10-28-86

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

OCT 28 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Chlordane Registration Standard Cover Memo

FROM: Michael P. Firestone, Ph.D.
Science Integration Staff
Hazard Evaluation Division (TS-769C)

TO: George LaRocca PM 15
Insecticide/Rodenticide Branch
Registration Division (TS-769C)

Thru: Amy S. Rispin, Director
Science Integration Staff
Hazard Evaluation Division (TS-769C)

INTRODUCTION

Chlordane, a chlorinated cyclodiene broad spectrum insecticide, was used extensively in the United States for almost 30 years. Most uses were cancelled or phased out by EPA in 1978. After 1983, termite control was the only major use retained. The basis of the cancellation/phase-out (Intent to Cancel Registrations - Pesticide Products Containing Heptachlor or Chlordane - FR Vol. 39, No. 229; November 11, 1974) was primarily concern with cancer risk and evidence of human exposure/biocentration; wildlife toxicity and persistance in the environment were also cited.

In animals, chlordane is metabolized by microsmal enzymes to oxychlordane, which is much more toxic than the parent compound. Oxychlordane accumulates in adipose tissue; results of the National Human Monitoring Program conducted between 1970 and 1974 demonstrated the occurance of oxychlordane in approximately 97% of 5000 human tissue samples at a geometric mean of 0.11 ppm.

Based on clinical case studies, the three toxic effects seen most frequently in humans are central nervous system (CNS) effects (such as irritability, salivation, labored respiration, muscle tremors, and convulsions to death), blood dycrasias, and neuroblastomas. Recently, the Agency has received clinical evidence that human optic neuritis may be associated with exposure to chlordane vapors in treated homes. Chlordane has been found to cause liver effects (such as increased liver weight, change in enzyme levels, hepatocellular swelling and necrosis in chronic rodent feeding studies. Also, chlordane has been found to increase the incidence of liver carcinomas and/or adenomas in mice and rats.

In November 1983, EPA issued the report "Analysis of the Risks and Benefits of Seven Termiticide Chemicals Used for Subterranean Termite Control" which included a comparative risk/benefit analysis of the termiticides as a cluster; chlordane was one of the seven termiticides considered. The report concluded that the benefits from the use of cyclodienes (chlordane included) outweigh the potential risks. The report also cited the lack of definitive data in certain areas, particularly on the extent and level of human exposure. In conjunction with this report, EPA required subchronic inhalation data, mutagenicity data, metabolism data, and indoor air monitoring data, in order to permit a more comprehensive risk assessment. Data submitted in response to the February 23, 1984 Data Call-In Notice have been reviewed in conjunction with this Registration Standard.

Concurrently with the Registration Standard process for chlordane, the Agency is developing a rule to classify all currently registered subterranean termite control pesticides (termiticides), including chlordane, for restricted use. The purpose of this rule is to decrease the chance for misuse/ misapplication of termiticide chemicals.

Included in this memo is a discussion of the assessments completed by Residue Chemistry Branch (RCB), Exposure Assessment Branch (EAB), Ecological Effects Branch (EEB), Toxicology Branch (TOX), and the Cancer Assessment Group (CAG).

DESCRIPTION OF CHEMICAL

Common Name: Chlordane

Chemical Name: 1, 2, 4, 6, 7, 8, 8 - Octachloro - 2, 3, 3a, 4, 7, 7a - hexahydro - 4, 7 - methano - 1H - indene

Empirical Formula: $C_{10}H_6Cl_8$

CAS Registry Number: 57-47-9

Shaughnessy Number: 058201

PRODUCT CHEMISTRY

Most of the 40 CFR 158.120 product chemistry data requirements have not been fulfilled. The following table summarizes the product chemistry data gaps.

Kind of Data Required	Guideline Reference No.
Description of beginning materials and manufacturing process	61-2
Discussion of formation of impurities	61-3
Preliminary analysis of product ingredients	62-1
Certification of limits	62-2
Analytical methods to verify certified limits	62-3
Physical and chemicals characteristics	63-2 to 63-21

RESIDUE CHEMISTRY AND ACTION LEVELS

There are no residue chemistry concerns since no food/feed uses for chlordane remain. Tha Agency is currently in the process of completing a Final Rule which would revoke existing tolerances for which registered uses have been cancelled and would replace them with action levels.

ENVIRONMENTAL FATE

Chlordane appears to be only slightly mobile and is very persistent in the environment. The results of a long-term study conducted in Beltsville, MD revealed that 45% of the chlordane applied to sandy loam soil was present 15 years after application.

