphs.

An FAO/WHO, 1968 report on chlordane exposure of 0.3 to 6.0 ppm to rats in a three-generation reproduction study reported that up to 30 ppm in the diet had no effect on number of litters, pup weight, growth, mortality of pups to weaning, number of young, or fertility.

Khera and Clegg (1969) (TBS 0022) reported that chlordane residues in rat milk caused toxicity to control pups fed by dams treated with 150 ppm chlordane in their diets.

This area of toxicity testing does not contain adequately reported studies to satisfy registration requirements. This area of testing is a data gap.

Mutagenicity

Mutagenicity studies are currently under review by the Agency. The results of these reviews will be added to the Toxicology Chapter later as an addendum.

85: - General Metabolism

There have been a large number of studies printed describing the various aspects of chlordane metabolism. The Agency has produced an overview (TBS 0027) which summarizes the available and pertinent studies on absorption, distribution, excretion, and biotransformation of cis and trans chlordane in several species.

Single dose absorption studies in rats suggest that a large percentage of ^{14}C-label is eliminated in feces via the bile. Only about 6 percent of the label is excreted in the urine.

Rabbits, however, were found to excrete from 30 to 50 percent in the urine of the total dose in a multiple dose study.

Dermal toxicity of chlordane was studied by Ambrose et al., 1953 in TBS 0027. That chlordane (i.e., 1953) was found to be more toxic to rats after application in cottonseed oil rather than when applied in ethyl alcohol.

The absorption of chlordane by the dermal route has not been quantitated. Respiratory absorption has been studied in rats using ^{14}Clabeled chlordane. The study by Dorough (1978) in TBS 0027 reported that the test animals did not absorb 100 percent of the test material that was inhaled. In fact, only 42 to 80 percent of the total ^{14}C respired was retained in the body following an inhalation period of from 15 to 45 minutes.

Data on tissue distribution of the ^{14}C label from cis or trans chlordane in a study using rats suggest that at 1 day after a single oral dose only fat tissues contained appreciable

^{14}C-residues. In addition, residues in fat tissue were higher in females than males and trans chlordane treatment resulted in higher residues than from use of the cis isomer.

The seventh day postexposure residue values in female rats treated with a single dose of oxychlordane were significantly higher than those following exposure to cis chlordane, but were similar to those following treatment with trans chlordane.

Oxychlordane has accounted for 50 to 60 percent of fat tissue residues following a single dose after 24 hours.

A study using a single 1-hour aerosol inhalation dose of ^{14}C-labeled chlordane in rats showed that as much as 23 percent of the dose remained in the lungs.

After feeding rats for 14 or 56 days of diets containing cis, or trans chlordane at levels of 15 or 25 ppm, residues were only found to be dose dependent and did not differ in tissue accumulation patterns. Following an increased time-off of treatment, oxychlordane became an increasingly greater percentage of the accumulated ^{14}Cactivity. Trans chlordane treatment residue resulted in severalfold greater levels of oxychlordane than did the cis isomers.

Excretion of chlordane or its metabolites has been studied in rats, rabbits, mice, and cows.

Single doses of the cis or trans isomers of chlordane were given rats who eliminated the cis isomer at a faster rate than the trans isomer. Most of the ^{14}C activity was eliminated by the bile through the fecal route. Only a small percentage of a dose (2 to 8%) was eliminated in the urine.

Oxychlordane, in contrast to chlordane isomers, generally remains in the body fat after administration by the oral route. Only 21 percent of oxychlordane was excreted after 7 days compared to approximately 90 percent for either isomer of chlordane. However, the route of excretion, the feces, was the same as for the chlordane isomers.

In order to compare excretion by species in rats and mice, only males were examined to exclude sex influence. Dorough (1984) found that the excretion rates in mice were faster in the first day. They were otherwise similar with regard to the pattern of excretion.

Repeated doses of ^{14}C labeled chlordane in rats produced excretion patterns similar to those seen in single dose studies.

Rabbits on the other hand excreted about equal amounts of chlordane cis and trans isomers in the feces and about 35 percent of the trans isomer in the urine [slightly more than for the cis isomer (28%)] following a four-dose regimen.

