CASWELL FILE

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

MAR 28 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: LOC for Harmony in Ground Water CASWELL # 573 S

To: Henry Jacoby,
Mission Support Staff, HED

From: Marcia van Gemert, Ph.D. M. van Gemert 3/25/88
Head, Section III
Toxicology Branch, HED

Thru: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch, HED

I have attached the 8-point summary on the data base for Harmony. Essentially, Harmony (and harmony acid) have a complete data base. The Agency-wide Rfd Committee met March 23, 1988 on the data for Harmony and agreed with the Toxicology Branch Rfd for Harmony which is based on a 2-year rat chronic/oncogenicity study where the systemic NOEL = 1.25 mg/kg/day. Using an uncertainty factor of 100, the Rfd would be 0.0125 mg/kg/day.

Concerning Harmony Levels of Concern (LOC) for leachates in ground water with an Rfd of 0.0125 mg/kg/day, the LOC is based on the following calculations:

0.0125 mg/kg/day X 1000 ugm/mg X 60 kg person = 750 ugm/day

750 ugm/day/2 liters/day = 375 ugm/liter = 375 ppb

375 ppb x 0.5 safety factor x 0.2 standard constant for drinking water = 37.5 ppb

LOC = 37.5 ppb

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WASHINGTON, D.C. 20460

MEMORANDUM

Subject: 8-point summary on Harmony

To: Ms. Vicki Walters, PM-25
Registration Division, TS-767C

From: Marcia van Gemert, Ph.D.
Head, Section III
Toxicology Branch, HED

Thru: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch, HED

Chemical: Harmony

Caswell No: 573S

1. Data Available:

DPX-M5316- 75% formulation

1. Acute oral LD_{50}- rat	LD_{50} > 5000 mg/kg	guideline
2. Acute dermal LD_{50}- rabbit	LD_{50} > 2000 mg/kg	minimum
3. Primary eye Irritation rabbit	moderate eye irritant	guideline
4. Primary dermal irritant- rabbit	No primary irritation	guideline
5. Dermal sensitization Guinea pig	Not shown to be a sensitizer	minimum

End Use Product- 6.8%

1. Acute oral LD_{50}- rat	LD_{50} > 5 gm/kg	guideline
2. Acute dermal LD_{50}- rabbit	LD_{50} > 2 gm/kg	guideline
3. Primary eye irritation- rabbit	At 25 hours- corneal opacity redness, chemosis and discharge, irritation in washed eye cleared by day 3, unwashed eye by day 7	guideline

4. Primary skin irritation- rabbit	At 72 hours, 3/6 exhibited very slight erythema, comp adhered to skin	guideline
5. Dermal sensitization rabbit	non-sensitizer	guideline

TECHNICAL:

1. Acute oral LD_{50}- rat	LD_{50} > 5000 mg/kg	guideline
2. Acute inhalation LC^{50} rat	LC_{50} > 7.9 mg/l/4 hours	minimum
3. Acute dermal LD_{50}- rabbit	LD_{50} > 2000 mg/kg	minimum
4. 90-day feeding and 1-generation reproduction study- rat	NOEL = 100ppm LEL = 2500 ppm based on decreased body weight gain and clinical pathology- reproductive NOEL = not established- insufficient numbers of animals per level	feeding= minimum reproductive= supplementary
5. 13-week dog study	NOEL = 1500 ppm LEL = 7500 ppm (body wt and adrenal wt decrease in males)	minimum
6. Teratology- rat	teratogenic NOEL = 159 mg/kg LEL = 725 mg/kg (absence of renal papilla) fetotoxic NOEL = 159 mg/kg LEL = 725 mg/kg maternal NOEL > 725 mg/kg (HDT)	minimum
7. Teratology- rabbit	Maternal NOEL = 158 mg/kg LEL = 511 mg/kg based on reduced body weight gain Developmental NOEL > 511 mg/kg	minimum
8. 1-year dog study	NOEL = 750 ppm LEL = 7500 ppm based on decreases in body weights and body weight gains in males	minimum
9. 2-generation reproduction study- rats	systemic and reproductive NOEL = > 2500 ppm, no effects seen	minimum
10. 2-year chronic/ oncogenicity study-rats	Systemic NOEL = 25 ppm LEL = 500 ppm based on lower body weight gains in males and decreased serum sodiums	minimum

[illegible] toxicity rats	NOEL = 25 ppm LEL = 750 ppm based on reduced body weight gains in males and females	[illegible]
11. Metabolism- rat	dose = 2000 mg/kg by gavage. no tissue or carcass accumulation evident. most parent compound eliminated in feces and urine intact with 3 minor metabolites in urine and feces	minimum with second metabolism study
12. Metabolism- rat	doses 20 or 2000 mg/kg by gavage 5 minor metabolites appeared in urine and 3 in fecal samples. No bioaccumulation evident. Mostly parent compound was excreted.	Minimum along with first metabolism study
14. Mutagenicity- reverse mutation assay in Salmonella	not mutagenic in Salmonella typhimurium strains with and without S-9	acceptable
15. Mutagenicity- Gene mutation	No increase in mutation frequency was seen at highest dose tested of 7 mM- the limit of solubility	acceptable
16. Mutagenicity- DNA synthesis/ rat hepatocytes in vitro	material did not induce significant increase in unscheduled DNA synthesis (UDS) in primary cultures	acceptable

TRIAZINE AMINE- (Plant metabolite and ground-water residue)