In order to fully assess the environmental fate and transport of chlordane, the following data, as per 40 CFR 158.130, will be required.

Kind of Data Required	Guideline Ref. No.
Hydrolysis	161-1
Photodegredation in water	161-2
Aerobic soil metabolism	162-1
Anaerobic soil metabolism	162-2
Aerobic aquatic metabolism	162-4
Leaching and absorption/desorption	163-1
Volatility (lab)	163-2[a]
Volatility (field)	163-3[a]
Terrestrial field dissipation	164-1
Aquatic (sediment) field dissipation	164-2[b]
Long-term field dissipation	164-5[c]
Fish accumulation	164-4[d]

a) Requirements for laboratory and field volatility data are reserved pending evaluation of the results of an indoor air monitoring study currently in progress.

b) Requirement for aquatic (sediment) dissipation data are reserved pending evaluation of the results of an aerobic aquatic metabolism study (162-4).

c) Requirement for long-term field dissipation data are reserved pending evaluation of the results of a field dissipation study (164-1).

d) Requirement for fish accumulation data are reserved pending evaluation of the results of the octanol/water partition coefficient study (63-11).

EAB has concluded that temiticide use of chlordane may result in surface water contamination (M. Lorber memo of June 10, 1986); thus, a study (either prospective or retrospective) will be required in which sump pump, drainage tile and sanitary sewer water, draining from home foundations known to have been properly treated with chlordane, should be sampled to determine the potential for chlordane to contaminate streams, lakes, and other surface waters.

The potential for contamination of ground water can not be assessed until the environmental fate and transport data requested above have been reviewed and evaluated.

ECOLOGICAL EFFECTS

There are sufficient data available to characterize technical chlordane as very highly toxic to freshwater fish, aquatic invertebrates, and birds. Requirements for data concerning acute toxicity to estuarine/marine organisms (guideline ref. no. 72-3) and embryolarvae and life-cycle studies of fish and aquatic invertebrates (guideline ref. no. 72-4) will be reserved until the results of a special surface water contamination study (described above in the Environmental Fate section) have been received and evaluated.

INDOOR AIR EXPOSURE

Preliminary results of an interim report covering the first 90 days of a one-year indoor air monitoring study have been received by the Agency. The study reflected treatment of slab and crawl space (but not basement) houses with Termide, a formulation containing a 2:1 mixture of technical chlordane: technical heptachlor. Ambient air levels of 4 chlordane isomers, trans-nanachlor and heptachlor were monitored. The Agency is working with the registrant of chlordane through its Beltsville laboratory to interpret and validate the air monitoring data. On the basis of these interim results, HED is requesting that the registrant of chlordane submit all validation data (including chromatograms, calculations, GC-MS confirmation of all significant peaks, etc.) so that the Agency can assess the adequacy of data. Until these validation data have been received and reviewed, it is not possible to even estimate likely annual exposures in treated homes.

At such time as EAB is able to estimate various exposure scenarios, SIS will issue an addendum to this cover memo.

APPLICATOR EXPOSURE

The registrant will need to submit data which will allow the Agency to ascertain the likely level of applicator exposure via both inhalation and dermal routes.

TOXICOLOGY

As noted in the Toxicology Chapter, many of the chlordane studies carried out in the 1950's and 1960's are considered to fall below the level of quality expected by today's standards. In addition, the material tested in these older studies may be different from that currently produced.

Acute Toxicity

On the basis of available acute data, technical chlordane appears to fall into Category II of 40 CFR 162.10(h); however, many data gaps exist including:

Kind of Data Required	Guideline Ref. No.
Acute oral toxicity[a]	81-1
Acute dermal toxicity[b]	81-2
Acute inhalation toxicity[b]	81-3
Primary dermal irritation[a] also Primary (eye)	81-5

a) technical material and formulations
b) technical material only

Subchronic Toxicity

The primary subchronic effects of chlordane are those of the liver including "CHIRL" (chlorinated hydrocarbon insecticide rodent liver), centrolobular cell hypertrophy, peripheral migration of cytoplasmic granules and bodies, increased cytochrome P-450 levels, liver lesions, and increases in liver weight. An LEL (lowest effect level) of 2.5 ppm has been determined for the CHIRL effect.

