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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO Richard Mountfort. Product Manager #23
Registration Division (TS-767)

THRU: Judith Hauswirth, Ph. D., Section Head
Review Section 6
Toxicology Branch
Hazard Evaluation Division (TS-769) Judith W. Hauswirth 1/15/88

FROM: Roger Gardner, Toxicologist
Toxicology Branch Roger Gardner 1-15-88
Hazard Evaluation Division (TS-769) 1/29/88

SUBJECT: Review of Acute Toxicity Studies of DPX L5300 (EPA Reg. No. 352-LRU)
Tox. Chem. No. 419S. Tox. Proj. No. 8-0219)

Actions Requested

Review of reports on primary eye irritation, primary dermal irritation, and dermal sensitization studies.

Recommendations and Conclusions

1. The primary eye irritation study is supplementary because there was an insufficient number of animals used.

2. The primary dermal irritation study is supplementary since its purpose was to find an irritating dose of the diluted technical grade material for use in the dermal sensitization study rather than to characterize the irritation potential of the undiluted pesticide.

3. A core minimum dermal sensitization study indicated that technical grade DPX L5300 is not a skin sensitizer in guinea pigs.

4. Primary eye and skin irritation studies are needed to support registration of technical grade DPX L5300.

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I. Background

A. Introduction

DPX L5300 (chemical name: benzoic acid, 2-[[[[N-4-methoxy-6-methyl-1,3,5-triazin-2-yl)-N-methylamino]carbonyl] sulfonyl]-, methyl ester) is a new chemical that has been proposed as a herbicide for use on wheat and barley. It is to be formulated for that purpose as a dry flowable (75% active ingredient).

A previous Toxicology Branch review (Gardner, 1986) noted:

> There are no primary eye irritation, skin irritation, or dermal sensitization studies available on the technical grade material. However, studies with a 75% Dry Flowable formulation indicated that DPX-L5300 is associated with no skin irritation (Toxicity Category IV) or sensitization and moderate eye irritation (Toxicity Category III). In addition, there were no signs of skin reactions noted in the acute dermal toxicity study on technical grade DPX-L5300.

The submitted studies addressing those comments are described below (Section II. and Appendix I.).

B. Previously Submitted Data

The results of acute toxicity studies on technical DPX L5300 and a 75% flowable formulation indicated that both should be classified into Toxicity Category III for acute dermal toxicity (see Appendix II. below).

Results of eye and skin irritation studies with the 75% flowable formulation showed that it should be classified into Toxicity Categories III and IV, respectively. No dermal sensitization was observed in guinea pigs treated with that formulation.

II. Discussion

A. New Data

There were indications of mild eye irritation in the washed and unwashed eyes of two rabbits after instillation of 10 mg technical grade DPX L5300 (Gargus, 1983a). Redness with vessels injected above normal was observed in both rabbits at the 1 and 4 hour observation periods. The study is classified as supplementary because only two rabbits were used in the study.

There were no signs of skin irritation or sensitization after dermal applications of 7% or 70% technical grade IN L5300 in dimethyl phthalate to the shaved skin of male guinea pigs (Gargus, 1983b). Slight to well-defined erythema with blanching was observed 24 hours after intradermal injections of the test substance during the induction phase of the experiment. The reported results indicate that under the test conditions technical grade IN L5300 is not a dermal sensitizer.

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D. Data Gaps

Since the primary eye irritation study used only two animals, and since the dermal irritation study was conducted to find an irritating dose for the technical grade material, the need for those two studies to support registration of DPX L5300 still exists.

III. References

Gardner, R. Memorandum dated February 18, 1986. Subject: Experimental Use Permit (EPA Reg. No. 352-EUP-RGN) and Temporary Tolerances fo: Residues of DPX-L5300 in/on Wheat and Barley grain (0.05 ppm) and straw (0.1 ppm); Petition No. 5G3296. Tox. Chem. No. 419S. Tox. Proj. Nos. 407 and 408). To: Richard Mountfort, Product Manager #23, Registration Division.