1. Mutagenicity- Ames Salmonella	negative in repeat experiments at concentrations up to 10,000ug/plate with and without S-9	acceptable
2. acute oral LD_{50}-rats	LD_{50} = 1680 mg/kg (males only)	minimum
3. acute inhalation LD_{50}- rats	LC_{50} > 5.0 mg/L (males only)	minimum
4. Acute LD_{50}- range-finding, rat	LD_{50} around 1500 mg/kg	supplementary
5. Acute dermal LD_{50} rabbit	LD_{50} > 5000 mg/kg (males only)	supplementary
6. Skin irritation and sensitization- Guinea Pigs	not a sensitizer at 3 or 30%	minimum
7. Eye irritation- rabbits	mildly irritating to both washed and unwashed eyes	supplementary
8. Subacute oral toxicity in rats	one dose group used= 300 mg/kg dosed for 14 days. No mortality seen, however, liver and heart are target organs, NOEL < 300 mg/kg	Supplementary

2. Data gaps: Presently there are no data gaps for Harmony.

3. Action being taken to obtain the missing information: none

4. Tolerances granted: This is a new chemical

5. % of ADI used: The tolerance printout is available through the Residue Chemistry Branch's TAS system.

6. ADI: The ADI committee's deliberations are appended for reference. The ADI is 0.013 mg/kg based on a NOEL of 25 ppm (1.25 mg/kg/day) with a 100 fold safety factor on the 2-y[illegible] feeding/[illegible] study.

7. Regulatory actions pend[illegible]

REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Harmony (DPX-M6316)

CAS #: 79277-27-3
Caswell #: 573S

Carcinogenicity: No evidence of oncogenicity in two adequate animal studies.

Systemic Toxicity: See below.

Preparation Date: 2/05/88

Endpoint	Experimental Doses	UF	MF	RfD
Haskell Labs (1986) 2-Year Rat Feeding/ Oncogenicity Study Lower body weight gains in males, serum sodium in males and females were sporadically lower thoughout the study	25 ppm (1.25 mg/kg/day) Systemic NOEL 500 ppm (25 mg/kg/day) Systemic LEL	100	1	0.013 mg/kg/day

Conversion factor (rat): 1 ppm = 0.05 mg/kg/day

Endpoint and Experimental Doses:

Haskell Laboratories (Sponsored by EI Dupont de Nemours and Co.)
2-Year Rat Feeding/Oncogenicity Study
Study No. 4980-001, 261-86; June 26, 1986

Harmony was administered at dietary levels of 0, 25, 500, and 2500 ppm to 62 rats/sex/group for 24 months. There was an interm sacrifice of 10 animals/sex/group at 12 months. The following parameters were evaluated: mortality, physical signs, body weights, food consumption, hematology, clinical chemistry, urinalysis, macroscopic and microscopic pathology changes. No treatment-related changes were seen in mortality, clinical signs, food consumption, hematology, urinalysis, organ weights, macro or microscopic pathology. A slight but significant body weight reduction was seen in high dose males, body weight gains were significantly lowere in mid and high-dose animals. Serum sodiums were sporadically lower in mid and high-dose males and females throughout the study.

Uncertainty Factors (UFs):

An uncertainty factor of 100 was used to account for the inter- and intraspecies difference.

Modifying Factors (MFs):

None

Additional Comments:

Data Considered for Establishing the RfD

1) 2-Year Feeding/Oncogenicty - Rat Systemic NOEL = 25 ppm (1.25 mg/kg/day), Systemic LEL = 500 ppm (25 mg/kg/day)(lower body weight gains in males, serum sodium in males and females were sporadically lower thoughout the study); Core grade minimum

2) 1-Year Feeding - Dog Systemic NOEL = 750 ppm (18.75 mg/kg/day), Systemic LEL = 7500 ppm (187.5 mg/kg/day)(decreased body weights and body weight gains; increased liver weights in males); Core grade minimum

3) 2-Generation Reproduction - Rat Systemic and Reproductive NOEL > 2500 ppm (125 mg/kg/day)(HDT); No toxic effects were demonstrated at any dose; Core grade minimum

4) Teratology - Rat Maternal NOEL > 750 mg/kg/day (HDT); Teratogenic NOEL = 159 mg/kg/day, Teratogenic LEL = 725 mg/kg/day (absence of renal papilla); Fetotoxic NOEL = 159 mg/kg/day, Fetotoxic LEL = 725 mg/kg/day (lower mean fetal body weights); Core grade minimum

5) Teratology - Rabbit Maternal NOEL = 158 mg/kg/day, Maternal LEL = 511 mg/kg/day (reduced weight gain); Developmental NOEL > 511 mg/kg/day (HDT); Core grade minimum

Data Gap(s)

None

Other Data Considered

1. 18-Month Oncogenicity - Mice Systemic NOEL = 25 ppm (3.75 mg/kg/day), Systemic LEL = 750 ppm (112.5 mg/kg/day)(reduced body weight gains in males and females); Core grade minimum

2. 90-Day Feeding - Rat NOEL = 100 ppm (5 mg/kg/day), LEL = 2500 ppm (125 mg/kg/day) (decreased body weights and body weight gains in both sexes; decreased spleen liver and heart weights in males; relative brain, kidney and testes weights were increased in males and relative brain and heart weights were increased in females); Core grade minimum

3. 13-Week Feeding - Dog NOEL = 1500 ppm (37.5 mg/kg/day), LEL = 7500 ppm (187.5 mg/kg/day (body weight and adrenal weight suppression in males); Core grade minimum

Confidence in the RfD:

Study: Medium Data Base: High RfD: High

The critical study is of adequate qualityand is given a medium confidence rating. Additional studies are supportive and therefore the data base is given a high confidenc rating. High confidence in the RfD follows.

Documentation of RfD and Review:

Registration Files

Agency RfD Review:

First Review:
Second Review:
Verification Date:

U.S. EPA Contact:

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