The 1984 Data-Call-In (DCI) required a rat subchronic inhalation study in which the lowest tested must be 0.005 mg/m^3, the National Academy of Science (NAS) airborne guideline level. NOEL's derived from 90-day studies using rat and monkeys (submitted in response to the 1984 DCI but actually conducted earlier) were determined to be 0.1 mg/m^3 and 1.0 mg/m^3, respectively, based on liver effects. The rat study is not considered adequate because of its short duration (less than one year) and the fact that the lowest dose tested was 20-times higher than the NAS guideline level requested by the DCI.

Oxychlordane, the primary storage metabolite of chlordane, was found to be more toxic than the parent compound. Histologic liver effects were noted in male rats, even at the lowest dose tested - 5 ppm. In addition to histological effects of the liver, oxychlordane also produced adverse effects in the white matter of the spinal cord and brain (spongiosis) in rats. In view of the oxychlordane neurotoxicity data, further examination by specialists in nerve pathology of already existing brain (including optic nerve) and spinal cord tissues from treated rats will be required.

The registrant will need to conduct an additional inhalation study of one to two week duration with either guinea pigs or rats to further delineate the irritative capabilities to mucous membranes of chlordane, formulation solvents, and the combination (i.e., formulated products).

Teratogenicity

The lack of teratogenicity studies in two species (guideline reference number 83-3) represents a data gap for technical chlordane.

Reproductive Effects

The lack of adequately reported 2-generation reproduction studies (guideline reference number 83-4) represents a data gap for technical chlordane.

Mutagenicity

Mutagenicity studies are currently under review by Toxicology Branch. The conclusions and acceptability of available studies will be submitted as an addendum to the Toxicology Registration Standard Chapter for chlordane.

General Metabolism

The metabolism and excretion of chlordane has been studied in a variety of animals including rats, mice, rabbits, and cattle. The preferential metabolic route of chlordane and subsequent metabolites may vary among different species. The metabolic profile of chlordane is complex due to the fact that technical chlordane is actually a mixture which includes various chlordane isomers, nonachlor and heptachlor.

Although the epoxide metabolite of chlordane, oxychlordane, is the major residue found in fatty tissue in rats, human fat samples often contain the technical impurity trans-nonachlor as the major residue. Heptachlor epoxide is also found at significant levels in human tissue.

Further general metabolism studies are not required.

Special Testing

The Agency has recently been appraised of reported cases of optic neuritis associated with home termiticide treatment. To accelerate clarification of this potential adverse effect, neuropathologists specializing in optic tissues pathology should, if possible, reexamine existing eye tissues from the most recent chronic study (1983 rat study).

Chronic Toxicity/ADI Determination

Based on available rodent (mice, rats) and dog feeding, studies, the principal chronic effects were those related to the liver including increased organ weights, hepatocellular swelling and degeneration, necrosis, fatty degeneration, and hepatocellular adenomas.

Data gaps exist for two-year rat and dog feeding studies since available studies do not fulfill registration requirements to determine NOEL's (no-effect levels).

Based on liver effects (increase in liver weight due to hepatocellular swelling) attributable to technical chlordane ingestion for 2.5 years even at the lowest dose tested in male rats (i.e., 1 ppm), an LEL (lowest effect level) of 0.05 mg/kg/day has been determined.

Utilizing an uncertainty factor of 1,000, a provisional ADI or PADI of $5x10^{-5}$ has been set (this is equivalent to to the Agency's RfD).

Oncogenicity

The Agency's Cancer Assessment Group (CAG) has conducted a weight-of-the-evidence review of the carcinogenicity of chlordane (December, 1985 Draft).

Based on the evidence of significant liver tumor responses in four mouse studies (increased incidence in both males and females at medium and high doses) and in a 1983 rat study, CAG has classified chlordane as a probable human carcinogen, Group B2. According to CAG, "epidemiologic studies provide inadequate evidence due to methodology and data limitations."

Utilizing the mouse studies and a linear low-dose extrapolation model, a cancer potency value (Q^*-1) determined for chlordane to be 1.3 per mg/kg/day for the general population; this value represents a plausible upper bound for the increased cancer risk from chlordane, meaning that the true risk is not likely to exceed these estimates and may be lower.

RISK ASSESSMENT

Until EAB is able to adequately evaluate ambient air exposure levels in chlordane-treated homes, it is not possible to estimate either the cancer risk or the chronic non-oncogenic hazard to residents in treated homes. When these data become available, SIS will issue an addendum to this cover memo.

cc: M. Firestone, J. Melone, A. Barton, A. Rispin, HED Branch Chiefs, S. Wayland, L. Rossi