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WASHINGTON, D.C. 20460

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

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SUBJECT: Registration Standard: KELTHANE

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Attached are the Topical Discussions, Toxicology Profile, Toxicology Hazard Assessment and Data Requirement Tables for Kelthane.

cc Stuart Cohen
Ann Barton
Judy Heckman

SCIENCE REVIEWS FOR DICOFOL

ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDE PROGRAMS
WASHINGTON, D.C. 20460
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PLEASE NOTE:

These five chapters were completed in 1981. Some of the data requirement guideline references have changed, as well as some of the guideline requirements. Please refer to the Guidance Document for the most recent requirements.

If you have any questions concerning these scientific reviews or the references, please contact Bruce Kapner at 703/557-7400, or by mail at (TS-767C) 401 Street, SW, Washington, DC 20460

KELTHANE

DISCIPLINARY REVIEW

Toxicolgy Profile
Toxicology Hazard Assessment
General Data Gaps

TOXICOLOGY PROFILE

Manufacturing - Use Kelthane

Sufficient Data are available to show that Kelthane has a moderate acute oral toxicity as seen in the following table:

TABLE 1

Summary of acute oral LD_{50} values (mg/kg) for manufacturing-use Kelthane

Animal	% Active Ingredient	LD_{50}	Toxicity Catergory	Reference
Rat (M) Rat (F)	unspecified unspecified	809 ± 33mg/kg 684 ± 16mg/kg	III	Haag and Larson 19?? #00004373
Rat (M)	unspecified	970 ± 260mg/kg	III	Haag and Larson 19?? (MRID # 00004365)
Rat (M)	84.8%	1495mg/kg (95% (CI 039-2150mg/kg	III	Brown et al 1969 (MRID # 05002571)
Rabbit (M)	unspecified	1810 ± 350mg/kg	III	Haig and Larson 19?? (MRID #00004374)

There are sufficient data to demonstrate that Kelthane has a relatively high degree of acute dermal toxicity. The dermal LD_{50} is 2.1 ± 0.3g/kg in rabbits (Haag and Larson 19?? ; MRID #00004366).

There are no data available for the manufacturing-use formulation with respect to acute inhalation toxicity; testing is required.

Although no data were available to assess the eye irritation potential of the manufacturing-use product, the results with the formulation intermediate (See Toxicology Profile for End-Usae Products for details) indicate that the manufacturing-use formulation is probably a severe eye irritant. Based on this data, testing of the mmanufacturing-use formulation is not required and will be considered a severe eye irritant.

There are no data available to assess the dermal irritation or skin senstization potential. Testing is required.

There are insufficient data on the subchronic oral toxicity of manufacturing-use Kelthane. The rat study (Haag and Larson 1952; MRID #00004429) indicated that the no-observable-effect level is 20ppm. This study only partially fulfills the subchronic data requirement, a test in a second species (preferably a dog) is required.

There are no adequate data available regarding the 21-day subchronic dermal toxicity. Testing is required.

No adequate data were available to assess the chronic feeding toxicity. Testing is required.

The available data is insufficient to satisfactorily assess the onocogencity of Kelthane. Two studies were conducted on mice and rats (National Cancer Institute 1978; MRID #_____). The results suggest that Kelthane induces hepatocellular carcinoma in male mice. However, the purity of the "Technical Grade Kelthane" used in these studies was estimated to be 40% and 60%. Impurities could not be accurately identified. In addition the test compound liquified to an extent described as "significant" during the second year of the studies. This information suggests that Kelthane used in these studies decomposed extensively and the failure to determine the compostion of the compound prohibit drawing a conclusion based on these results. The data do indicate that additional testing is required.

No data were available to assess the teratogenicity of Kelthane. Testing in two mammalian species is required.

Several adequate reproduction studies were available. Mice were fed diets containing 0, 7, 25, 100, 225, or 500ppm of technical Kelthane (84.8% Active Ingredient) through five generations (Brown 1967; MRID #00004424). The data indicated that the no-observable-effect level is 100ppm for mice. In the other reproduction study, rats were fed diets containing 0, 25, 75, 100, 500, or 100ppm of technical Kelthane (Purity Unspecified) for two generations (Brown 1965; MRID #00004312). The data indicated that the no-observable-effect level is 100ppm for rats.

No data were available to assess the mutagenicity of Kelthane. Testing is required.

End-Use Products of Kelthane

There are four formulations which have substantially similar compostion according to the Confidential Statements of Formula. Those formulations are: formulation intermediates, emulsifiable concentrates, ready-to-use and wettable powder/dusts.

There are sufficient data to demonstrate that the formulations of Kelthane have a moderate acute oral toxicity. The acute oral LD_{50} was 1.52 + 0.16 g/kg for rats (sex unspecified)(Terrell and Gilman 1973; MRID #00004356).

There are sufficient data to indicate that the acute dermal toxicity of the formulations is moderately high. The acute dermal LD_{50} was estimated to be greater than 3.0g/kg for male rabbits (Apsokardu and Gilman 1973; MRID #00004354).

There are no data available to assess the acute inhalation toxicity of Kelthane formulations. Testing of the manufacturing-use formulation should be sufficient when it is completed.

There are data indicating that the formulation intermediate is severely irritating to the eyes of rabbits (Apsokardu and Gilman 1973; MRID #00004357). Corneal damage persisted in some rabbits (unwashed eyes) for 7 days. Based on this data all formulations are considered corrorsive to the eye.

No data were available to assess the dermal irritation and dermal sensitization. Testing is required.

Generic Data Gaps

Manufacturing-Use Kelthane

Acute inhalation
Primary dermal irritation
Dermal sensitization
Subchronic oral (dogs)
Subchronic 21-day dermal (rabbits)
Chronic feeding (rats)
Oncogenicity (rat and mouse)
Teratology (2 mammalian species)
Mutagenicity
Metabolism

End-Use Formulations

Primary skin irritation
Dermal sensitization

Toxicity Hazard Assessment

Manufacturing-use Kelthane

The acute oral toxicity of Kelthane is moderate, and the acute dermal toxicity is high. Insufficient data were available to assess the chronic, oncogenic, mutagenic and teratogenic effects of this chemical. It should be noted that Kelthane is a severe eye irritant.

End-Use Kelthane

The formulation intermediates, emulsifiable concentrates, ready-to-use and wettable powder/dusts are substantially similiar in compostion. The acute oral and acute dermal toxicities are moderate. Kelthane formulations are potential severe eye irritants.

TOPICAL DISCUSSIONS: KELTHANE

Acute Testing

Acute Oral Toxicity (163.81-1)

The minimum data requirement for testing acute oral toxicity (LD_{50}) is one test on the technical chemical and on each manufacturing use and formulated product, preferably using the laboratory rat.

Technical

Adequate Acute Oral Toxicity Studies were conducted as indicated in the following table:

Animal	% Active Ingredient	LD_{50}	TOX Cat.	Reference
Rat (M) Rat (F)	Unspecified Unspecified	809 ± 33 mg/kg 684 ± 16 mg/kg	III III	Haag and Larson 19?? (MRID#00004373)
Rat (M)	Unspecified	970 ± 260 mg/kg	III	Haag and Larson 19?? (MRID#0004365)
Rat (M)	84.8%	1495 mg/kg (95% CI 1039-2150 mg/kg)	III	Brown et al 1969 (MRID# 05002571)
Rabbit (M)	Unspecified	1810 ± 350 mg/kg	III	Haag and Larson 19?? (MRID# 00004374)

The reported clinical signs of toxicity were weakness and coma; in addition the rabbits experienced diarrhea. These data place technical Kelthane in Toxicity Category III (See Appendix), corresponding to moderate oral toxicity.

Formulation Intermediate (FI)

A supplementary acute oral toxicity study was conducted on rats (sex unspecified) gavaged with a 35.5% FI of Kelthane (Terrell and Gilman 1973; MRID#00004356). The LD_{50} was estimated to be 1.52 ± 0.16 g/kg (standard error 0.16). Clinical signs of toxicity were respiratory distress, piloerection and lack of coordination. The data suggests that this product has a low acute oral toxicity potential. Further elaboration of the sex of the animals tested, is required.

No data were available concerning the acute oral toxicity of the formulation intermediates containing other percentages of Kelthane. However, since the confidential statements of formulation do not indicate an anticipated change in the acute oral toxicity further testing is not required.

Emulsifiable Concentrates (EC)

No data were available concerning the acute oral toxicity of the EC's containing Kelthane. However, since the confidential statements of formula do not indicate an anticipated change in acute oral toxicity, no testing is required.

Ready-To-Use (RTU)

No data were available concerning the acute oral toxicity of RTU's containing Kelthane. However since the confidential statements of formula do not indicate an anticipated change in acute oral toxicity, no testing is required.

Wettable Powder/Dust (WP/D)

No data were available concerning the acute oral toxicity of WP/D's containing Kelthane. However since the confidential statements of formula do not indicate an anticipated change in the acute oral toxicity, testing is not required.

Acute Dermal Toxicity (163.81-2)

The minimum data requirement for testing acute dermal toxicity (LD_{50}) is one test on the technical chemical and on each manufacturing use and formulated product, preferably using the albino rabbit.

Technical

An adequate acute dermal toxicity test was conducted (Haag and Larson 19??, MRID#00004366) using male rabbits exposed to a single dose of technical Kelthane applied to clipped intact skin. The acute dermal LD_{50} for intact skin was 2.1 + 0.3 g/kg, with death preceded by general weakness and coma. This data is sufficient to satisfy the data requirement and assign Toxicity Category II for acute dermal toxicity (See Appendix).

Formulation Intermediate (FI)

An adequate acute dermal toxicity study was conducted on male rabbits using a 35.5% formulation intermediate of Kelthane (Apsorardu and Gilman 1973; MRID#00004354). The acute dermal LD_{50} was estimated to be greater than 3.0 g/kg for male rabbits (abraded and unabraded skin). No deaths on clinical signs of toxicity were observed at this dose. These data indicate that this product should be placed in Toxicity Category III for acute dermal toxicity.

