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Circuit # 532

OFFICE OF PESTICIDES AND TOXIC SUBSTANC

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MEMORANDOM

Subject: Paradichlorobenzene, Toxicology Chapter of the Registration Standard

To: Walter C. Francis PM
Registration Division (TS-767)

From: Robert P. Zendzian PhD 11/18/86
Pharmacologist
Mission Support Staff
Toxicology Branch, HED (TS-769)

Through: Robert P. Zendzian PhD 11/18/86
Registration Standard Coordinator
Toxicology Branch

William Burnam, Deputy Chief 11/18/86
Toxicology Branch

Attached is the Toxicology Chapter of the Registration Standard for Paradichlorobenzene.

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Zendzian
Coberly

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Toxicology Chapter

of the

Paradichlorobenzene

Registration Standard

Prepared by

Robert P. Zendzian PhD
Pharmacologist
Mission Support Staff
Toxicology Branch, HED
November 18, 1986

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A. Toxicology Summary

Paradichlorobenzine, the active ingredient of mothballs, is largely used for killing moths and their larvae, roaches and other household insects; for preserving furs, woolen clothes and rugs; in household and toilet deodorizers; and for soil fumigation. It is supplied as solid balls, flakes and cakes, usually of 99% paradichlorobenzene.

The compound is volatile (sublimes easily) so that the usual route of exposure is by inhalation. About 50 million pounds are used domestically, about 40 million by consumers (10-17 million pounds for moth control, 13 million pounds for toilet deoderant and 9 million pounds for garbage pail deodorant).

Approximately 30,000 workers are exposed in production processing and commercial application. An estimated minimum of 50 million persons are exposed to household uses of paradichlorobenzene.

No toxicological data are available on paradichlorobenzene. Considering the widespread human exposure to this compound a complete toxicological data base is required.

Paradicholorobenzene has been identified as oncogenic in two studies performed by the National Toxicology Program. These studies were 2-year gavage studies in Fisher 344 rats and $B6C3F_1$ mice. Tubular cell adenocarcinomas of the kidney were observed in male rats. Tumors of the liver in male and female mice and of the adrenal gland in male mice were observed.

The Office of Toxic Substances (OTS) of the EPA has the lead in evaluating the data on the oncogenicity of paradichlorobenzene. Results of this evaluation will be provided as they become available.

B. Toxicology Profile

81 Series Acute toxicity and Irritation Studies

81-1 Acute Oral

No data are available on the acute oral toxicity of paradichlorobenzene. A study is required.

81-2 Acute Dermal

No data are available on the acute dermal toxicity of paradichlorobenzene. A study is required.

81-3 Acute Inhalation

No data are available on the acute inhilation toxicity of paradichlorobenzene. A study is required.

81-4 Primary Eye Irritation

No data are available on the primary eye irritation properities of paradichlorobenzine. A study is required.

81-5 Primary Dermal Irritation

No data are available on the primary dermal irritation properities of paradichlorobenzine. A study is required.

81-6 Dermal Sensitization

No data are available on the primary dermal sensitization properities of paradichlorobenzine. A study is required.

81-7 Acute Delayed Neurotoxicity

No data are available on the acute neurotoxic effects of paradicholorobenzene. This test is required only for compounds which are organophosphate inhibitors of cholinesterase, or related to such inhibitors or metabolites of such inhibitors. Paradicholorobenzene is not an organophosphate, therefore, a study is not required.

82 Series Subchronic Testing

82-1 Subchronic Oral

No data are available on the subchronic oral toxicity of paradichlorobenzene. Studies are required in rodent and nonrodent.

82-2 Subchronic Dermal (21-day)

No data are available on the subchronic dermal toxicity of paradichlorobenzene. A study is required.

82-3 Subchronic Dermal (90-day)

No data are available on the 90-day subchronic dermal toxicity of paradichlorebenzene. Based on our present knowledge of the exposure to this compound no study is required.

82-4 Subchronic Inhalation

No data are available on the subchronic inhalation toxicity of paradichlorbenzene. A study is required.

82-5 Subchronic Neurotoxicity

No data are available on the subchronic neurotoxicity of paradichlorobenzene. Since an acute neurotoxicity study is not required and there is no evidence of neurotoxicity in mammalian species, this study is not required.

83 Series Chronic and Long Term Studies

83-1 Chronic Toxicity

No data are available on the chronic toxicity of paradichlorobenzene. Studies are required in the rodent and nonrodent species. Since the major route of exposure to this compound is by the inhalation route, chronic inhalation studies are required.

