6/13/83 MRID 125826 - 125841

OB-581
TXR-2990

Rev. 4/14/82 Toxicology Branch/HED Review

Caswell No(s).: 419 H 002990

To: Taylor/Remmers Acc. Nos. 071435 and 071488

Registration No(s).:

Pesticide Petition No(s).: 3G2834

Chemical(s): DPX-T6376 (methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate.

Requested Action(s): E.U.P. with temporary tolerance 0.05 ppm each for wheat grain and barley grain.

Recommendation: The above temporary tolerances can not be toxicologically supported.

Inert(s) cleared 180.1001: [redacted]

% of ADI occupied: Existing: none Resulting: 20.7% TWE

Resulting % increase in TMRC: —

Data considered in setting the ADI: 13-week feeding in rat and others attached. Safety factor: 2000

Attached (?): ADI printout: YES/~~NO~~; TOX "one-liner": YES/~~NO~~; DER: YES/~~NO~~

Existing regulatory actions against registration: none

RPAR status: none

New Data: see attachments

Data gaps: none for temporary tolerances.

Comments: Note that material from acc. no. 071488 was received by HED as a separate reg. act.

Reviewer: W Thomas Edwards 5-19-83 Date:

Section Head: William H Butler 6/13/83 Branch Chief:

1 of 27

Grant Inspection Information
13 not inspected

NO CFR NUMBER LPX-16376 5/17/83

Unverified Printout

ACCEPTABLE DAILY INTAKE DATA

002990

RAT,Older NOEL mg/kg	NOEL ppm	S.F.	PADI mg/kg/day	MPI mg/day(60kg)
1.250	25.00	2000	0.0006	0.0375

Current Action 332834

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Barley(6)	0.050	0.03	0.00002
Wheat(170)	0.050	10.36	0.00777

MPI	TMRC	% ADI
0.0375 mg/day(60kg)	0.0078 mg/day(1.5kg)	20.79

****

DRAFT

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TOXICOLOGY BRANCH
DATA REVIEW

002990

Study Type: Acute Oral Toxicity (92.9%), technical

Accession Number: 071435

MRID Number:

Sponsor: DuPont

Contracting Lab: Haskell Laboratory, Report No. 207-82

Date: March 30, 1982

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3, 5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376, Technical, 92.9%). 417 L

Protocol: A single dose level was used, 5000 mg/kg. 5 male and 5 female rats were treated. Single doses of test material suspended in corn oil were administered by gavage to fasted animals. After 14 days observation, all were killed and given gross pathological examination.

Results:

Dose (mg/kg)	Fasted Average Body Weight (g)	Suspension %	Average Dose (ml)	Mortality Ratio	LD_{50}
Males					
5,000	208	25	4.16	0/5	>5,000 mg/kg
Females					
5,000	164	20	4.10	0/5	>5,000 mg/kg

Conclusions:

LD_{50} greater than 5000 mg/kg
Acute Oral Toxicity Category: IV

CORE Classification:

Minimum

W. Thomas Edwards
5-19-83

TOXICOLOGY BRANCH
DATA REVIEW

002990

Study Type: Acute Oral Toxicity, 70% formulation

Accession Number: 071435

MRID Number:

Sponsor: DuPont

Contracting Lab: Haskell Laboratory, Report No. 212-82

Date: April 2, 1982

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3, 5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-21, 70% formulation).

Protocol: A single dose level was used, 5000 mg/kg. 5 male and 5 female rats were treated. Single doses of test material suspended in corn oil were administered by gavage to fasted animals. After 14 days observation, all were killed and given gross pathological examination.

Results:

Dose (mg/kg)	Fasted Average Body Weight (g)	Suspension %	Average Dose (ml)	Mortality Ratio	LD_{50}
Males					
5,000	205	25	4.10	0/5	>5,000 mg/kg
Females					
5,000	153	20	3.82	0/5	>5,000 mg/kg

Conclusions:

LD_{50} greater than 5000 mg/kg
Acute Oral Toxicity Category: IV

CORE Classification:

Minimum

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TOXICOLOGY BRANCH
DATA REVIEW

002990

Study Type: Acute Dermal Toxicity (92.9%), Technical

Accession Number: 071435

MRID Number:

Sponsor: DuPont

Contracting Lab: Haskell Laboratory, Report No. 321-82

Date: May 19, 1982

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3, 5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376, Technical, 92.9%).