No data were available concerning the acute dermal toxicity of FI's containing other percentages of Kelthane. However since the confidential statements of formula do not indicate an anticipated change in the acute dermal toxicity, further testing is not required.

Emulsifiable Concentrate (EC)

The available data was not adequate to assess the acute dermal toxicity potential of EC formulations. However since the confidential statements of formula do not indicate an anticipated change in acute dermal toxicity, further testing is not required.

Ready-To-Use (RTU)

No data were available to assess the acute dermal toxicity of ready-to-use formulations containing Kelthane. However since the confidential statements of formulation do not indicate an anticipated change in acute dermal toxicity, testing is not required.

Wettable Powder/Dust (WP/D)

No data were available concerning the acute dermal toxicity of the WP/D products containing Kelthane. However, since the confidential statements of formula do not indicate an anticipated change in the acute dermal toxicity, testing is not required.

Acute Inhalation Toxicity (163.81-3)

The minimum data requirement for testing acute inhalation toxicity (LC_{50}) is one test on the technical chemical and on each manufacturing use and formulated product, preferably using the laboratory rat.

An acute inhalation toxicity (LC_{50}) test is required for each formulation that causes a respirable vapor, or if 20% or more of the aerodynamic equivalent is composed of particles not larger than 10 microns.

Technical

No data were available to assess the acute inhalation toxicity of technical Kelthane. Testing is required.

Formulation Intermediate (FI)

No data were available to assess the acute inhalation toxicity of FI's containing Kelthane. Since the confidential statements of formula do not indicate an anticipated change in the acute inhalation toxicity, testing of technical Kelthane should be sufficient.

Emulsifiable Concentrate (EC)

No data were available to assess the acute inhalation toxicity EC's containing Kelthane. Since the confidential statements of formula do not indicate an anticipated change in the acute inhalation toxicity, testing of technical Kelthane should be sufficient.

Ready-To-Use (RTU)

No data were available to assess the acute inhalation toxicity of RTU's containing Kelthane. Since the confidential statements of formula do not indicate an anticipated change in the acute inhalation toxicity, testing of technical Kelthane should be sufficient.

Wettable Powder/Dust

A supplementary acute inhalation toxicity study was conducted on male mice exposed to a chamber concentration of 2.0 mg/liter of 25% Dust Kelthane for a 6-hour exposure as a priliminary test for chronic inhalation studies (Leong and Drews 1967; MRID#00004359). No deaths were reported. This study is not sufficient to meet the data requirement due to the lack of reporting of methods employed (i.e. method of measuring chamber concentrations and paricle size distribution) and details of the study (lack of individual animal data for pathology, body weight, etc.).

Since the confidential statements of formula do not indicate an anticipated change in the acute inhalation toxicity, testing of technical Kelthane will be sufficient.

519

Primary Eye Irritation (163.81-4)

The minimum data requirement for primary eye irritation is one test on each manufacturing use and formulated product, preferably using the albino rabbit. A primary eye irritation study is not required for each formulation that has a pH of 1-3 or 12-14 because these test substances will be considered corrosive to the eye.

Technical

No data were available to assess the eye irritation potential of technical Kelthane. ~~Testing is required.~~ As per the data available for FI formulations, no testing is required. Technical Kelthane will be considered a potential severe eye irritant.

Formulation Intermediate (FI)

An adequate eye irritation study was conducted (Apsokardu and Gilman 1973; MRID#00004357). Rabbit eyes (washed and unwashed) were treated with 0.1 ml of a 35.5% FI of Kelthane. The reaction to Kelthane treatment in the unwashed eyes was more severe than in the washed eyes. The maximum mean irritaiton scores were 15/110 and 0/110 for washed eyes and 36/110 and 26/110 for unwashed eyes at 24 hours and 7 days respectively. Damage to the cornea and conjunctivae were evident at 7 days in 3 of 3 animals whose eyes remained unwashed after treatment. These results are sufficient to place this 35.5% FI in Toxicity Category I, indicating a very severe potential for eye damage.

Since the confidential statements of formula do not indicate an anticipated change in primary eye irritation potential, further testing of FI products is not required.

Emulsifiable Concentrate (EC)

No data were available to assess the eye irritation potential of emulsifiable concentrates containing Kelthane. Testing is ~~required~~. Not required. EC formulations will be considered a potentially severe eye irritant (see FI section for details).

Ready-To-Use (RTU)

No data were available to assess the eye irritaiton potential of ready-to-use formulations containing Kelthane. Testing is required. (NC)
RTU formulations will be considered a potentially severe eye irritant (see FI section for details).

Wettable Powder/Dust (WP/D)

No data were available to assess the eye irritation potential of WP/D's containing Kelthane. Testing is required. (NC) WP/D formulations will be considered a potentially severe eye irritant (see FI section for details).

Primary Dermal Irritation (163.81-5)

The minimum data requirement for primary dermal irritation is one test on each manufacturing use and formulated product, preferably using the albino rabbit.

A primary dermal irritation study is not required for each formulation that has a pH of 1-3 or 12-14; a test substance with a pH of 1-3 or 12-14 will be considered corrosive to the skin.

Technical

No data were available to assess the dermal irritation potential of technical Kelthane. Testing is required.

Formulation Intermediate

No data were available to assess the dermal irritation potential of formulation intermediates containing Kelthane. Testing is required.

Wettable Powder/Dust

No data available to assess the dermal irritation potential of wettable powder/dust formulations containing Kelthane. Testing is required.

Emulsifiable Concentrate

No data were available to assess the dermal irritation potential of emulsifiable concentrates containing Kelthane. Testing is required.

Ready-To-Use

No data were available to assess the dermal irritation potential of ready-to-use formulations containing Kelthane. Testing is required.

Dermal Sensitization (163.81-6)

The minimum data requirement for dermal sensitization is an intradermal test for each manufacturing use and formulated product, prederably using the guinea pig.

Technical

No data were available to assess the dermal sensitization potential of technical Kelthane. Testing is required.

Formulation Intermediates (FI)

No data were available to assess the dermal sensitization potential of formulation intermediates containing Kelthane. Testing is required.

Wettable Powder/Dust

No data were available to assess the dermal sensitization potential of wettable powder/dust formulations containing Kelthane. Testing is required.

Emulsifiable Concentrate

No data were available to assess the dermal sensitization potential of emulsifiable concentrates containing Kelthane. Testing is required.

Ready-to-Use

No data were available to assess the dermal sensitization potential of ready-to-use formulations containing Kelthane. Testing is required.

Acute Delayed Neurotoxicity (163.81-7)

The minimum data requirement for acute delayed neurotoxicity is one test on the technical chemical, using the adult hen.

An acute delayed neurotoxicity test is required if the active ingredient or any of its metabolites, degradation products, or impurities causes esterase depression or is structurally related to a substance that induces delayed neurotoxicity.

An acute delayed neurotoxicity test is not required because Kelthane does not depress esterase activity, and it is not structurally related to a compound that induces neuropathy or delayed neurotoxicity.

Subchronic Oral Toxicity (163.82-1)

The minimum data requirement for subchronic oral toxicity is one test on the technical chemical in two mammalian species, preferably using the rat and dog.

A subchronic oral toxicity test is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires the issuance of a food additive regulation, or is likely to result in repeated human exposure through the oral route.

The subchronic oral toxicity test is required for Kelthane because its use (application to food crops) requires a tolerance.

In an adequate subchronic study, male and female rats were fed diets containing 0, 20, 100, 500, 1250 or 2500 ppm of Kelthane for a period of 3 months (Haag and Larson 1952; MRID#00004429). High mortality was observed at the 1250 ppm dose (60% for females and 50% for males); the 2500 ppm dose was terminated at 2 weeks. Weight depression was noted in females receiving 100 ppm or higher and in males, it was only in the high dose. Dose related increases were observed in the liver-to-body weight ratios in both male and female rats. However, histopathologic examinations revealed no lesions that could be related to the ingestion of Kelthane. Therefore, the NOEL is considered to be 20 ppm.

To complete the data requirement for subchronic oral toxicity, a test is required in dogs.

Subchronic 21-Day Dermal Toxicity (163.82-2)

The minimum data requirement for subchronic 21-day dermal toxicity is one test for the technical chemical, preferably using the albino rabbit.

A subchronic 21-day dermal toxicity test is required if pesticidal use is likely to result in repeated human skin contact.

The subchronic 21-day dermal test is required for Kelthane because its use could result in repeated human skin contact.

No data were available to assess the subchronic 21-day dermal toxicity of Kelthane. Testing is required.

Subchronic 90-Day Dermal Toxicity (163.82-3)

The minimum data requirement for subchronic 90-day dermal toxicity is one test for the technical chemical, preferably using the albino rabbit.

The subchronic 90-day dermal toxicity test is required if pesticidal use will involve purposeful application to the skin or its use will result in exposure comparable to, for example, that caused by swimming pool additives or pesticide-impregnated fabrics.

A subchronic 90-day dermal toxicity test is not required because Kelthane is not intentionally applied to skin and its use will not result in human exposure comparable to, for example, that caused by swimming pool additives or pesticide-impregnated fabrics.

Subchronic Inhalation Toxicity (163.82-4)

The minimum data requirement for subchronic inhalation toxicity is one test on the technical chemical, preferably using the laboratory rat.

A subchronic inhalation toxicity test is required if pesticidal use may result in repeated inhalation exposure at a concentration that is likely to be toxic, as determined from results of acute inhalation testing.

Technical

An acute inhalation test for Kelthane is not available; therefore, at this time it is not possible to determine if a subchronic inhalation test is needed.

Wettable Powder/Dust

Mice exposed to a 25% dust formulation of Kelthane (0.012 mg/L) for 125 days did not differ from controls for mortality or lung tumor incidence (Leong and Crews 1967; MRID#00004359). However, histopathologic examination of the lungs of 4 (total of 5 animals examined) revealed emphysematous changes; further details were not given.

