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TOXICOLOGY ENDPOINT SELECTION DOCUMENT: last revision October 1994

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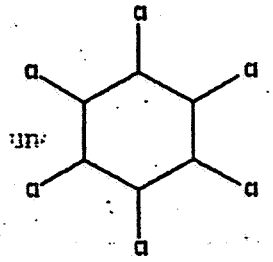
Chemical Name: **Lindane**



PC Code: **009001**

Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

Reviewer: Marion Copley Marion Copley Date: 10/4/94

Branch Chief: Karl Baetcke Karl D. Baetcke Date: 10/4/94

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Dermal Absorption Data

MRID: 40056107

% absorbed: Since the absorption into the body is dependent on the time and dose applied, the dermal absorption should be determined using the anticipated exposure magnitude and duration in conjunction with the following table.

Percent Dermal Absorption by Rats Based on Exposure and Duration

Applied dose/rat (mg/kg)[1]	Exposure Duration		
	4 hr	10 hr	24 hours
0.1 mg (.25 mg/kg)	10.1	18.1	27.7%
1.0 mg (2.5 mg/kg)	5.3	8.3	20.9%
10.0 mg (25 mg/kg)	2.0	2.8	5.0%

NOTE: A human dermal absorption study (published in Toxicology and Applied Pharmacology. 27:(1974), H.Maibach and RJF) states that 9.3±3.7 % of lindane applied as an acetone solution was absorbed from human forearms (HED Doc. # 004704). The above table is not inconsistent with the human data. The human data is limited with respect to dose and duration.

Based on the expected exposure scenarios the most appropriate rate of dermal absorption is considered to be 10 %.

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[1] This assumes a 400 kg rat (age and weight were not presented in the DER).

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Acute Dietary Endpoint (One Day)

Studies Selected - Guideline No.:

Developmental rat study (83-3a)

MRID: 42808001

Summary:

In a developmental rat study lindane was administered to CFY (derived from Charles River CD) rats by gavage from days 6 through 15 of pregnancy at doses of 0, 5, 10 or 20 mg/kg/day.

Maternal toxicity was observed at 10 and 20 mg/kg/day based on decreased body weight and weight gain (13 and 23 % decrease for mid and high dose animals during treatment) and food consumption. There were 2 deaths at 20 mg/kg/day. **The LEL for maternal toxicity is 10 mg/kg/day based on decreased body weight and food consumption. The NOEL for maternal toxicity is 5 mg/kg/day.**

Developmental toxicity was observed at 10 mg/kg/day and consisted of an increase in pups and litters with 14th ribs (12.7, 21.0, 31.7 and 40 % ($p<0.05$) of the litters effected, controls to high dose) and total pups affected with skeletal variations. **The developmental LEL is 20 mg/kg/day based on increased incidence of 14th ribs and skeletal variations. The developmental NOEL is 10 mg/kg/day. (RfD document-8/25/93).**

This study (when taken together with another study) is classified core-minimum data for developmental toxicity in the rat (83-3b) and satisfies the guideline requirements.

Endpoint and dose for use in risk assessment:

none

Comments about study and/or endpoint:

It was concluded in an internal HED meeting on 12/20/93 that the endpoints in the above developmental study (including death of the dams) were not appropriate for acute dietary risk assessment since more than one dose appeared to be necessary for toxicity to occur.

This risk assessment is not required. No end point was identified from the data base which indicated the potential for adverse effects after a single dietary exposure.

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Short Term Occupational or Residential Exposure (1 to 7 Days)

Developmental rat study (83-3a)

MRID: 42808001

Summary:

In a developmental rat study lindane was administered to CFY (derived from Charles River CD) rats by gavage from days 6 through 15 of pregnancy at doses of 0, 5, 10 or 20 mg/kg/day.

Maternal toxicity was observed at 10 and 20 mg/kg/day based on decreased body weight and weight gain (13 and 23 % decrease for mid and high dose animals during treatment) and food consumption. There were 2 deaths at 20 mg/kg/day. **The LEL for maternal toxicity is 10 mg/kg/day based on decreased body weight and food consumption. The NOEL for maternal toxicity is 5 mg/kg/day.**

Developmental toxicity was observed at 20 mg/kg/day and consisted of an increase in pups and litters with 14th ribs (12.7, 21.0, 31.7 and 40.8 % ($p < 0.05$)of the litters effected, controls to high dose) and total pups affected with skeletal variations. **The developmental LEL is 20 mg/kg/day based on increased incidence of 14th ribs and skeletal variations. The developmental NOEL is 10 mg/kg/day. (RfD document- 8/25/93).**

This study (when taken together with another study) is classified core-minimum data for developmental toxicity in the rat (83-3b) and satisfies the guideline requirements.