Protocol: One dose level was used, 2000 mg/kg. 5 male and 5 female rabbits were treated. Test material was applied to abraded skin on backs, covered with gauze, plastic wrap, and adhesive bandage. After 24 hours exposure, covering was removed and treated sites wiped with a dry towel. Observation time before killing was 14 days.

Results: (Abraded Skin)

Sex	No.	Dose "As Received" mg/kg	Dose "As Received" gr (Avg.)	Average Wt. (g) Initial	Average Wt. (g) 14-Days	Mortality
Male	5	2,000	6.48	3240	3193	0/5
Females	5	2,000	4.78	2388	2940	0/5

Conclusions:

LD_{50} greater than 2000 mg/kg
Acute dermal toxicity. Category III only is justified.

CORE Classification:

Minimum for Category III

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5-19-83

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TOXICOLOGY BRANCH
DATA REVIEW

002990

Study Type: Acute dermal toxicity 70% formulation.

Accession Number: 071435

MRID Number:

Sponsor: DuPont

Contracting Lab: Haskell Laboratory, Report No. 348-82

Date: June 1, 1982

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-21, 70% formulation).

Protocol: One dose level was used, 2000 mg/kg. 5 male and 5 female rabbits were treated. Test material was applied to abraded skin on backs, covered with gauze and plastic wrap held by adhesive bandage. After 24 hours exposure, covering was removed and treated sites wiped with a dry towel. Observation time before killing was 14 days.

Results: (Abraded Skin)

Sex	No.	Dose "As Received" mg/kg	Dose "As Received" gr (Avg.)	Average Wt. (g) Initial	Average Wt. (g) 14-Days	Mortality
Male	5	2,000	6.70	3350	3419	0/5
Females	5	2,000	4.85	2427	2829	0/5

Conclusions:

LD_{50} greater than 2000 mg/kg
Acute dermal toxicity. Category III only is justified.

CORE Classification:

Minimum for Category III

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5-19-83

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TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Acute inhalation toxicity (dust), technical.

Accession Number: 071435

MRID Number:

Sponsor: DuPont

Contracting Lab: Haskell Laboratory, Report No. 784-82

Date: January 1, 1983

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3, 5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376, technical, 92.9%).

Protocol: Two groups, each of 10 male and 10 female rats (restrained in holders), were exposed for single 4-hour periods. Dust concentrations were determined at 15 minute intervals. Percent respirable particle sizes were determined.

Results:

Concentration (mg/L)			% Respirable	Mass Medium Diameter of Respirable Particulate (um)	Fractional Mortality (# Deaths/ # Exposed)	
Mean	S.D.	Range			Males	Females
5.3	1.8	2.3-8.3	74	4.8	0/10	0/10
5.3	1.6	3.4-8.8	69	5.2	0/10	0/10

Conclusions:

Acute inhalation category: IV

Core Classification:

Guideline.

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TOXICOLOGY BRANCH
DATA REVIEW

002990

Study Type: Eye irritation, 70% formulation.

Accession Number: 071435

MRID Number:

Sponsor: DuPont

Contracting Lab: Haskell Laboratory, Report No. 305-82

Date: June 6, 1982

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3, 5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-21, 70% formulation).

Protocol: Right eyes of 9 male rabbits were treated with 28.8 mg of solid test material. 3 of 9 eyes were washed.

Results:

Some opacity and irritation was seen which cleared in 2-3 days.

Conclusions:

Category 11

CORE Classification:

Guideline

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5-10-83

TOXICOLOGY BRANCH
DATA REVIEW

002990

Study Type: Primary dermal irritation, 70% formulation-rabbit.

Accession Number: 071435

MRID Number:

Sponsor: DuPont

Contracting Lab: Haskell Laboratory, Report No. 277-82

Date: May 12, 1982

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-21, 70% formulation).