Subchronic Neurotoxicity (163-82-5)

The minimum data requirement for subchronic neurotoxicity testing is one test for the technical chemical, using either the adult hen or a mammalian species.

A subchronic neurotoxicity test is required if the pesticide has shown positive results in the acute delayed neurotoxicity test or induced irreversible neurological toxicity in a mammalian species.

A subchronic neurotoxicity test is not required because Kelthane does not depress esterase activity, and it is not structurally related to a compound that induces neuropathy or delayed neurotoxicity.

Chronic Testing

Chronic Feeding (163.83.1)

The minimum data requirement for chronic feeding is one test for the technical chemical, preferably using the laboratory rat.

A chronic feeding test is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires the issuance of a food additive regulation, or is likly to result in repeated human exposure over a significant portion of the life span.

The chronic test is required for Kelthane because its uses (application to food crops) require a tolerance.

No data were available to assess the chronic feeding toxicity of technical Kelthane; testing in the laboratory rat is required.

Oncogenicity (163.83-2)

The minimum data requirement for oncogenicity is testing in two mammalian species, preferably the rat and mouse, using the technical chemical.

An oncogenicity test is required if the active ingredient, or any of its metabolites, degradation products, or impurities, is structurally related to a recognized carcinogen or causes a mutagenic effect; requires a tolerance or an exemption from a tolerance; requires the issuance of a food additive regulation; or if pesticidal use is likely to result in repeated human exposure over a significant portion of the life span.

Oncogenicity testing is required for Kelthane because certain use (application to food crops) require a tolerance. Two supplementary oncogenicity tests were conducted using mice and rats (National Cancer Institute 1978; MRID#0000).

Group of 50 B6C3F1 mice were fed diets initially containing 150 or 300 ppm (males), 55 or 110 ppm (females), or 0 ppm (control) Kelthane. Dietary levels were subsequently increased so that the time-weighted average dietary levels for males were 264 or 528 ppm and 122 or 243 ppm for females. (Dosages were increased because there was no indication that the MTD has been attained). The treatment period lasted 78 weeks and was followed by a 14 or 15 week observation period. No effects were observed on food consumption or survival of treated mice when compared to control mice. Mean body weights were decreased in a dose related manner following the 40th week of the study in female mice only. The only lesion with significantly increased incidences in treated groups were hepatocellular carcinomas in males. The incidence of hepatocellular carcinomas in male mice was 3 of 18, 22 of 50, and 35 of [redacted] groups, respectively. These data suggest that Kelthane induces hepatocellular carcinomas in male mice.

526

In another experiment, Osborne-Mendel rats were fed time-weighted diets of 471 or 942 ppm (males) and 380 or 760 ppm (females) and 0 ppm (controls) Kelthane. The treatment period lasted 78 weeks followed by a 34 week observation period. A dose-related decrease in mean body weight was observed thoughout the study. No other effects attributable to Kelthane were reported. These data suggest that Kelthane is not carcinogenic in rats.

These data are not sufficient to characterize the carcinogenic potential of Kelthane. The purity of the "Technical Grade Kelthane" used in these studies was estimated to be 40% and 60%. Impurities could not be accurately identified because of thermal decomposition of the test material during the analytical procedure (gas chromotography). In addition, the test compound liquified to an extent, described as significant, during the second year of the studies. This information suggests that the Kelthane used in these studies decomposed extensively and the failure to determine the composition of the compound prohibit drawing any conclusions. However, these data do indicate that additional oncogenicity testing is required.

Teratogenicity (163.83-3)

The minimum data requirement for teratogenicity is testing is two mammalian species using the technical chemical.

Teratogenicity testing is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires the issuance of a food additive regulation, or is likely to result in significant exposure to females.

Teratogenicity testing is required for Kelthane because certain uses (application to food crops) require a tolerance.

No data were available to assess the teratogenicity of technical Kelthane. Testing in two mammalian species is required.

Reproduction (163.83-4)

The minimum data requirement for reproduction is testing in one mammalian species, preferably the laboratory rat, using the technical chemical and lasting for two generations.

Reproductive testing is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires the issuance of a food additive regulation, or is likely to result in significant human exposure.

Reproductive testing is required for Kelthane because certain uses (application to food crops) require a tolerance.

In a reproduction study, mice were fed diets containing 0, 7, 25, 100, 225 or 500 ppm technical Kelthane (84.8% A.I.) (Brown 1967; MRID#00004424). A summary of results are presented in the following table:

Parameters	Dietary Kelthane concentration, ppm					
	0	7	25	100	225	500
Siblings/litter at birth	9.6	8.8	9.2	9.1	8.5	7.7
Siblings/litters at 21 days	7.6	7.1	7.4	7.7	7.0	6.0
% Mortality at 5 days	16.9	14.8	14.6	12.9	12.7	22.7
% Mortality at 21 days	25.5	24.4	22.8	20.6	25.3	33.8
Average sibling weight, % of control at 21 days	100	102.6	99.8	101.0	96.0	88.7
Fertility Index	97.9	97.2	97.2	97.3	98.0	91.2
Viability Index	84.6	83.2	86.0	87.9	82.4	78.3
Lactation Index	76.5	74.2	81.0	74.0	74.0	67.4

The no effect level in mice is 100 ppm. The effects in the 225 and 500 ppm Kelthane treated groups include reduction in the litter size, reduced survival of offspring until weaning, and reduced body weight of offspring at 21 days of ages. In addition, the fertility, viability and lactation indices were reduced in the 500 ppm group.

In another reproduction study, albino rats were fed diets containing 0, 100, 500 and 1000 ppm Technical Kelthane (purity unspecified) (Experiment 1) or 0, 25, 75 or 225 ppm Technical Kelthane (purity unspecified) (Experiment 2) for two generations (Brown 1965; MRID#00004312). Although this study had numerous deficiencies (i.e., the diet was altered in the middle of both experiments; the reproductive performance of the control animals was unacceptable [The F_2 generations in the first experiment and the F_1 generations in the second experiment both indicate a low rate of fecundity]) the study does suggest that a no-effect-level on rat reproduction was between 100 and 225 ppm; higher levels (500 and 1000 ppm) proposed a severe inpairment of reproductive function (although no histological abnormalities were revealed; the examination included the testes and ovaries) as shown in the following table:

Reproduction study in rats on kelthane (Experiment No. 1)

Generation	Dietary kelthane, ppm	# mated	# litter born	#siblings at birth	5 days	21 days	Average weight (g) at 21 days
F_{1a}	0	26	24	237	190	69(17)[a]	35.3
	100	27	23	221	174	97(6)	28.6
	500	27	8	71	11	11	25.7
	1000	27	1	2	0	0	----
F_{1b}	0	24	16	159	111	75(10)	37.9
	100	21	16	150	109	74(11)	37.6
	500	21	3	22	8	0	----
	1000	21	0	0	0	0	----
F_{2a}	0	21	8	71	21	18	45.8
	100	21	8	82	27	0	----
F_{2b}	0	21	11	116	[illegible]	[illegible]	[illegible]
	100	21	9	90	31	31	87.2

[a]Numbers in parentheses indicate the numbers of animals killed on 5th day after birth to reduce the litter size to 10.

Summary of reproduction study in rats on kelthane (Experiment No. 2)

Generation	Dietary Kelthane, ppm	# mated	# litters born	# sibling at birth	# sibling at 5 day	# sibling at 21 day	Average Weight (g) at 21 days
F_{1a}	0	21	11	85	47	36	43.0
	25	21	9	87	43	28	49.8
	75	21	9	73	50	33	49.8
	225	21	2	13	0	0	----
F_{2a}	0	21	12	105	98	90	96.3
	25	19	11	87	43	34	86.5
	75	21	12	96	58	52	89.6
	225	21	0	0	0	0	----

In summary, the two available reproduction studies (mice and rats) are sufficient to satisfy the data requirement for Kelthane. The NOEL for both mice and rats is 100 ppm.

Mutagenicity

Mutagenicity (163.84.1 through 4)

Although the Agency's mutagenic testing requirements are not final, refer to our proposed Guidelines (FR 43, No. 163, Tues., August 22, 1978) for information concerning the types of studies the Agency is considering.

The following studies are representative and are likely to be required:

1) Microbial point mutation

2) Mammalian *in vitro* point mutation

3) *In vitro* *in vivo* cytogenetics or one of the following: heritable translocation or dominant lethal

4) Primary DNA damage e.g. sister chromated exchange or unscheduled DNA synthesis

Choices within these categories must be accompanied with rationale. Substitutions *will* be considered after discussion with the Agency.

Testing is required.

Metabolism

Metabolism (163.85-1)

The minimun data requirement for metabolism is a single dose using the analytically pure grade of the active ingredient in the radioactively labeled form. In both of the available studies, the unlabeled, rather than the radioactively labeled, chemical was used.

Kelthane was administered to rats in a single intraperitoneal dose of 230 mg/kg (Brown et al. 1969, MRID#05002571). Peak concentration levels were reached in blood, kidney, lung, heart, brain, testis, muscle, and liver in 32 to 40 hours; levels of Kelthane in fat, however, were still increasing at 96 hours. Two metabolites of Kelthane, 4,4'-dichlorobenzophenone (DCB) and 1,1-bis(4-chlorophenyl)-2,2-dichloroehtylene (DDE), were detected in all tissues except brain tissue. In the same study, Kelthane was also administered orally to rats in repeated doses of 75 mg/kg/day for 40 days. After repeated oral dosing, the presence of Kelthane, DDE, and DCB were confirmed in urine, feces, and all tissues (heart, kidney, testes, muscle, lung, fat, and brain). However, in each case, the bulk of the material present was Kelthane; the metabolites were detected only in trace amounts. From this study, it is not possible to tell what percentage of the administered dose of Kelthane is metabolized; it is also not possible to determine what percentages are excreted in urine and feces, or what fraction is retained in tissues and for how long. The kinetics of excretion cannot be determine from the data.