83-2 Oncogenicity

No data are available on the oncogenic potential of paradichlorobenzene. Studies are required in two species. Since the major route of exposure to this compound is by the inhalation route, inhalation studies are required.

83-3 Teratogenicity

No data are available on the teteratogenic potential of paradichlorobenzene. Studies are required in two species. Since the major route of exposure to this compound is by the inhalation route, inhalation studies are required.

83-4 Reproduction

No data are available on the reproductive toxicity of of paradichlorobenzene. A study is required. Since the major route of exposure to this compound is by the inhalation route, an inhalation study is required.

84 Series Mutagenicity

84-2 Mutagnicity Tests.

No data are available on the mutagenic potential of paradichlorobenzene. Studies are required.

85 Series Special Studies

85-1 Metabolism

No data are available on the metabolism of paradichlorobenzene. A study is required. Since the major route of exposure to this compound is by the inhalation route, an inhalation study is required.

B. Data Gaps

Paradichlorobenzene is registered for numerous uses providing direct and long term exposure to humans in the household. Therefore the following Guideline toxicology studies are required for registration.

81-1 Acute Oral
81-2 Acute Dermal
81-3 Acute Inhalation
81-4 Primary Eye Irritation
81-5 Primary Dermal Irritation
81-6 Dermal Sensitization

82-1 Subchronic Oral, two species
82-2 Subchronic Dermal (21-day)
82-4 Subchronic Inhalation

83-1 Chronic Toxicity, two species (by the inhalation route)
83-2 Oncogenicity, two species (by the inhalation route)
83-3 Teratogenicity, two species (by the inhalation route)
83-4 Reproduction, (by the inhalation route)

84-2 Mutagnicity Tests.

85-1 Metabolism (by the inhalation route)

Based on this assesment of the toxicology data base all of the above listed Guideline toxicology studies have been identified as data gaps and are required.

C. Tolerances and Tolerance Reassesment

No tolerances have been established for paradichlorobenzene.

D. Toxicological Issues

Paradicholorobenzene has been identified as oncogenic in two studies performed by the National Toxicology Program. These studies were 2-year gavage studies in Fisher 344 rats and $B6C3F_1$ mice (MRD RZ001) .

Fifty Fisher 344 rats per sex per dose were dosed orally by gavage at 0, 150 and 300 mg/kg/day for males and 0, 300 and 600 mg/kg/day for females. Test compound was administered in corn oil. The results of this study are quoted from the abstract of the NTP report.

"Administration of 1,4-dichlorobenzene to male rats increased the average severity of nephropathy and caused epithelial hyperplasia of the renal pelvis (1/50; 30/50; 32/50), mineralization of the collecting tubules in the renal medulla (4/50; 46/50; 47/50) and focal hyperplasia of renal tubular epithelium (0/50; 1/50; 9/50). There were dose-related increased incidences of nephropathy in female rats receiving 1,4-dichlorobenzene compared with vehicle control rats (21/49; 32/50; 41/49). 1,4-dichlorobenzene produced a dose-related increase in the incidence of tubular cell adenomas of the kidney in male rats (1/50; 3/50; 7;50); one tubular cell adenoma was observed in a high dose male rat. There were no tubular cell tumors in dosed or vehicle control female rats. There was a marginal increase in the incidence of mononucear cell leukemia in doses male rats compared with that in vehicle controls (5/50; 7/50; 11/50)."

Fifty $B6C3F_1$ mice/sex/dose were dosed orally by gavage at 0, 300 and 600 mg/kg/day. Test compound was administered in corn oil. The results of this study are quoted from the abstract of the NTP report.

"1,4-dichlorobenzene increased the incidences of nonneoplastic lesions in male and female mice, including alteration in cell size (cytomegaly and karyomegaly), hepatocellular degeneration, and individual cell necrosis. 1,4-dichlorobenzene increased the incidences of nephropathy in male mice and renal tubular regeneration in female mice. 1,4-dichlorobenzene increased the incidences of hepatocellular carcinomas in high dose male mice (14/50; 11/49/; 31/50) and high dose female mice (10/50; 6/48; 21/50). Hepatoblastomas were observed in four high dose male mice but not in vehicle controls. An increase in thyroid gland follicular cell hyperplasia was observed in dosed male mice (1/47; 4/48; 10/47), and there was a marginal positive trend in the

incidence of follicular cell adenomas of the thyroid gland in female mice (1/47; 4/48; 10/47). Pheochromocytomas (benign or malignant, combined) of the adrenal gland occured with a positive trend in dosed male mice, and the incidence in the high dose group was significantly greater than that in the vehicle controls (0/47; 2/48/; 4/49). The incidence of adrenal gland medullary hyperplasia was 2/47; 4/48 and 4/49 in male mice. Focal hyperplasia of the adrenal gland was also observed in dosed male mice (11/47; 21/48 and 28/49)."