Protocol: Six rabbits were clipped on trunk and lateral areas and placed in FDA type stocks. Solid test material (moistened with saline) was applied to 2 abraded and 2 intact areas under 1" x 1" gauze squares with rubber sheeting held in place by adhesive tape. After 24 hours, remaining material was wiped off. Observations were made at 24, 48, and 72 hours after removal and after 6 and 9 days of treatment. Scoring was made according to Draize.

Conclusions:

Primary dermal irritation category: III

CORE Classification:

Minimum

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TOXICOLOGY BRANCH
DATA REVIEW

002990

Study Type: Sensitization and primary skin irritation, 70% formulation, guinea pig.

Accession Number: 071435

MRID Number:

Sponsor: E.I. DuPont

Contracting Lab: Haskell Laboratory, Report No. 310-82

Date: April 16, 1982

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3, 5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-21, 70% formulation).

Procedure: Four groups of guinea pigs were used, 10 per group. Two groups which were to be sensitized were first tested for direct irritation. One with 35% test material in dimethyl phenylate. The other with 3.5%. Observations were made at 24 and 48 hours.

Beginning two days after the above testing, each animal of these two groups received 4 intradermal injections (one each week) of 0.1 ml each of 1.0% test material in saline. After 14 days the animals were challenged by applying and lightly rubbing in 0.5 ml of 35% or 3.5% suspensions on shaved skin.

Two groups which had received no injection were also challenged similarly.

Results: The 35% solution was moderately irritating. No irritation from the 3.5% solution was reported. Irritations were no greater after injections (to sensitize) than without them, i.e., results of sensitization test were negative.

Conclusion: The 70% formulation of DPX-T6376 was not found to be sensitizing.

CORE Classification:

Minimum

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5-19-83

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TOXICOLOGY BRANCH

DATA REVIEW

Study Type: Ninety-day feeding and one-generation reproduction study in rats.

Accession Number: 071435

MRID Number:

Sponsor: DuPont

Contracting Lab: Haskell Laboratory, Report No. 180-82

Date: October 5, 1982

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazion-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376 technical)

Protocol:

Sixteen male and 16 female rats per dosage level (0, 100, 1000, 750 ppm a.i.) were fed 97% DPX-T6376.

After 90 days, 5 male and 5 female rats were killed, necropsied and examined microscopically. The remaining rats continued on a one-generation one-litter reproduction study.

Results:

Fertility was "not meaningfully evaluated" because of low fertility in control and in test groups. No adverse effects were shown in indices of reproduction and lactation performance or weanling body weights.

Significantly lower body weights and body weight gains were found in females of the 7500 ppm group.

Serum protein was decreased in females of the 7500 ppm group.

Possibly compound-related changes, "statistically significant increased incidence of a decrease in cytoplasmic clearing of hepatocytes" were observed in all treated males. The biological significance, if any was undetermined.

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Conclusions:

Results of the one-generation study was not positive.

The study is not adequate for determining a NOEL.

Core Classification:

Supplementary

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DATA REVIEW

Study Type: 13-week feeding study - rat (interim report of feeding study with two-generation reproduction.

Accession Number: 071435

MRID Number:

Sponsor: DuPont

Contracting Lab: Hazleton Laboratories, Project No. 201-562

Date: October 22, 1982

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazion-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376 Technical)

Protocol:

Ninety male and 90 female rats (192.1-262.5 gm) per dosage level were fed DPX-T6376 (0, 5, 25, 500, 2500, or 5000 ppm). Observations were made. Samples for clinical pathology were taken after weeks 4 and 13. Ten animals from each sex and dosage level were killed after 13 weeks and examined grossly. Body weights and organ weights were determined. Livers of these were examined histopathologically.

Results:

There were no treatment-related deaths.

Treatment related, statistically significant, depressed growth rates were found at dosage levels 500, 2500, and 5000 ppm in males and females. Mean absolute and relative liver weights were decreased in males at 2500 and 5000 ppm and in females at 500, 2500, and 5000.

Elevations in platelet counts were reported to be statistically significant after 13 weeks in females at 25, 2500, and 5000 ppm. The increases were 15.6%, 13.3%, and 13.3%. Any relationship to treatment of these or meaning of these charges was not determined.

Conclusion:

NOEL was 25 ppm
LEL: 500 ppm

Core Classification:

Minimum.