Kelthane accumulated in the body fat when fed to rats at a level of 1, 3.2, 10, or 32 ppm in the diet for 8 weeks (Haag and Larson, MRID#00004304). Cessation of feeding led to a gradual elimination of Kelthane from body fat. Two weeks after cessation of feeding, 75% of the accumulated Kelthane had disappeared from the body fat of males and 40% of the accumulated Kelthane had disappeared from the body fat of females. Eight weeks after cessation of feeding, over 90% of the accumulated Kelthane had disappeared from the body fat of both males and females.

The above information is not sufficient to satisfy the data requirement. Additional testing is required.

Clincal Trials

Report No. 173 of the Pesticide Incident Monitoring System, Office of Pesticides Programs, EPA (1979) cited 78 incidents of Kelthane exposure that were reported to the Pesticide Incident Monitoring System from 1966 to 1979. Of the 78 incidents, 73 involved human exposure, 2 involved domestic animals, and the remaining incidents involved environmental or widlife exposure. Of these reports, 14 involved Kelthane alone and 64 involved Kelthane in combination with other ingredients.

Reports of symptoms were provided for only eight of the cases involving Kelthane alone. Of these eight cases, one involved Kelthane ingestion (amount unspecified) leading to nausea, dizziness, and vomiting; two involved dermal exposure (amount unspecified) resulting in skin irritation in the first case and rash (allergic reaction) in the second case; two involved ocular exposure resulting in conjunctivitis; and three involved inhalation exposure resulting in dizziness, weakness, nausea, and vomiting in two cases and sinus congestion in one case. Although most of these incidents were not fully described, the available data suggested that human exposure to Kelthane can lead to conjunctivitis, skin irritation, and such generalized effects as nausea, vomiting, dizziness, and weakness.

In Price et al. (1972, MRID#05004704), levels of Kelthane in the diet, urine, and feces of 32 girls, aged 7-9 years, were monitored for 20 days using gas-liquid chromatography. The diet consumed over this period was considered typical of lower socioeconomic groups in the southeastern United States. The analysis determined that the daily diet contained from a trace to 1.8 ug of Kelthane, of which a maximum of only 3.12% was recovered in urine and 6.21% was recovered in feces. Dietary supplements of calcium, nitrogen, or ammonium citrate did not affect the levels of Kelthane detectable in the excreta. However, because residues of only the parent compound were measured in excreta, litter information could be concluded regarding the storage or metabolism of Kelthane.

Emergency Treatment

No information on the prevention and treatment of Kelthane intoxication was reviewed.

Appendix

Hazard Indicators	Toxicity Categories I	II	III	IV
Oral LD_{50}	Up to and including 50 mg/kg	From 50-500 mg/kg	From 500-5000 mg/kg	Greater than 5000 mg/kg
Inhalation LC_{50}	Up to and including 0.2 mg/liter	From 0.2-2 mg/liter	From 2-20 mg/liter	Greater than 20 mg/liter
Dermal LD_{50}	Up to and including 200 mg/kg	From 200-2000 mg/kg	From 2,000-20,000 mg/kg	Greater than 20,000 mg/kg
Eye Effects	Corrosive corneal opacity not reversible within 7 days	Corneal opacity reversible within 7 days; irritation persisting for 7 days	No corneal opacity; irritation reversible within 7 days	No irritaiton
Skin Effects	Corrosive	Severe irritation at 72 hours	Moderate irritation at 72 hours	Mild or slight irritation at 72 hours or no effects

Bibliography

Apsokardu, T., and Gilman, M.R. 1973. Report: The Acute Dermal Toxicity Study of Kelthane OM on Abraded and Non-abraded Skin of New Zealand Albino Rabbits. (Unpublished study received October 9, 1973, under 707-114; prepared by Cannon Laboratories, Inc., submitted by Rohm and Haas Co., Philadelphia, Pa.; CDL:050429-A) (MRID#00004354, 15A-0002c)

Apsokardu, T., and Gilman, M.R. 1973. Report: The Effects of Kelthane OM on the Eye Mucosa of New Zealand Rabbits. (Unpublished study received October 9, 1973, under 707-114; prepared by Cannon Laboratories, Inc., submitted by Rohm and Haas Co., Philadelphia, Pa.; CDL:050429-D) (MRID#00004357, 15A-0003c)

Brown, J.R. 1965. Toxicologic Studies on the Effects of Kelthane in the Diet of Albino Rats on Reproduction. (Unpublished study received April 29, 1966, under 6H2025; prepared by University of Toronto, Department of Physiological Hygiene, submitted by Rohm and Haas Co., Philadelphia, Pa.; CDL:221622-R) (MRID#00021671, 15c-0001c)

Brown, J.R. 1965. Toxicologic Studies on the Effects of Kelthane in the Diet of Albino Rats on Reproduction. (unpublished study, including first, second, and third interim reports, received January 28, 1966, under 6F0472; prepared by University of Toronto, Department of Physiological Hygiene, submitted by Rohm and Haas Co., Philadelphia, Pa.; CDL:090524-B) (MRID#00004312, 15A-0004c)

Brown, J.R. 1967. Toxicological Studies on 2,2-Bis(chlorophenyl-2,2,2-trichloroethanol) (Kelthane): The Effect of Dietary Kelthane on Mouse Reproduction. (Unpublished study received on unknown date under PP0590; prepared by Brown Biological Laboratories, Ltd., Canada, submitted by Chevron Chemical Co., Richmond, Calif., CDL:097533-A) (MRID#00004424, 15A-0005c)

Brown, J.R. 1967. Three Generation Reproductive Study on Rats Receiving Technical Kelthane in Their Diet. (Unpublished study received June 19, 1967, under 7F0590; prepared by University of Toronto, Department of Physiological Hygiene, and Brown Biological Laboratories, Ltd., submitted by Rohm and Haas Co., Philadelphia, Pa.; CDL:090757-C) (MRID#000021698, 15C-0002)

Brown, J.R., Hughes, H.P., and Viriyanondha, S. 1969. Storage, distribution, and metabolism of 1,1-bis(4-chlorophenyl)2,2,2-trichloroethanol. Toxicol. Appl. Pharmacol. 15:30-37 (MRID#05002571, 15A-0006)

Gvineriya, I.S., and Sindzharadze, E.A. 1976. [Charcteristics of the effect of Kelthane on the body when inheld.] Sb. Tr. Nauch. Issled. Inst. Gig. Tr. Prof. Tifl. 15:93-100 (Russian) (MRID#05018672, 15A-00041)

Haag, H.B., and Larson, P. 1952? Toxicologic Study on the Effect of Adding FW-293 to the Diet of Rats for a Period of Three Months. (Unpublished study received Februaryl, 1956, under PP0060; prepared by Medical College of Virginia, submitted by Rohm and Haas Co., Philadelphia, Pa; CDL:092340-D) (MRID#00004429, 15A-0036)

Haag, H.B., and Larson, P. 19?? Acute Oral Toxicity of FW-293 (Technical Grade, Lot SW-4807), FW-293 (Pure, Lot W-569), o,p-z-33 (Lot N-1818) and p,p-z-33 (Lot N-1811). (Unpublished study received August 13, 1956, under PP0108; prepared by Medical College of Virginia, submitted by Rohm and Haas Co., Philadelphia, Pa.; CDL:090138-G) (MRID#00004365, 15A-0015c)

Haag, H.B., and Larson, P. 19?? Acute Oral Toxicity of FW-293 (Technical Grade, Lot SW-5508) to Rabbits. (Unpublished study received August 13, 1956, under PP0108; prepared by Medical College of Virginia, submitted by Rohm and Haas Co., Philadelphia, Pa.; CDL:090138-O) (MRID#00004374, 15A-0016c)

Haag, H.B., and Larson, P. 19?? Acute Oral Toxicity of FW-293 to Dogs. (Unpublished study received August 13, 1956, under PP0108; prepared by Medical College of Virginia, CDL:090138-P) (MRID#00004375, 15A-0017c)

Haag, H.B., and Larson, P. 19?? Acute Oral Toxicity of Technical Grade FW-293, Lot 5508, to the Rat. (Unpublished study received August 13, 1956, under PP0108; prepared by Medical College of Virginia, submitted by Rohm and Haas Co., Philadelphia, Pa.; CDL:090138-N) (MRID#00004373, 15A-0019c)

Haag, H.B., and Larson, P. 19?? Storage of Kelthane in the Adipose Tissues of the Rat. (Unpublished study received October 12, 1957, under PP0154; prepared by Medical College of Virginia, submitted by Rohm and Haas Co., Philadelphia, Pa.; CDL:090180-H) (MRID#00004304, 15A-0022c)

Haag, H.B., and Larson, P. 19?? The Acute Percutaneous LD_{50} of Compound FW-293 Technical in Rabbits. (Unpublished study received August 13, 1956, under PP0108, prepared by Medical College of Virginia, submitted by Rohm and Haas Co., Philadelphia, Pa; CDL:090138-H) (MRID#00004366, 15A, 0018c)

Haag, H.B., and Larson, P. 19?? The Effects of the Continued Application of FW-293 Wettable Powder to the Skin of Rabbits. (Unpublished study received August 13, 1956, under PP0108; prepared by Medical College of Virginia, submitted by Rohm and Haas Co., Philadelphia, Pa.; CDL:090138-K) (MRID#00004433, 15A-0021c)

Leong, K.J., and Crews, L.M. 1967. Effects of Chronic Inhalation Exposure to Chemical Vapors and Aerosols. (Unpublished study received January 9, 1978, under 707-76; prepared by Hazelton Laboratories, Inc., submitted by Rohm and Haas Co., Philadelphia, Pa.; CDL:232615-A) (MRID#00004359, 15A-0027c)