Gargus, J. L. June 6, 1983. IN L5300 Eye Irritation Test in Rabbits Unpublished Report No. 201-616 prepared by Hazleton Laboratories America, Inc. Submitted by E. I. DuPont de Nemours and Co., Haskell Laboratories MRID No. 403574-01

Gargus, J. L. September 12, 1983. IN L5300 Primary Skin Irritation and Sensitization Test on Guinea Pigs Unpublished Report No. 201-617 prepared by Hazleton Laboratories America, Inc. Submitted by E. I. DuPont de Nemours and Co., Haskell Laboratories MRID No. 403574-02

APPENDIX I

Data Evaluation Records for the Following Studies

Gargus, J. L. June 6, 1983. IN L5300 Eye Irritation Test in Rabbits Unpublished Report No. 201-616 prepared by Hazleton Laboratories America, Inc. Submitted by E. I. DuPont de Nemours and Co., Haskell Laboratories MRID No. 403574-01

Gargus, J. L. September 12, 1983. IN L5300 Primary Skin Irritation and Sensitization Test on Guinea Pigs Unpublished Report No. 201-617 prepared by Hazleton Laboratories America, Inc. Submitted by E. I. DuPont de Nemours and Co., Haskell Laboratories MRID No. 403574-02

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Section 6, Toxicology Branch (TS 769C)
Secondary Reviewer: Judith Hauswirth, Ph. D. Judith W Hauswirth 1/15/88
Section 6, Toxicology Branch (TS 769C)

DATA EVALUATION RECORD

STUDY TYPE: Primary Eye Irritation (Guideline §81-4)

MRID NUMBER: 403574-01

TEST MATERIAL: Technical grade (minimum of 95% active ingredient) was described as a yellow powder.

SYNONYMS: DPX-L5300; benzoic acid, 2-[[[[N-4-methoxy-6-methyl-1, 3, 5-triazin-2-yl)-N-methyl-amino] carbonyl]amino]-sulfonyl]-, methyl ester.

STUDY NUMBER(S): Haskell Laboratory Report No. 199-83, Hazleton Project No. 201-616

SPONSOR: E. I. DuPont de Nemours and Co., Haskell Laboratories

TESTING FACILITY: Hazleton Laboratories America, Inc.

TITLE OF REPORT: IN L5300 Eye Irritation Test in Rabbits

AUTHOR(S): Gargus, J. L.

REPORT ISSUED: June 6, 1983

DISCUSSION AND CONCLUSIONS: There were indications of mild irritation in the washed and unwashed eyes of two rabbits after instillation of 10 mg technical grade DPX L5300. Redness with vessels injected above normal was observed in both rabbits at the 1 and 4 hour observation periods.

Core classification: Supplementary. Only two animals were used.

I. PROTOCOL

A. Test species: Male and female New Zealand White strain rabbits were used.

B. Experimental procedure: One male and one female rabbit previously examined and found without signs of corneal damage were used in the experiment. Ten mg of the test substance was instilled into the right eye of each rabbit, and the eyelids were gently held together for one second. The eye of one rabbit was observed for 30 to 60 seconds after instillation of the test material, and the treated eye was left unrinsed. Twenty seconds after instillation of the test material in the other rabbit, the treated was rinsed for one minute with lukewarm tapwater.

B. Observations: All eyes were examined 1, 4, 24, 48, and 72 hours after instillation of the test substance and 4 and 7 days after treatment. Ocular reactions were scored according to the following scales:

Cornea

Degree of density	Area of cornea involved
1 - scattered or diffuse area, details of iris visible	1 - one-quarter (or less but not zero)
2 - easily discernible translucent areas, details of iris slightly obscured	2 - greater than one-quarter to less than one-half
3 - opalescent areas, no details of iris visible, size of pupil barely discernible	3 - greater than one-half to less than three-quarters
4 - opaque, iris invisible	4 - greater than three-quarters

score = score for degree x score for extent x 5 (maximum = 80)

Iris

1 - folds above normal, congestion, swelling, circumcorneal injection (any one or a combination of these), iris still reacting to light (sluggish reaction is positive)

2 - no reaction to light, hemorrhage, gross destruction (any one or all of these)

score = score for iris x 5 (maximum score = 10)

Conjunctivae

Redness	Chemosis
1 - vessels definitely injected above normal	1 - any swelling above normal (including nictitation membrane
2 - more diffuse, deeper crimson red, individual vessels not discernible	2 - obvious swelling with parital eversion of the lids
3 - diffuse beefy red	3 - swelling of lids about half closed
	4 - swelling of lids about half to completely closed

Discharge

1 - any amount different from normal (does not include small amount in inner canthus of normal animals)
2 - discharge with moistening of the lids and hairs just adjacent to the lids
3 - discharge with moistening of the lids and considerable area around the eye

Score = sum of values for redness, chemosis, and discharge multiplied by 2. (Maximum = 20)

II. REPORTED RESULTS

The report stated that both rabbits exhibited redness (grade 1) at 1 and 4 hours, and the redness had cleared by the 24 hour observation. There were no other signs of eye irritation.

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Secondary Reviewer: Judith Hauswirth, Ph. D. Judith W. Hauswirth 1/15/88
Section 6, Toxicology Branch (TS 769C)

DATA EVALUATION RECORD

STUDY TYPE: Primary Skin Irritation and Sensitization (Guideline §81-4 and §81-6)

MRID NUMBER: 403574-02

TEST MATERIAL: Technical grade (minimum of 95% active ingredient) was described as a yellow powder.