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002990

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: 13-week progress report (for a combined 3-month and 1-year feeding study in dogs.

Accession Number: 071488

MRID Number:

Sponsor: DuPont

Contracting Lab: Hazleton Lab. project no. 201-571

Date: March 7, 1983

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-22, technical).

Protocol:

Ten male and 10 female dogs per dosage level, 0, 50, 500, 5000 ppm were fed DPX-T6376. Mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry and urinalysis were observed or determined and recorded.

After 13 weeks 4/sex/dosage level were killed, necropsied, weighed, and selected organs weighed. Tissues were subjected to histopathological examination.

Results:

These were no mortalities during the first 13 weeks. Reported clinical observations were lacrimation, dermal irritation, ear "sores," alopecia of the ears.

Histopathology indicated that the above referred to observed effects were due to topical irritation.

No histomorphologic changes were found which indicated systemic toxicity.

No behavioral signs were reported.

W Thomas Edwards

Conclusions:

. The only toxic effects reported were from irritation.

The indicated NOEL for systemic toxicity was 5000 ppm, the highest dosage tested.

Core Classification:

Minimum.

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5-19-83

TOXICOLOGY BRANCH

DATA REVIEW

Study Type: Teratogenicity - rat

Accession Number: 071435

MRID Number:

Sponsor: Du Pont, Haskell Laboratory

Contracting Lab: Argus Research Laboratories, Inc. project 104-002

Date: September 21, 1982

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376, 92.9%, Technical)

Protocol:

DPX-T6376 was given in corn oil (5 ml doses) by gavage to 25 female rats per group on days 5-14 of gestation. Dosage levels were 0, 40, 250, and 1000 mg a.i./kg/day. All dams were killed on gestation day 20 and examined. Half the fetuses in each litter were killed, evicerated and stained with alizerin red-S and examined.

Results:

No external or visceral or skeletal malformations were atributed to treatment. All fetal variations were due to delayed development. Incidences did not occur in a dosage-related pattern and were not significantly different among the dosage groups ($P>0.05$).

Treatment did not adversely affect the average number of carpora lutea or incidence of pregnancy, implantation, resorption, litter size, fetal viability or fetal body weight.

Increased incidence of physical signs was seen at 250 mg/kg and above, especially salivation which was significantly high statistically at 1000.

Incidences of the following were also reported:

Vocalization (increased incidences) at 40, 250 and 1000 mg/kg.

Ungroomed coat at 40, 250, and 1000.
Tip-toe walk at 250 and 1000.
Hyperactivity at 40 and 250.

Conclusion:

Not teratogenic on embryotoxic.

Maternal toxicity NOEL not determined. Very slight (not statistically significant) effect at 40 mg/kg.

Core classification:

Minimum.

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5-19-83

TOXICOLOGY BRANCH

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DATA REVIEW

Study Type: Teratogenicity-rabbit

Accession Number: 071435

MRID Number:

Sponsor: DuPont, Haskell Laboratories

Contracting Lab: Argus Research Laboratories, Inc., Project 104-003.

Date: October 7, 1982

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazon-2-yl)amino]carbonyl]amino] amino]carbonyl]amino] sulfonyl]-benzoate. (DPX-T6376,92.9%,technical).

Protocol:

Six months rabbits, 19 or 20 per group, were given 2 ml portions of test material in 0.5% aqueous methocel by gavage during dogs 6-18 of presumed gestation. The dosage levels were 0, 25, 100, 300 and 700 mg a.i./kg. Animals were observed at least daily on gestation days 6-18. On day 18 al does were killed.

Results:

Treated rabbits did not differ from controls significantly in average number of corpora lutea, incidence of pregnancy, implantation, or resorption, or in mean body weight of fetuses. Teratogenicity was not demonstrated in gross external or soft tissue or by skeletal malformations or variations.

The following mortality was observed in does and considered to be agent related.

Dosage (mg/kg)	Deaths
100	1
300	2
700	12 ($p < .001$)

Antimortem signs and weight gain effects which appeared to be dose related were the following:

1. Anorexia and red or orange colored urine at 100, 300, and 700 mg/kg levels, ~~2. Decreased motor activity and impaired righting reflex at 300 and 700 mg/kg levels~~.