National Cancer Institute (NCI). 1978. Bioassay of Dicofol for Possible Carcinogenicity. CAS No. 115-32-2. NCI Carcinogenesis Technical Report Series No. 90, Washington, D.C. DHEW (NIH) Publication No. 78-1340 (MRID# None, 15A-0039)

National Cancer Institute, Carcinogenesis Testing Program. 1978. Bioassay of Sulfallate for Possible Carcinogenicity. By the National Cancer Institute, Carcinogenesis Testing Program, Division of Cancer Cause and Prevention. Bethesda, Md.: National Cancer Institute. (NCI Carcinogenesis Technical Report Series No. 115; DHEW Publication No. (NIH) 78-1370; available from: NTIS, Springfield, VA; PB-286 386; NCI-CG-TR-112; unpaged appendices) (MRID#05020531, 15c-0007)

Pesticide Incident Monitoring System. 1979. Summary of Reported Pesticide Incidents Involving Kelthane: Report No. 173. Human Effects Monitoring Branch, Hazard Evaluation Division, Office of Pesticides Program, Environmental Protection Agency (MRID# None, 15A-0040)

Planche, G., Croisy, A., Malaveille, C., Tomatis, L., and Bartsch, H. 1979. Metabolic and mutagenicity studies on DDT and 15 derivatives. Detection of 1,1-bis(p-chlorophenyl)-2,2-dichloroethane and 1,1-bis(p-chlorophenyl) -2,2,2-trichloroethyl acetate (kelthane acetate) as mutagens in Salmonella typhimurium and of 1,1-bis (p-chlorophenyl) ethylene oxide, a likely metabolite, as an alkylating agent. Chem. Biol. Interact. 25:157-175 (MRID#05016389, 15A-0044)

Terrell, Y., and Gilman, M.R. 1973. Report: The Acute Oral Toxicity Study of Kelthane OM in Rats. (Unpublished study received October 9, 1973, under 707-114; prepared by Cannon Laboratories, Inc., submitted by Rohm and Haas Co., Philadelphia, Pa; CDL:050429-C) (MRID#00004356, 15A-0030c)

WARF Institute, Inc. 1975. Report: WARF No. 4120988. (Unpublished study received May 7, 1975, under 538-134; submitted by O.M. Scott and Sons, Marysville, Ohio; CDL:140169-A) (MRID#00004349, 15A-0032c)

Zavon, M.R. 1964. Diagnosis and treatment of pesticide poisoning. Arch. Environ. Health 9:615-620 (MRID#05017173, 15A-0047)

KELTHANE

Toxicology (see Chapter VI)
XXXXXXXXX Product-Specific Data Requirements for Manufacturing-Use Products

Guideline Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.81-1	Acute Oral Toxicity	(yes)/no	- Y	(yes)/no	00004365; 05001571; 00004414	yes/(no)
163.81-2	Acute Dermal Toxicity	(yes)/no	- Y	(yes)/no	00004366	yes/(no)
163.81-3	Acute Inhalation Toxicity	(yes)/no	- Y	yes/(no)	00004369	(yes)/no
163.81-4	Primary Eye Irritation	(yes)/no Y/	- Y	yes/no	-	yes/no
163.81-5	Primary Dermal Irritation	(yes)/no	- Y	yes/(no)	-	(yes)/no
163.81-6	Dermal Sensitization	(yes)/no	- Y	yes/(no)	-	(yes)/no

Y Technical Grade Active Ingredient

Y/ Based on the primary eye irritation data available on Formulation Intermediates, Technical Kelthane is considered a potentially severe eye irritant.

539

KELTHANE

Toxicology (see Chapter VI)
XXXXXXXXX Product-Specific Data Requirements for Manufacturing-Use Products

Guideline Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.81-7	Acute Delayed Neurotoxicity	yes/(no)	-	yes/no	-	yes/no
163.82-1	Subchronic Oral Toxicity	(yes)/no	- Y	PARTIAL Y yes/no	[illegible]	(yes)/no
163.82-2	Subchronic 21-Day Dermal Toxicity	(yes)/no	- Y	yes/(no)	-	(yes)/no

Y Technical Grade Active Ingredient

Y The rat study is adequate, testing in a second species, preferably dog, is required.

540

KELTHANE

Toxicology (see Chapter VI)
XXXXXXXXX Generic Data Requirements For Manufacturing-Use Products

Guideline Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.82-3	Subchronic 90-day Dermal Toxicity	yes/(no)	-	yes/no	-	yes/no
163.82-4	Subchronic Inhalation Toxicity	yes/no 4	- Y	yes/no	-	yes/no
163.83-1	Chronic Feeding Toxicity	(yes)/no	- Y	yes/(no)	-	(yes)/no
163.83-2	Oncogenicity	(yes)/no	- Y	yes/(no) 3	-	(yes)/no
163.83-3	Teratogenicity	(yes)/no	- Y	yes/(no)	-	(yes)/no
163.83-4	Reproduction	(yes)/no	- Y	(yes)/no	00004424; 00004512	yes/(no)
163.84-2 through -4	Mutagenicity	(yes)/no	- Y	yes/(no)	-	(yes)/no
163.85-1	Metabolism	YES	Y	NO	—	YES

Y Technical Grade Active Ingredient

4 Testicular requirement is pending results from the acute inhalation test.

3 Data available does suggest possible oncogenicity in male mice. However the studies are unacceptable due to extensive decomposition of the test material over the duration of these studies.

Kelthane

Toxicology (see Chapter VI)
XXXXXXXXX Product-Specific Data Requirements for End-Use Products

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
1. Ready-to-Use						
163.81-1	Acute Oral Toxicity	yes/no	- Y	yes/no	- Y	yes/no
163.81-2	Acute Dermal Toxicity	yes/no	- Y	yes/no	- Y	yes/no
163.81-3	Acute Inhalation Toxicity	yes/no Y	- Y	yes/no	-	yes/no
163.81-4	Primary Eye Irritation	yes/no	- Y	yes/no Y	-	yes/no
163.81-5	Primary Dermal Irritation	yes/no	- Y	yes/no	-	yes/no
163.81-6	Dermal Sensitization	yes/no	- Y	yes/no	-	yes/no

Y EACH PRODUCT OR SUBSTANTIALLY SIMILAR PRODUCT

Y BASED ON DATA AVAILABLE FOR THE MANUFACTURING-USE AND FORMULATION INTERMEDIATES (SEE THOSE SECTIONS FOR DETAILS) NO TESTING IS REQUIRED.

Y BASED ON CONFIDENTIAL STATEMENTS OF FORMULA, TESTING WITH THE MANUFACTURING USE PRODUCT WILL BE SUFFICIENT TO MEET THIS REQUIREMENT.

Y BASED ON THE PRIMARY EYE IRRITATION DATA AVAILABLE ON FORMULATION INTERMEDIATES, R-T-U PRODUCTS

5242

Kelthane

Toxicology (see Chapter VI)
XXXXXXXXX Product-Specific Data Requirements for End-Use Products

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
Formulated Intermediate						
2. ~~Technical Grade~~						
163.81-1	Acute Oral Toxicity	(yes)/no	- Y	(yes)/no	00004552	yes/(no)
163.81-2	Acute Dermal Toxicity	(yes)/no	- Y	(yes)/no	00004366	yes/(no)
163.81-3	Acute Inhalation Toxicity	(yes)/no Y	- Y	yes/no	-	yes/no
163.81-4	Primary Eye Irritation	(yes)/no	- Y	(yes)/no	00004357	yes/(no)
163.81-5	Primary Dermal Irritation	(yes)/no	- Y	yes/(no)	-	yes/(no)
163.81-6	Dermal Sensitization	(yes)/no	- Y	yes/(no)	-	yes/(no)

Y Each Product or Substantially Similar Product

Y Based on CSF, Testing with the manufacturing-use product will be sufficient to meet the data requirement.

543

Kelthane

Toxicology (see Chapter VI)
XXXXXXXXX Product-Specific Data Requirements for End-Use Products

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
3. ~~Impregnated Materials~~ Emulsifiable Concentrate						
163.81-1	Acute Oral Toxicity	(yes)/no	- Y	(yes)/no	- 2/	yes/(no)
163.81-2	Acute Dermal Toxicity	(yes)/no	- Y	(yes)/no	- Y	yes/(no)
163.81-3	Acute Inhalation Toxicity	(yes)/no 3/	- Y	yes/no	-	yes/no
163.81-4	Primary Eye Irritation	(yes)/no	- Y	(yes)/no 4/	-	yes/(no)
163.81-5	Primary Dermal Irritation	(yes)/no	- Y	yes/(no)	-	(yes)/no
163.81-6	Dermal Sensitization	(yes)/no	- Y	yes/(no)	-	(yes)/no

Y Each Product or Substantially Similar Product

2/ Based on the available data for the manufacturing use and formulation intermediates (see those sections for details) no testing is required.

3/ Based on CSF, testing with the manufacturing-use product will be sufficient

4/ Based on the primary eye irritation data available on FI, R-T-U products are considered to be corrosive eye irritants.

(4)

Kelthane

Toxicology (see Chapter VI)
XXXXXXXX Product-Specific Data Requirements for End-Use Products

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
9. ~~Wettable Powder~~ W/D						
8. ~~Impregnated Materials~~						
163.81-1	Acute Oral Toxicity	yes/no	- 1/	yes/no	- 2/	yes/no
163.81-2	Acute Dermal Toxicity	yes/no	- 1/	yes/no	- 2/	yes/no
163.81-3	Acute Inhalation Toxicity	yes/no 3/	- 1/	yes/no	-	yes/no
163.81-4	Primary Eye Irritation	yes/no	- 1/	yes/no 4/	-	yes/no
163.81-5	Primary Dermal Irritation	yes/no	- 1/	yes/no	-	yes/no
163.81-6	Dermal Sensitization	yes/no	- 1/	yes/no	-	yes/no

1/ Each Product or Substantially Similar Product

2/ Based on the available data for the manufacturing-use and FI (see those sections for details) no testing is required.

3/ Based on CSF, testing with the manufacturing-use product will be sufficient.