Endpoint and dose for use in risk assessment:

The endpoint for short term occupational or residential risk assessment determined to be appropriate for this exposure scenario is the developmental and maternal* NOEL, 10 mg/kg/day, from the rat developmental study. The LEL, 20 mg/kg/day, is based upon skeletal defects and maternal death. It should be noted that dermal absorption should be taken into account.

Comments about **study and/or endpoint:**

* Maternal effects (decreased weight gain and food consumption) noted at the study maternal LEL, 10 mg/kg/day, are not considered to be appropriate endpoints for this exposure scenario.

This risk assessment **is required.** Dermal absorption should be taken into account (page 2).

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Intermediate Term Occupational or Residential (1 Week to Several Months)

Study Selected - Guideline No.:

1) 90 day dermal rat (82-4)

MRID: 40821701

Summary:

In a 90 day dermal study in Wistar strain rat Crl:(WI)BR rats, lindane was administered at doses of 0, 10, 60 or 400 mg/kg/day.

Systemic toxicity was observed at 60 mg/kg/day and above based on increased liver weight, centrilobular hypertrophy of the liver, increased serum cholesterol and minor behavioral changes. Body weight was increased in both sexes. Deaths in the high dose females may have been due to treatment.

2) 90 day dermal rabbit (82-4)

MRID: 41427301

Summary:

In a 90 day dermal study in NZW rabbits, lindane was administered at doses of 0, 10, 60 and 320/350/400 mg/kg/day (doses were decreased in the high dose due to excessive toxicity).

Systemic toxicity was observed at 60 mg/kg/day and above based on hepatocellular centrilobular hypertrophy (males and females) and adrenal weight increases (male). At 320/350/400 mg/kg/day there were tremors and deaths, body weight decreases, alterations in RBC-parameters, and increased alkaline phosphatase and/or SGPT. The LEL is 60 mg/kg/day based on hepatic and adrenal changes. The NOEL is 10 mg/kg/day.

Endpoint and dose for use in risk assessment:

The endpoint for short term occupational or residential risk assessment is the NOEL (10 mg/kg/day) from the 90 day dermal rat and rabbit studies. The LEL (60 mg/kg/day) from these studies were based primarily on liver changes in both species.

Comments about study and/or endpoint:

It should be noted that in the rat study, renal lesions attributed to a2u-globulin are observed at all doses but are considered inappropriate for risk assessment purposes to humans. These are not noted in the rabbit study.

This risk assessment is required.

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Cancer Classification and Basis:

Lindane has not been classified by the HED Cancer Peer Review Committee. It was determined by the RfD/Peer Review Committee (8/25/93) that: "The mouse carcinogenicity data were considered insufficient because of major deficiencies associated with all studies available." Lindane however had been previously classified by the Cancer Assessment Group of the Office of Research and Development (memorandum dated 7/23/85 from R.E. McGaughy to Anne Barton) as a group B2/C carcinogen based on increased incidence of mouse liver tumors. The upper-bound slope of the dose-response was given in that memorandum as $Q1^* = 1.1\ (mg/kg/day)^{-1}$.

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RfD and Basis: The RfD is 0.0047 mg/kg/day based on a NOEL of 0.47 mg/kg/day (10 ppm). The LEL was 4.81 mg/kg/day based on systemic effects (periacinar hepatocyte hypertrophy, increased liver and spleen weight and increased platelets). (HED RfD document - 8/25/93)

NOEL for critical study: 0.47 mg/kg/day

Study Type - Guideline No.: Chronic/onco feeding study in the rat (83-5)

MRID: 41858701, 42871201

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Acute Toxicity Categories

STUDY TYPE	CATEGORY	RESULT
81-1 Acute oral (MRID 00049330)	II	LD_{50} 88 mg/kg - males 91 mg/kg - females
81-2 Acute dermal (MRID 00109141)	II	LD_{50} 1000 mg/kg - males 900 mg/kg - females
81-3 Acute inhalation (Acc. 263946)	III	LC_{50} 1.56 mg/L both sexes
81-4 Eye irritation (Acc. 263946)	III	PIS = 0.6 no corneal involvement irritation cleared after 24 hours
81-5 Dermal irritation (Acc. 263946)	IV	PIS = 0 not an irritant
81-6 Dermal sensitization (Acc. 263946)	NA	not a sensitizer

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