2. Decreased motor activity and impaired righting reflex at 300 and 700 mg/kg levels.

3. Decreases in body weight gains, significant at 100 and 300 mg/kg levels during days 6 through 9 of gestation.

At necropsy the following observations were made.

1. Hair in stomach, 100, 300, and 700 levels. (Statistically significant at 700).

2. Thin stomach walls (P=0.053).

3. Petechiae in stomach at 700.

Conclusion:

Neither teratogenicity nor embryo-fetal toxicity was demonstrated.

Maternal toxicity was shown by deaths and decreased weight gain during dosing days.

Maternal NOEL: 25 mg a.i/kg,
LEL: 100 mg/kg

Core classification:

Minimum.

W Thomas Edwards
5-19-82

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TOXICOLOGY BRANCH

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DATA REVIEW

Study Type: Mutagenicity evaluation in Salmonella typhimurium.

Accession Number: 071435

MRID Number:

Sponsor: Du Pont

Contracting Lab: Haskell Laboratory, report no. 927-80.

Date: November 14, 1980.

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-11, approximately 100%).

Protocol:

The following tests were performed according to the Ames procedure.

Salmonella typhimurium strain	Activation, S-9	Concentration ug/plate	Plates per concentration	Positive control ug/plate
TA 1535	no	0 to 50.0	4	MNNG 4
TA 1535	yes	0 to 50.0	4	2AA 10
TA 1537	no	0 to 5.0	3	9AAc 50
TA 1537	yes	0 to 10.0	3	2AA 10
TA 98	no	0 to 5.0	3	2NF 25
TA 98	yes	0 to 10.0	3	2AA 10
TA 100	no	0 to 5.0	3	MNNG 4
TA 100	yes	0 to 10.0	3	2AA 5

Test solvent and negative control: Dimethylsulfoxide
positive controls:

MNNG, N-methyl-N'-nitro-N-nitrosoguanidine
2AA, 2-aminoanthracene
9AAc, 9-aminoacridine
2NF, 2-nitro-fluorene

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Results:

Results as reported were all negative i.e., no increase in revertents over negative control. Additional data are needed. (1) Cytotoxicity data. (2) Mutant frequency data. Also exposure of TA 98 and TA 100 did not extend into the toxic range.

Conclusion:

Results provisionally accepted. Additional data are required. See above.

W. Thomas Edwards
5-19-83

TOXICOLOGY BRANCH

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DATA REVIEW

Study Type: CHO/HGPRT Assays for gene mutation.

Accession Number: 071435

MRID Number:

Sponsor: Du Pont

Contracting Lab: Haskell Laboratory, report no. 612-82.

Date: October 27, 1982.

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-22, Technical).

Protocol:

The Chinese Hamsters Ovary (CHO) cell line was used to detect mutations in a gene coding for the enzyme hypoxanthineguanine phosphoribosyl transferase (HGPRT).

Two assay trials were made without S-9 activation and 3 trials with S-9 activaiton. Dosage levels were 0, 0.5, 1.0, 2.0, 3.5, and 7.0 mM. The positive control without S-9 was methanesulfonic acid, ethyl ester (EMS). The positive control with S-9 was 7,2-dimethylbenz[a]anthracene. Additional plates were prepared for determining survival data for each trial.

Results:

All test results were negative i.e., no difference in change of enzyme activity, but survival results for exposed cells did not reach or closely approach criteria stated in experimental design (i.e., 10% of control survival).

Conclusions:

Results provisionally accepted; but testing with higher concentrations to meet stated criterion is required.

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TOXICOLOGY BRANCH

DATA REVIEW

Study Type: In vitro assay for chromosome aberrations in Chinese hamster ovary (CHO) cells.

Accession Number: 071435

MRID Number:

Sponsor: Du Pont

Contracting Lab: Haskell Laboratory, report no. 28-83.

Date: January 19, 1983.

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-22, technical, 92.9%).