SYNONYMS: DPX-L5300; benzoic acid, 2-[[[[N-4-methoxy-6-methyl-1, 3, 5-triazin-2-yl)-N-methyl-amino] carbonyl]amino]-sulfonyl]-, methyl ester.

STUDY NUMBER(S): Haskell Laboratory Report No. 369-83; Hazleton Project No. 201-617

SPONSOR: E. I. DuPont de Nemours and Co., Haskell Laboratories

TESTING FACILITY: Hazleton Laboratories America, Inc.

TITLE OF REPORT: IN L5300 Primary Skin Irritation and Sensitization Test on Guinea Pigs

AUTHOR(S): Gargus, J. L.

REPORT ISSUED: September 12, 1983

DISCUSSION AND CONCLUSIONS: There were no signs of skin irritation or sensitization after dermal applications of 7% or 70% technical grade IN L5300 in dimethyl phthalate to the shaved skin of male guinea pigs. However, slight to well-defined erythema with blanching was observed 24 hours after intradermal injections of the test substance during the induction phase of the experiment. The reported results indicate that under the test conditions technical grade IN L5300 is not a dermal sensitizer.

Core classification: Primary skin irritation - supplementary. The technical grade DPX L5300 was diluted for purposes of finding an irritating concentration rather than characterizing the irritation properties of the undiluted pesticide.

Dermal sensitization - minimum

I. PROTOCOL

A. Materials

1. Test species: Male Hartley strain guinea pigs were used.

2. Vehicle: The solvent used in the study was dimethyl phthalate since, according to the report, the test substance reacts with water.

B. Experimental procedures

1. Range finding study: Three animals were prepared for application of the test substance by shaving of their backs. The test substance was applied in 0.05 ml aliquots at concentrations of 25, 50, 60, and 70% (w/v) in dimethyl phthalate. Each concentration was applied at a separate site on each of the three animals, and the sites were examined for signs of irritation at 24 and 48 hours after dosing. The system used for scoring the observed skin reactions is described in Section I. C. below.

2. Sensitization study

a. Primary irritation phase: One group of 10 animals was used in this phase of the experiment. The dorsal skin from the shoulders to the mid back was shaved free of hair and two sites were selected. A 7% or 70% solution of the test substance in dimethyl phthalate was applied to a selected site on the back of each test animal.

b. Induction phase: The ten animals used in the primary irritation phase of the study had the sacral/hip region of their skin clipped free of hair, and a 0.1 ml aliquot of a 1% solution of test substance in dimethyl phthalate (w/v) was injected intradermally. The injections were repeated weekly for four consecutive weeks.

c. Challenge phase: Two weeks after the final injection in the induction phase, the backs of the 10 animals used in the previous phases of the experiment as well as those of an additional group of 10 animals were shaved. The 7 and 70% test substance solutions were applied to separate sites on each animal in both groups, and test sites were scored for skin reactions according to the scale described above.

C. Observations: At 24 and 48 hours after each application of the test substance in the primary irritation and challenge phases of the experiment, the test sites were examined and scored according to the following scales:

Erythema and eschar		Edema	
No erythema	0	No edema	0
Slight erythema	1	Very slight edema	1
Well-defined erythema	2	Slight edema	2
Moderate to severe erythema	3	Moderate edema	3
Severe erythema to slight eschar formation	4	Severe edema	4

The injection sites were examined for edema and necrosis 24 hours after each injection during the induction phase.

II. REPORTED RESULTS

There were no mortalities or signs of toxicity observed during the study according to the report.

II. REPORTED RESULTS (continued)

The only skin reactions were observed during the induction phase of the experiment. In that portion of the study all animals exhibited very slight to well-defined erythema with blanching. No necrosis or primary irritation was observed in any animal during other phases of the study.

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APPENDIX II

Toxicology Branch "One-Liners" for
DPX L5300 (Tox. Chem. No. 419S)

Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	ORE Grade/ Doc. No.
Teratology - rat; Argus Research Labs, Inc.; Report No. HD-513-85; August 16, 1985	Technical (96.8% a. i.)	073791	Maternal NOEL = 20 mg/kg/day Maternal LOEL = 125 mg/kg/day (decreased body weight gain and food consumption, increased liver-to-body weight ratio) Developmental NOEL = 20 mg/kg/day Developmental LOEL = 125 mg/kg/day (decreased body weight, at HDT increased resorptions and fetal deaths, incomplete ossification) A/D Ratio = 125/125 = 1 Doses tested = 0, 20, 125, and 500 mg/kg/day on gestation days 6-16		Guideline 004943
1-Generation reproduction) - rat; Haskell Labs; Report no. 413-83; June 6, 1985	Technical (96.8% a. i.)	073790	No final conclusions can be drawn because there were only 3 to 6 dams with litters available for analysis. Adult toxicity NOEL and LOEL (see "One-liner" for subchronic feeding phase of this study, Report no. 413-85, below) Developmental NOEL = 2500 ppm Developmental LOEL = 5000 ppm (decreased pup viability and weight gain Doses tested were 0, 100, 2500, and 5000 ppm in the diet		Supplementary 004943
90 Day feeding - dog; Bio/dynamics Inc.; Report No. HD-514-85; August, 1985	Technical (96.8% a. i.)	073788 073789	NOEL > 2500 ppm (HDT) Doses tested = 0, 50, 500, and 2500 ppm in diet for 90 days.		Minimum 004943

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
90 Day feeding - rat; Haskell Labs; Report no. 413-85; June 6,1985	Technical (96.8% a. i)	073790	NOEL = 100 ppm LOEL = 1750 ppm (decreased body weight gain, food consumption and food efficiency; decreased absolute heart, brain, liver, and kidney weights; relative organ weights for heart, liver, kidneys, testes, and spleen were increased; serum glucose, globulin and cholesterol were decreased) Doses tested = 0, 100, 1750, and 5000 ppm in diet for 90 days		Minimum 004943
Mutagenic (reverse mutations) - Salmonella; Haskell Lab; Report No. 245-83; May 25, 1985	Technical (96.8% a. i)	073790	Incomplete report		Unacceptable 004943
Mutagenic (point mutation) - CHO cells; Haskell Lab; Report No. 58-85; May 30, 1985.	Technical (96.8% a. i)	073790	Not mutagenic		Acceptable 004943
Mutagenic (in vivo cytogenetics) - rat; Haskell Lab; Report No. 236-85; June 14, 1985	Technical (96.8% a. i.)	073790	No genotoxicity		Acceptable 004943
Mutagenicity (micronucleus) - mouse; Haskell Lab; Report No. 420-85; July 22, 1985	Technical (96.8% a. i.)	073790	No genotoxicity		Acceptable 004943

Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenic (in vitro UDS) - rat ; Haskell Lab; Report no. 565-84; July 18, 1985	Technical (96.8% a. i.)	073790	No genotoxicity		Acceptable 004943
Acute oral LD_{50} - rat; Haskell Lab; Report No. 167-85; May 5, 1985	Technical (96.8% a. i.)		LD_{50} > 5000 mg/kg for both sexes (Limit Test)	IV	Minimum 004943
Acute oral LD_{50} - rat; Haskell Lab; Report No. 280-85; May 30, 1985	DPX-L5300 Herbicide (75%)		LD_{50} = 5700 mg/kg for males LD_{50} = 4800 mg/kg for females	IV III	Minimum 004943
Acute dermal - rabbit; Hazleton Lab; Report No. HLO-21-85; December 24, 1984.	Technical (96.8% a. i.)	073787	LD_{50} > 2000 mg/kg for both sexes (Limit test)	III	Minimum 004943
Acute dermal - rabbit; Hazleton Lab; Report No. HLO-234-85; April 11, 1985.	DPX-L5300 Herbicide (75% Dry Flowable)	073787	LD_{50} > 2000 mg/kg for both sexes (Limit test)	III	Minimum 004943
Acute inhalation -rat; Haskell Lab; Report No. 431-85; August 13, 1985	Technical (96.8% a. i.)	073787	LC_{50} > 6.7 mg/L for both sexes Four hour exposure. Concentrations tested = 6.7 mg/L and 1.3 mg/L. Nose only exposure.	III	Minimum 004943
Acute inhalation - rat;	DPX-L5300 Herbicide (75% Dry Flowable)	073787	Requirement waived because <0.5% of the formulations granules are <10μm in diameter.		004943
Primary eye irritation - rabbits: Hazleton Labs: HLO-305-85; May 24, 1985	DPX-L5300 Herbicide (75% Dry Flowable)	073787	Moderately irritating (no Primary Irritation Score given). Corneal opacity persisted for three days, redness persisted for 4 days.	III	Minimum 004943

Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary dermal irritation-rabbit;Hazleton Lab; Report No. 233-85; April 11, 1985	DPX-L5300 Herbicide (75% Dry Flowable)	073787	Primary Irritation Score = 0	IV	Minimum 004943
Dermal sensitization - guinea pig; Hazleton Lab; Report No. HLO-295-85; May 23, 1985	DPX-L5300 Herbicide (75% Dry Flowable)	073787	Not a sensitizer		Minimum 004943