The Office of Toxic Substances (OTS) of the EPA has the lead in evaluating the data on the oncogenicity of paradichlorobenzene. Results of this evaluation will be provided as they become available.

TABLE A
GENERIC DATA REQUIREMENTS FOR PARADICHLOROBENZENE

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology					
ACUTE TESTING:					
81-1 - Acute Oral - Rat	TGAI		No		Yes
81-2 - Acute Dermal -	TGAI		No		Yes
81-3 - Acute Inhalation - Rat	TGAI		No		Yes
81-4 - Eye Irritaion - Rabbit	TGAI		No		Yes
81-5 - Dermal Irritation - Rabbit	TGAI		No		Yes
81-6 - Dermal Sensitization - Guinea Pig	TGAI		No		Yes
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI		No		No 4/
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding -					
Rodent	TGAI		No		Yes
Non-rodent	TGAI		No		Yes

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§158.135 Toxicology (Cont.)					
82-2 - 21-Day Dermal-	TGAI		No		Yes
82-3 - 90-Day Dermal-	TGAI		No		No
82-4 - 90-Day Inhalation -	TGAI		No		Yes
82-5 - 90-Day Neurotoxicity-	TGAI		No		No 5/
CHRONIC TESTING:					
83-1 - Chronic Toxicity -					
Rodent	TGAI		No		Yes 6/
Non-rodent	TGAI		No		Yes 6/
83-2 - Oncogenicity Study -					
Rat	TGAI		No		Yes 6/
Mouse	TGAI		No		Yes 6/
83-3 - Teratogenicity -					
Rat	TGAI		No		Yes 6/
Rabbit	TGAI		No		Yes 6/
83-4 - Reproduction -	TGAI		No		Yes 6/

TABLE A
GENERIC DATA REQUIREMENTS FOR PARADICHLOROBENZENE

Data Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology (continued)					
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI		No		Yes
84-2 - Chromosomal Aberration	TGAI		No		Yes
84-2 - Other Mechanisms of Mutagenicity	TGAI		No		Yes
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA		No		Yes 6/

1/ Composition: TGAI Technical Grade Active Ingredient; PAI = Pure Active Ingredient; PAIRA = Pure Active Ingredient, RAdiolabelled; Choice = Choice of several test substances determined on a case-by-case basis.
2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C = Aquatic, Food Crop; D = Aquatic, Non-Food; E = Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor; IP = Industrial Preservative.
3/ Unless otherwise specified data must be submitted no later than six months after publication of this Standard
4/ This test is required only for compounds which are organophosphate inhibitors of cholinesterase, or related to such inhibitors or metabolites of such inhibitors. Paradicholorobenzene is not an organophosphate, therefore, a study is not required.
5/ Since an acute neurotoxicity study is not required for this compound and there is no evidence of neurotoxicity in mammalian species, this study is not required.
6/ These studies are to be performed by the inhalation route.

TABLE B
PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING PARADICHLOROBENZENE

Data Requirement	Composition 1/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 2/
§158.135 Toxicology				
ACUTE TESTING				
81-1 - Acute Oral - Rat	MP	No		Yes
81-2 - Acute Dermal	MP	No		Yes
81-3 - Acute Inhalation - Rat	MP	No		Yes
81-4 - Primary Eye Irritation - Rabbit	MP	No		Yes
81-5 - Primary Dermal Irritation - Rabbit	MP	No		Yes
81-6 - Dermal Sensitization Guinea pig	MP	No		Yes

1/ Composition: MP = Manufacturing-use product.
2/ Unless otherwise specified data must be submitted no later than six months after publication of this Standard

Bibliography

MRID Number

RZ001 Goldstein, J., NTP Technical Report on the Toxicology and Carcinogenesis Studies of 1.4-dichlorobenzene, (Cas No 106-46-7) in F 344 Rats and B6C3F$_1$ Mice (Gavage Studies), NTP Publication No. 86-2575, undated draft.