Protocol:

Chinese Hamster Ovary (CHO) cells were used in one trial assay without S-9 activation and 3 trials with S-9 for determining chromosome aberrations from exposure to DPX-T6376. Concentrations of DPX-T6376 ranged from 0 to 7.90 mM (3.0 mg/ml). The positive control without activation was methanesulfonic acid, ethyl ester (EMS), 4.83 mM in phosphate buffer. Positive control with activation was cyclophosphamide (CP), 0.10 mM in phosphate buffer.

Results:

Without activation (one trial):

These was significant induced clastogenic increase at 7.90 mM (3.0 mg/ml), the highest concentration tested. No significant effect at 2.63 mM or lower concentrations.

With activation (3 trials):

Combined analysis of trials I and II showed significantly increased clastogenic effect at $\geq$2.63 mM (1.0 mg/ml), none at 1.32 or lower concentrations. The third activated trial showed clastogenic effect at 7.90 mM (3.0 mg/ml), but not at 2.63 or lower concentrations.

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Cytotoxicity was determined (except for the third activated trial) by cell count in tests conducted in parallel with the chromosome aberration assays. Relative survival results for each of two plates 24 hours after initiation of treatment follow:

	Relative % (to control = 100%)
Without S-9	64.9
	52.4
First with S-9	52.0
	37.1
Second with S-9	66.4
	67.6

Conclusions: DPX-T6376 was shown to be clastogenic, causing chromosome aberrations in Chinese hamster ovary cells. It is noted that concentrations used in trials did not cause as high a level of cytotoxicity as would be required if results had been negative.

Thomas Edwards
5-19-83

002990

TOXICOLOGY BRANCH 419H

DATA REVIEW

Study Type: In vivo bone marrow cytogenetic assay in rats.

Accession Number: 071435

MRID Number:

Sponsor: Du Pont

Contracting Lab: Haskell Laboratory, project no. 201-575.

Date: January 7, 1983.

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-22, technical, 92.9%).

Protocol:

Observations were made of increases in numerical and structural aberrations at first mitotic division treatment in rat bone marrow cells. Single doses were given by gavage to 20 males and 20 females per dose level: 0, 500, 1000, and 5000 mg/kg. Five males and 5 females of each dose level were killed at 6, 12, 24, and 48 hours after the single doses. The diluent was corn oil. The positive control was cyclophosphamide.

Results:

No statistically significant increases in frequency of chromosomal aberrations or any statistically significant differences between mean modal numbers or mean mitotic indices of test groups compared to negative controls.

Conclusions:

This assay for cytogenetic damage is incomplete. A multiple dosage schedule is also required (usually for 5 days). Determination is needed that enough compound was absorbed to cause, (1) toxicity to animal, and (2) cytotoxic effect in bone marrow. UNACCEPTABLE DATA.

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5-19-83

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TOXICOLOGY BRANCH

DATA REVIEW

Study Type: Unscheduled DNA synthesis (UDS) assay, rat hepatocytes in vitro.

Accession Number: 071435

MRID Number:

Sponsor: Du Pont

Contracting Lab: Haskell Laboratory, report no. 770-82.

Date: January 6, 1983.

Test Material: Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376-22, technical).

Protocol:

Freshly isolated hepatocytes from the livers from an unstated number of eight-week old male Charles River Sprague-Dawley rats were treated with DPX-T6376 in vitro and the incorporation of ^{3}H-thymidine measured as a measure of unscheduled DNA repair. Detection of 5 grains or more (after background correction) over a nucleus is considered a positive response.

Solvent was DMSO, present in all tests, as well as in negative and positive controls. Positive control substance was 7,12dimethylbenz[a]anthacene (DMBA).

Test compound concentrations were 0, 1×10^{-4}, 1×10^{-3}, 1×10^{-2}, 0.1, and 1.0 mM DPX-T6376 in trial I, and 0, 1×10^{-5}, 1×10^{-4}, 1×10^{-3}, 1×10^{-2}, 0.1, and 1.0 mM in trial 2.

Results:

Negative, i.e., <5 grains/nucleus at any concentrations tested.

Conclusions:

Unacceptable data, since

1. No cytotoxicity data.
2. At least 3 animals of each sex are required.
3. Treatment to toxicity levels must be performed.
4. Suggest that hepatocytes isolated from treated animals be sampled for UDS.

rv Thomas Edwards
5-17-83