4/ Based on the Primary eye irritation data available on FI, WP/D products are considered to be potential severe eye irritants.

54C1

TOXICOLOGY

A. Disciplinary Review

1. Toxicology Profile

a. Manufacturing - Use Dicofol

There are enough data see Table VI-1 to show that dicofol for manufacturing use has a moderate acute oral toxicity, as shown in

TABLE VI-1

Summary of Acute Oral LD
50 Values (mg/kg) for Manufacturing-use dicofol

psl

Animal	% Active Ingr.	LD 50	Toxicity Cat.	Reference
Rat (M) Rat (F)	unspecified unspecified	809 + 33mg/kg 684 + 16mg/kg	III	Haag and Larson 19?? #00004373
Rat (M)	unspecified	970 + 260mg/kg	III	Haag and Larson 19?? (MRID # 00004365)
Rat (M)	84.8%	1495 mg/kg (95% (CI 1039-2150mg/kg	III	Brown et al. 1969 (MRID #05002571)
Rabbit (M)	unspecified	1810 + 350mg/kg	III	Haag and Larson 19?? (MRID #00004373)

There are sufficient data to shown that dicofol has a relatively high degree of acute dermal toxicity. The dermal LD_{50} is 2.1 + 0.3g/kg in rabbits (Haag and Larson 19??; MRID #00004366), which is Toxicity Category II.

There are no data available on the acute inhalation toxicity of the manufacturing-use formulation; testing is required.

Although no data were available to assess the eye irritation potential of the manufacturing-use product, the results with the formulation intermediate (see Toxicology Profile for End-Use Products) suggest that the manufacturing-use formulation is probably a severe eye irritant. Based on these data, testing of the manufacturing-use formulation is not required and it will be considered a severe eye irritant (Toxicity Category I).

375

There are no data available to assess the dermal irritant or skin senstization potential of the manufacturing-use formulation. Testing is required.

There are insufficient data on the subchronic oral toxicity of manufacturing-use dicofol. The rat study cited above (00004429) indicates that the no-observable-effect level (NOEL) is 20ppm. This study only partially fulfills the subchronic data requirement. A test in a second species (preferably a dog) is required.

There are no adequate data available on the 21-day subchronic dermal toxicity of manufacturing-use dicofol. Testing is required.

There were no adequate data to assess the chronic feeding toxicity of manufacturing-use dicofol. Testing is required.

The available data are insufficient to satisfactorily assess the oncogencity of manufacturing-use dicofol. Two studies were conducted on mice and rats (National Cancer Institute 1978; MRID #GS0021-051). The results suggest that the compound tested can induce hepatocellular carcinoma in male mice. However, the purity of the "technical grade dicofol" used in these studies was estimated to be between 40% and 60%. The impurities could not be accurately identified. In addition, the test compound was reported to have liquified "significantly" during the second year of the studies. This suggests that the dicofol used in these studies decomposed extensively; the failure to determine the composition of the test compound prohibits the drawing of a conclusion based on these results. The data do indicate that additional testing is required.

No data were available to assess the teratogenicity of manufacturing-use dicofol. Testing in two mammalian species is required.

There were two adequate reproduction studies (Brown 1967; MRID #00004424 and Brown 1965; MRID #00004312). In the first study, mice were fed diets containing 0, 7, 25, 100, 225, or 500 ppm of technical dicofol (84.8% active ingredient) through five generations. The data indicate that the no-observable-effect level (NOEL) in 100ppm for mice. In the second study, rats were fed diets containing 0, 25, 75, 100, 500, or 100 ppm of technical dicofol, (purity unspecified) for two generations (0004312). These data also indicated that the NOEL is 100 ppm for rats.

No data were available to assess the mutagenicity of dicofol. Testing is required.

b. <u>End-Use Kelthane Products</u>

There are four types of formulations with substantially similar compositions, according to the Confidential Statements of Formula: formulation intermediates, emulsifiable concentrates, ready-to-use formulations and wettable powder or dusts.

There are sufficent data to demonstrate that these formulations of dicofol have a moderate acute oral toxicity (00004356). The acute oral LD_{50} was 1.52 $\pm$ 0.16g/kg for rats (sex unspecified).

There are sufficient data to show that the acute dermal toxicity of these formulations is moderately high. The acute dermal LD_{50} was estimated to be greater than 3.0 g/kg for male rabbits (#00004354).

There are no data available to assess the acute inhalation toxicity of dicofol formulations. Testing of the manufacturing-use formulation should be sufficient when it is completed.

There are data indicating that the formulation intermediate is a severe irritant to the eyes of rabbits (00004357). Corneal damage in some rabbits with unwashed eyes persisted for 7 days. Based on these data, all formulations are considered corrosive to the eye.

No data were available to assess dermal irritation and dermal sensitization. Testing is required.

c. Generic Data Gaps (See Chapter III for further information)

1) Manufacturing-Use Kelthane

Acute inhalation
Primary dermal irritation
Dermal sensitization
Subchronic oral (dogs)
Subchronic 21-day dermal (rabbits)
Chronic feeding (rats)
Oncogenicity (rats and mice)
Teratology (2 mammalian species)
Mutagenicity
Metabolism

2) End-Use Formulations

Primary skin irritation
Dermal sensitization

2. Toxicity Hazard Assessment

a. Manufacturing-Use Kelthane

The acute oral toxicity of manufacturing-use dicofol is moderate, and the acute dermal toxicity is high. dicofol is a severe eye irritant. There were insufficient data to assess the chronic, oncogenic, mutagenic and teratogenic effects of this chemical.

b. End-Use Kelthane

The formulation intermediates, emulsifiable concentrates, ready-to-use formulations, and wettable powder or dusts are substantially similar in composition. The acute oral and acute dermal toxicities are moderate. dicofol formulations are potential severe eye irritants.

B. Topical Discussions

1. Acute Testing

a. Acute Oral Toxicity (163.81-1)

The minimum data requirements for testing acute oral toxicity (LD_{50}) is one test on the technical chemical and one test on each manufacturing use and formulated product, preferably using the laboratory rat.

1) Technical

Adequate Acute Oral Toxicity Studies were conducted, as shown in Table VI-2.

Table VI-2

Acute Oral Toxicity Studies

Animal	% Active Ingr.	LD 50	Toxicity Cat.	Reference
Rat (M) Rat (F)	unspecified	809 + 33mg/kg 684 + 16mg/kg	III	Haag and Larson 19?? #00004373
Rat (M)	unspecified	970 + ∠60mg/kg	III	Haag and Larson 19?? (MRID # 00004365)
Rat (M)	84.8%	1495 mg/kg (95% (CI 1039-2150mg/kg	III	Brown et al 1969 (MRID #05002571)
Rabbit (M)	unspecified	1810 + 350mg/kg	III	Haag and Larson 19?? (MRID #00004373)

The reported clinical signs of toxicity were weakness and coma; the rabbits also had diarrhea. These data place technical dicofol in Toxicity Category III (See Table VI-6), that is, moderate oral toxicity. Toxicity Category III oral LD_{50} ranges from 500-5000 mg/kg.

2) Formulation Intermediate (FI)

A supplementary acute oral toxicity study was conducted on rats (sex unspecified) gavaged with a 35.5% formulation intermediate dicofol (00004356). The LD_{50} was estimated to be 1.52 + 0.16 g/kg. Clinical signs of toxicity were respiratory distress, piloerection, and lack of coordination. The data suggest that this product has a low acute oral toxicity (Toxicity Category IV).

No data were available on the acute oral toxicity of the formulation intermediates containing other percentages of dicofol. However, since the Confidential Statements of Formula on file in EPA do not indicate an change in the acute oral toxicity, further testing is not required.

3) Emulsifiable Concentrates (EC), Ready to Use (RTU) Wettable Powder/Dust (WP/D)

No data were available on the acute oral toxicity of the dicofol EC's, RTUs, and WP/Ds. However, since the confidential statements of formula on file do not indicate an change in acute oral toxicity, no testing is required.

b. Acute Dermal Toxicity (163.81-2)

The minimum data requirement for testing acute dermal toxicity (LD_{50}) is one test on the technical chemical and one on each manufacturing use and formulated product, preferably using albino rabbits.

1) Technical

An adequate acute dermal toxicity test was conducted (Haag and Larson 19??, MRID #00004366) using male rabbits exposed to a single dose of technical dicofol applied to clipped intact skin. The acute dermal LD_{50} for intact skin was 2.1 + 0.3 g/kg., with death preceded by general weakness and coma. This data is sufficient to satisfy the data requirement and assign Toxicity Category II for acute dermal toxicity (see Table VI-6).

2) Formulation Intermediate (FI)

An adequate acute dermal toxicity study was conducted on male rabbits using a 35.5% dicofol formulation intermediate (00004354). The acute dermal LD_{50} was estimated to be greater than 3.0 g/kg for male rabbits (abraded and unabraded skin). No deaths or clinical signs of toxicity were observed at this dosage. This product should be placed in Toxicity Category III for acute dermal toxicity.

3) Emulsifiable Concentrate (EC), Ready-to-Use (RTU), Wettable Powder/Dust (WP/D)

The available data were not adequate to assess the acute dermal toxicity potential of dicofol EC's, RTU's, and WP/D formulations. However, since the confidential statements of formula on file do not indicate change in acute dermal toxicity, further testing is not required, and these products should considered to be in Toxicity Category II.

c. Acute Inhalation Toxicity (163.81-3)

The minimum data requirement for testing acute inhalation toxicity (LC_{50}) is one test on the technical chemical and one on each manufacturing use and end-use product, preferably using laboratory rats.

An acute inhalation toxicity (LC_{50}) test is required for each formulation if it forms a respirable vapor, or 2) if 20% or more of the aerodynamic equivalent is composed of particles not larger than 10 microns.

379

1) Technical

No data were available to assess the acute inhalation toxicity of technical dicofol. Testing is required.