The exact metabolic pathway for chlordane is extremely complex and not completely known because several possible pathways to produce the many metabolic products are possible.

In addition, it appears that the preferential metabolic route of chlordane and subsequent metabolites may differ from species to species.

Technical chlordane contains several components including heptachlor and trans-nonachlor.

Although oxychlordane has been found to be a major fat tissue residue in rats, human fat samples frequently contain trans-nonachlor as the major residue. It is thought that the rat liver readily metabolizes trans-nonachlor and allows a greater subsequent excretion rate than does the human liver.

Human adipose tissue sampled in a nationwide study found oxychlordane at an average of 0.11 ppm in more than 92 percent of the samples analyzed.

Heptachlor expoxide was also found in about 90 percent of samples in the study at levels of 0.08 to 0.09 ppm.

Unfortunately, very limited information on the in vivo metabolism of chlordane, metabolites, or other manufacturing reaction products exist. Probably the human chlordane poisoning cases provide the closest similarity to metabolism studies in humans.

Following an ingestion of chlordane by a 20-month-old male, investigators determined blood and fat concentrations of the pesticide for over 90 days. Fat concentrations remained as high as 20 ppm at 94 days following the ingestion and the serum half-life for chlordane was estimated to be 21 days.

This area of toxicity testing has been fulfilled to the extent that registration requirements have been met. Further general metabolism studies are not required.

Setting an ADI/PADI

Chlordane has been tested in chronic rodent studies which have provided NOEL's for nononcogenic effects. A lowest effect

level (LEL) for a rat 2 1/2 year feeding study was 1 ppm of chlordane in the diet (0.05 mg/kg/day).

Certain other studies deemed necessary to more fully evaluate other toxicity end points of chlordane are absent from the data base. As a result of the existing LEL, an additional modification of the safety factor is considered warranted. The total thousandfold safety factor is applied to the LEL of 0.05 mg/kg/day producing a PADI or reference dose (Rfd) of 0.00005 mg/kg/day.

86:3 Exposure in Housing

The registered use of chlordane as a termiticide in residential dwellings has produced some concern for the possible exposure to the pesticide emanating from that use.

An exposure study of houses treated with chlordane under label conditions is being completed. Results of that study will be reported when completed and factored into an exposure scenario as an addendum to the Registration Standard.

Additional Exposures

The Agency recognizes that residues of various termiticides including chlordane have the capability to enter the food chain. Determining the sources of these residues in such food items as fish has become an important problem and is necessary to provide more reasonable methods for treatment to eliminate these sources of contamination.

The applicators of termiticides are expected to be exposed mainly by the dermal route. Although no dermal exposure study has been submitted to the Agency, normal exposure to the applicator following labeled usage is expected to be low enough to adequately preclude an acute hazard.

Exposure to applicators by the inhalation route is believed to be minor, with about 40 to 80 percent of the inhaled dose retained. Additionally, the absorption of chlordane aerosols suggests that absorption of chlordane by the lungs is not an unlimited and rapid route of exposure (TBS-0027).

Cancer Risk

The Agency does not presently have exposure data upon which to evaluate any possible cancer risk using animal data.

The Agency has requested, and the registrant is supplying, a study to delineate the inhalation exposure to residents of treated buildings.

Epidemiological Evidence

The Q^*_1 (1.3 per mg/kg/day) for chlordane has been determined from the Cancer Assessment Group (CAG) (TBS-0028) and will be used in conjunction with the air monitoring data when they are submitted to estimate a possible cancer risk from exposure to chlordane.

Special Issues

The Agency has recently been apprised of the existence of optic neuritis associated with habitat treatment and subsequent exposure to humans (letter of G. Marack, TBS-0029). The Agency requests the registrant to reexamine existing treated eye tissues by neuropathologists specializing in optic tissue pathology. These reexaminations are necessary to evaluate the observation of optic neuritis in humans. This issue should be addressed as soon as possible.

Cases of irritation of the upper respiratory passages have been reported (TBS-0030). These type problems require addressing and possible further study by the registrant.

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