2) Formulation Intermediate (FI), Emulsifiable Concentrate (EC), Ready-to-Use (RTU)

No data were available to assess the acute inhalation toxicity of dicofol FI's, RTU's and EC's. Since the Confidential Statements of Formula do not indicate an anticipated change in acute inhalation toxicity, testing of technical dicofol should be sufficient.

3) Wettable Powder/Dust(WP/D)

A supplementary acute inhalation toxicity study was conducted on male mice exposed to a chamber concentration of 2.0 mg/liter of 25% dust dicofol for a 6-hour exposure as a preliminary test for chronic inhalation studies (Leong and Crews 1967; MRID #00004359). No deaths were reported. This study is not sufficient to meet the data requirement due to the lack of reporting of methods employed (i.e., methods of measuring chamber concentrations and particle size distribution) and details of the study (lack of individual animal data for pathology, body weight, etc.).

Since the confidential statements of formula do no indicate change in the acute inhalation toxicity, testing of technical dicofol will be sufficient.

d. Primary Eye Irritation (163.81-4)

The minimum data requirement for primary eye irritation is one test on each manufacturing use and one on each formulated product, preferably using albino rabbits. A primary eye irritation study is not required for each formulation that has a pH of 1-3 or 12-14 because these test substances will automatically be considered corrosive to the eye (Toxicity Category I).

1) Technical

No data were available to assess the eye irritation potential of technical dicofol. As for the data available for formulation intermediates, no testing is required. Technical dicofol will be considered a potential severe eye irritant.

2) Formulation Intermediate (FI)

An adequate eye irritation study was conducted (Apsokardu and Gilman 1973; MRID #00004357). Rabbit eyes (washed and unwashed) were treated with 0.1 ml of a 35.5% dicofol FI. The reaction to dicofol treatment in the unwashed eyes was more severe than in the washed eyes. The maximum mean irritation scores were 15/110 and 0/110 for washed eyes and 36/110 and 26/110 for unwashed eyes at 24 hours and 7 days, respectively. Damage to the cornea and conjunctivae was evident at 7 days in all 3 animals whose eyes remained unwashed after treatment. These results are sufficient to place this 35.5% FI in Toxicity Category I, indicating a very severe potential for eye damage.

3) Emulsifiable Concentrate (EC), Ready-to-Use (RTU), Wettable Powder/Dust (WP/D)

No data were available to assess the eye irritation potential of dicofol EC's, RTU's and WP/D's. Testing is not required. These formulations of dicofol will be considered potentially severe eye irritants, Toxicity Category I (see FI section for details).

e. Primary Dermal Irritation (163.81-5)

The minimum data requirement for primary dermal irritation is one test on each manufacturing use and formulated product, preferably using the albino rabbit.

A primary dermal irritation study is not required for each formulation that has a pH of 1-3 or 12-14; a test substance with a pH of 1-3 or 12-14 will be considered corrosive to the skin.

No data were available to assess the dermal irritation potential of technical dicofol. Testing is required for the following categories: technical, formulation intermediate (FI), wettable powder/dust (WP/D), emulsifiable concentrate (EC), and ready-to-use (RTU).

f. Dermal Sensitization (163.81-6)

The minimum data requirement for dermal sensitization is an intradermal test for each manufacturing use and each formulated product, preferably using guinea pigs.

No data were available to assess the dermal sensitization potential of dicofol. Testing is required for the following categories: technical, formulation intermediate, wettable powder/dust, emulsifiable concentrate, and ready-to-use.

g. Acute Delayed Neurotoxicity (163.81-7)

An acute delayed neurotoxicity test is not required for dicofol because dicofol does not depress cholinesterase activity, and it is not structurally related to a compound that induces neuropathy or delayed neurotoxicity.

h. Subchronic Oral Toxicity (163.82-1)

The minimum data requirement for subchronic oral toxicity is one test on the technical chemical in two mammalian species, preferably using rats and dogs.

A subchronic oral toxicity test is necessary if pesticidal use 1) requires a tolerance or an exemption from a tolerance, 2) requires the issuance of a food additive regulation, or 3) is likely to result in repeated human exposure through the oral route.

The subchronic oral toxicity test is required for dicofol because its use (application to food crops) requires a tolerance.

In an adequate subchronic study, male and female rats were fed diets containing 0, 20, 100, 500, 1250 or 2500 ppm of dicofol for 3 months (00004429). High

mortality was observed at the 1250 ppm dose (60% for females and 50% for males); the 2500 ppm dose was terminated at 2 weeks. Weight depression was noted in females receiving 100 ppm or higher while in males it was only in the high dose. Dose related increases were observed in the liver-to-body weight ratios in both male and female rats. However, histopathologic examinations revealed no lesions that could be related to the ingestion of dicofol. Therefore, the NOEL is considered to be 20 ppm.

To complete the data requirement for subchronic oral toxicity, a test is required in dogs.

i. Subchronic 21-Day-Dermal Toxicity (163.82-2)

The minimum data requirement for subchronic 21-day dermal toxicity is one test for the technical chemical, preferably using albino rabbits.

A subchronic 21-day dermal toxicity test is required if pesticidal use is likely to result in repeated human skin contact. This test is required for dicofol because its use could result in repeated human skin contact.

No data were available to assess the subchronic 21-day dermal toxicity of dicofol. Testing is required.

j. Subchronic 90-Day Dermal Toxicity (163.82-3)

The minimum data requirement for subchronic 90-day dermal toxicity is one test for the technical chemical, preferably using albino rabbits.

The subchronic 90-day dermal toxicity test is not required because dicofol is not intentionally applied to skin and its use will not result in human exposure similar to that caused by swimming pool additives or pesticide-impregnated fabrics.

k. Subchronic Inhalation Toxicity (163.82-4)

The minimum data requirement for subchronic inhalation toxicity is one test for the technical chemical, preferably using laboratory rats.

A subchronic inhalation toxicity test is required if pesticidal use may result in repeated inhalation exposure at a concentration that is likely to be toxic, as determined from results of acute inhalation testing.

1) Technical

An acute inhalation test for dicofol is not available; therefore, at this time it is not possible to determine if a subchronic inhalation test is needed. After review of an adequate acute inhalation test, a subchronic test may be required.

2) Wettable Powder/Dust

Five mice exposed to a 25% dust formulation of dicofol (0.012 mg/L) for 125 days did not differ from controls for mortality or lung tumor incidence (Leong and Crews 1967; MRID #00004359). However, histopathologic examination of the

382

lungs of 4 (total of 5 animals examined) revealed emphysematous changes; further details were not given. These data are supplementary only.

1. Subchronic Neurotoxicity (163.82-5)

The minimum data requirement for subchronic neurotoxicity testing is one test for the technical chemical, using either adult hens or a mammalian species.

A subchronic neurotoxicity test is required if the pesticide has shown positive results in the acute delayed neurotoxicity test or induced irreversible neurological toxicity in a mammalian species.

A subchronic neurotoxicity test is not required for dicofol because it does not depress esterase activity, and it is not structurally related to a compound that induces neuropathy or delayed neurotoxicity.

2. Chronic Testing

a. Chronic Feeding (163.83.1)

The minimum data requirement for chronic feeding is one test for the technical chemical, preferably using laboratory rats.

A chronic feeding test is required if pesticide use requires a tolerance or an exemption from a tolerance, requires the issuance of a food additive regulation, or is likely to result in repeated human exposure over a significant portion of the life span. The chronic test is required for dicofol because its uses (application to food crops) require a tolerance.

No data were available to assess the chronic feeding toxicity of technical dicofol; testing in the laboratory rat is required.

b. Oncogenicity (163.83-2)

The minimum data requirement for oncogenicity is testing in two mammalian species, preferably rats and mice, using the technical chemical.

An oncogenicity test is required if the active ingredient, or any of its metabolites, degradation products, or impurities is structurally related to a recognized carcinogen or causes a mutagenic effect, requires a tolerance or an exemption from a tolerance, requires the issuance of a food additive regulation, or if pesticidal use is likely to result in repeated human exposure over a significant portion of the life span.

Oncogenicity testing is required for dicofol because certain uses (application to food crops) require a tolerance. Two supplementary oncogenicity tests were conducted using mice and rats (National Cancer Institute 1978; MRID #0000).

Groups of 50 B6C3F1 mice were fed diets initially containing 150 or 300 ppm (males), 55 or 110 ppm (females), or 0 ppm (controls) dicofol. Dietary levels were subsequently increased so that the time-weighted average dietary levels for males were 264 or 528 ppm and 122 or 243 ppm for females. (Dosages were increased because there was no indication that the maximum tolerated dose (MTD) had been attained). The treatment period lasted 78 weeks and was followed by a

14 or 15 week observation period. No effects were observed on food consumption or survival of treated mice when compared to control mice. In female mice only, mean body weights were decreased in a dose-related manner following the 40th week of the study. The only lesion with significantly increased incidences of hepatocellular carcinomas was in males. The incidence of hepatocellular carcinomas in male mice was 3 of 18, 22 of 50, and 35 of 47 in controls, low, and high dose groups, respectively. These data suggest that the compound tested induces hepatocellular carcinomas in male mice.

In the other part of the study, Osborne-Mendel rats were fed time-weighted diets of 471 or 942 ppm (males) and 380 or 760 ppm (females) and 0 ppm (controls) dicofol. The treatment period lasted 78 weeks followed by a 34-week obervation period. A dose-related decrease in mean body weight was observed thoughout the study. No other effects attributable to dicofol were reported. These data suggest that the compound tested is not carcinogenic in rats.

These data are not sufficient to characterize the carcinogenic potential of dicofol. The purity of the "technical grade dicofol" used in these studies was estimated to be 40% - 60%. The impurities could not be accurately identified because of reported thermal decomposition of the test material during the analytical procedure (gas chromatography). In addition, the test compound was reported to have liquified to a "significant" extent during the second year of the studies. These data do indicate, however, that additional oncogenicity testing is required.

c. Teratogenicity (163.83-3)

The minimum data requirement for teratogenicity is testing in two mammalian species using the technical chemical.

Teratogenicity testing is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires the issuance of a food additive regulation, or is likely to result in significant exposure to females.

Teratogenicity testing is required for dicofol because certain uses (application to food crops) require a tolerance.

No data were available to assess the teratogenicity of technical dicofol. Testing in two mammalian species is required.

d. Reproductive Testing (163.83-4)

The minimum data requirement for assessing reproductive effects is testing the technical chemical in one mammalian species, preferably laboratory rat, for two generations.

Reproductive testing is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires the issuance of a food additive regulation, or is likely to result in significant human exposure.

Reproductive testing is required for dicofol because certain uses (application to food crops) require a tolerance.

In a two-generation reproduction study, mice were fed diets containing 0, 7, 25, 100, 225, or 500 ppm technical dicofol (84.8% active ingredient (00004424). A summary of results are presented in Table VI-3:

Tabel VI-3

Two generation Reproduction Study (Mice)

	Dietary kelthane concentration, ppm					
Parameters	0	7	25	100	225	500
Siblings/litter at birth	9.6	8.8	9.2	9.1	8.5	7.7
Siblings/litter at 21 days	7.6	7.1	7.4	7.7	7.0	6.0
% Mortality at 5 days	16.9	14.8	14.6	12.9	12.7	22.7
% Mortality at 21 days	25.5	24.4	22.8	20.6	25.3	33.8
Average sibling weight, % of control at 21 days	100	102.6	99.8	101.0	96.0	88.7
Fertility Index	97.9	97.2	97.2	97.3	98.0	91.2
Viability Index	84.6	83.2	86.0	87.9	82.4	78.3
Lactation Index	76.5	74.2	81.0	74.0	74.0	67.4

The no-effect level in mice is 100 ppm. The effects in the 225 and 500 ppm dicofol-treated groups include reduction in the litter size, reduced survival of offspring until weaning, and reduced body weight of offspring at 21 days. In addition, the fertility, viability, and lactation indices were reduced in the 500 ppm group.

In another two-generation reproduction study, albino rats were fed diets containing 0, 100, 500, and 1000 ppm technical dicofol (Experiment 1) or 0, 25, 75 or 225 ppm technical dicofol (Experiment 2) for two generations (00004312). This study has numerous deficiencies. The purity of the dicofol used was not specified. The diet was altered in the middle of both experiments; the reproductive performance of the control animals was unacceptable. The F_2 2 generation in the first experiment and the F_1 generation in the second experiment both indicate a low rate of fecundity. Nevertheless, the study does suggest that a no-observable-effect-level (NOEL) on rat reproduction was between 100 and 225 ppm. Higher levels (500 and 1000 ppm) proposed a severe impairment of reproductive function (although no histological abnormalities were revealed; the examination included the testes and ovaries) as shown in Tables VI-4 and VI-5.

Table VI-4

Reproduction Study in Rats on Kelthane (Experiment No. 1)

Generation	Dietary dicofol, ppm	# mated	# litter born	# siblings at birth	5 days	21 days	Average weight at 21 days
F_{1a}	0	26	24	237	190	69(17) a/	35.3
	100	27	23	221	174	97(6)	28.6
	500	27	8	71	11	88	25.7
	1000	27	1	2	0	0	——
F_{1b}	0	24	16	159	111	75(10)	37.9
	100	21	16	150	109	74(11)	37.6
	500	21	3	22	8	0	——
	1000	21	0	0	0	0	——
F_{2a}	0	21	8	71	21	18	45.8
	100	21	9	82	27	0	——
F_{2b}	0	21	11	116	25	20	79.8
	100	21	9	90	31	31	87.2

a/ Numbers in parentheses indicate the numbers of animals killed on 5th day after birth to reduce the litter size to 10.

Table VI-5

Summary of Reproduction Study in Rats on Kelthane (Experiment No. 2)

Generation	Dietary dicofol ppm	# mated	# litters born	#sibling at birth	5 day	21 day	Average Weight(g) at 21 days
F_{1a}	0	21	11	58	47	36	43.0
	25	21	9	87	43	28	49.8
	75	21	9	73	50	33	49.8
	225	21	2	13	0	0	——
F_{2a}	0	21	12	105	98	90	96.3
	25	21	11	87	43	34	86.5
	75	21	12	96	58	52	89.6
	225	21	0	0	0	0	——

In summary, the two available reproduction studies (mice and rats) are sufficient to satisfy the data requirement for dicofol. The NOEL for mice and for rats is 100 ppm.

3. Mutagenicity

Mutagenicity (163.84.1 through 4)

Although the Agency's mutagenic testing requirements are not final, proposed Guidelines (FR 43, No. 163, Tues., August 22, 1978) show the types of studies the Agency is considering.

The following studies are representative and are likely to be required: 1) microbial point mutation; 2) mammalian *in vitro* point mutation; 3) *in vitro*, *in vivo* cytogenetics or either heritable translocation or dominant lethal; 4) primary DNA damage (e.g., sister chromatid exchanges or unscheduled DNA synthesis).

Choices within these categories must be accompanied with a rationale. Substitutes will be considered after discussion with the Agency.

Testing is required.

4. Metabolism

Metabolism (163.85-1)

The minimum data requirement for metabolism is a single dose study using radiolabeled, analytically pure grade of the active ingredient. In both of the

387

available studies, the unlabeled rather than the radiolabeled chemical was used.

Unlabelled dicofol (purity unspecified) was administered to rats in a single intraperitoneal dose of 230 mg/kg (Brown et al. 1969, MRID #05002571). Peak concentration levels were reached in blood, kidney, lung, heart, brain, testis, muscle, and liver in 32 to 40 hours; levels of dicofol in fat, however, were still increasing at 96 hours. DCBP, (4,4'-dichlorobenzophenone), and DDE (1,1-bis-(4-chlorophenyl)-2,2-dichloroethylene) were detected in all tissues except brain tissue. In this same study, dicofol was also administered orally to rats in repeated doses of 75 mg/kg/day for 40 days. After repeated oral dosing, the presence of dicofol, DDE, and DCBP were confirmed in urine, feces, and all tissues (heart, kidney, testes, muscle, lung, fat, and brain). However, in each case, the bulk of the material present was dicofol; the other materials were detected only in trace amounts. From this study, it is not possible to tell what percentage of the administered dose of dicofol is metabolized; it is also not possible to determine what percentages are excreted in urine and feces, or what fraction is retained in tissues and for how long. The kinetics of excretion cannot be determined from the data.

Dicofol accumulated in the body fat when fed to rats at a level of 1, 3.2, 10, or 32 ppm in the diet for 8 weeks (Haag and Larson, MRID #00004304). Cessation of feeding led to a gradual elimination of dicofol from body fat. Two weeks after cessation of feeding, 75% of the accumulated dicofol had disappeared from the body fat of males and 40% of the accumulated dicofol had disappeared from the body fat of females. Eight weeks after cessation of feeding, over 90% of the accumulated dicofol had disappeared from the body fat of both males and females.

The information is not sufficient to satisfy the data requirement. Additional testing is required.

5. Clinical Trials

Report No. 173 of the Pesticide Incident Monitoring System, Office of Pesticides Programs, EPA (1979) cited 78 incidents of dicofol exposure that were reported to the Pesticide Incident Monitoring System from 1966 to 1979. Of the 78 incidents, 73 involved human exposure, 2 involved domestic animals, and the remaining involved environmental or wildlife exposure. Of these reports, 14 involved dicofol alone and 64 involved dicofol in combination with other ingredients.

Reports of symptoms were provided for only eight of the cases involving dicofol alone. Of these eight cases, one involved dicofol ingestion (amount unspecified) leading to nausea, dizziness, and vomiting; two involved dermal exposure (amount unspecified) resulting in skin irritation in the first case and rash (allergic reaction) in the second case; two involved ocular exposure resulting in conjunctivitis; and three involved inhalation exposure resulting in dizziness, weakness, nausea, and vomiting in two cases and sinus congestion in one case. Athough most of these incidents were not fully described, the available data suggest that human exposure to dicofol can lead to conjunctivitis, skin irritation, and such generalized effects as nausea, vomiting, dizziness, and weakness.

In Price et al. (1972, MRID #05004704), levels of dicofol in the diet, urine, and feces of 32 girls, aged 7 to 9 years, were monitored for 20 days using gas-liquid chromatography. The diet consumed over this period was considered typical of lower socioeconomic groups in the southeastern United States. The analysis determined that the daily diet contained from a trace to 1.8 ug of dicofol, of which a maximum of only 3.12% was recovered in urine and 6.21% was recovered in feces. Dietary supplements of calcium, nitrogen, or ammonium citrate did not affect the levels of dicofol detectable in the excreta. However, because residues of only the parent compound were measured in excreta, little could be concluded regarding the storage or metabolism of dicofol.

6. Emergency Treatment

No information on the prevention and treatment of dicofol intoxication was reviewed.

Table VI-6

Kelthane Toxicity Category Indicators

Hazard Indicators	Toxicity Categories I	II	III	IV
Oral LD_{50}	Up to and including 50 mg/kg	From 50-500 mg/kg	From 500-5000 mg/kg	Greater than 5000 mg/kg
Inhalation LC_{50}	Up to and including 0.2 mg/liter	From 0.2-2 mg/liter	From 2-20 mg/liter	Greater than 20 mg/liter
Dermal LD_{50}	Up to and including 200 mg/kg	From 200-2000 mg/kg	From 2,000-20,000 mg/kg	Greater than 20,000 mg/kg
Eye Effects	Corrosive corneal opacity no reversible within 7 days	Corneal opacity reversible within 7 days; irritation persisting for 7 days	No corneal opacity; irritation reversible within 7 days	No irritation
Skin Effects	Corrosive	Severe irritation at 72 hours	Moderate irritation at 72 hours	Mild or slight irritation at 72 hours or no effects