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

OCT 18 1985

004722

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Ally (DPX-T6376)

FROM: Thomas Edwards; Pharmacologist
Hazard Evaluation Division (TS-769)

TO: Robert Taylor/Vickie Walters
Registration Division (TS-767)

THRU: Clint Skinner, Section Chief
Review Section III

and

Theodore Farber, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Theodore M. Farber

Chemical: Ally (DPX-T6376)

Caswell No: 419H

EPA Registration No.: 352-UGL, 4F3127

Accession Nos.: 072758-68, 073071-2, 073332-45.

Record Nos.: 126730, 126736, 136885, 136886, 145582, 146963, 146964

Requested Actions:

Registration and the following tolerances.

	PPM
Wheat grain	0.05
Wheat straw	0.1
Wheat green forage	5.0
Barley grain	0.05
Barley straw	o.1
Barley green forage	5.0
Milk	0.05
Meat, fat, and meat by-products (except kidney and liver) of cattle, goats, hogs, horses, and sheep	0.1
Kidney and liver of cattle, goats, hogs, horses, and sheep	0.1

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Reco

Requ

MRIDs 145007, 141821 - 141836,
145008, 145009,
151135, 151028, 151029,
154477

(1A)

Free Standing Summary for Setting Tolerances for the Pesticide Ally, DPX-T6376

1. Summary of Toxicology Data Considered in Setting the Tolerances

DATA ON TECHNICAL

Study	Results
Accute oral LD_{50} - rat	LD_{50} > 5000 mg/kg (only dose tested)
2-Year feeding/oncogenic - rat	INTERIM REPORT NOEL = 25 ppm LEL: 500 ppm (depressed growth rates and decreased liver weights) Mean absolute and relative liver weights were decreased in males at 2500 and 5000 ppm and in females at 500, 2500, and 5000 ppm. Final Report Oncogenic NOEL>5000ppm(HDT) Systemic NOEL: 500 ppm Systemic LEL: 5000 ppm (HDT)(decreased body weight).
18-Month oncogenic - mouse	Oncogenic NOEL > 5000 ppm (HDT). Male and female CRL:CD-1 (ICR) BR mice were fed 0, 5, 25, 500, 5000 ppm. Equivocal MTD determination NOEL: more than 5000 ppm (HDT).
1-Year feeding - dog	NOEL = 50 ppm LEL=500 ppm (decreased serum LDH)
Teratology - rat	Teratogenic NOEL > 1000 mg/kg/day Maternal toxic NOEL<40 mg/kg/day (LDT)(hyperactivity, ungroomed coat) Fetal toxic NOEL > 1000 mg/kg/day (HDT)
Teratology - rabbit	Teratogenic NOEL > 700 mg/kg/day(HDT). Maternal toxic NOEL = 25 mg/kg/day. Maternal toxic LEL = 100 mg/kg/day. (decreased weight gain and death) Fetal toxic NOEL > 700 mg/kg/day(HDT) The 300 and 700 mg/kg/day levels produced decreased motor activity and impaired righting reflex.

Background:

Ally is a herbicide.
An EUP and temporary tolerances on wheat grain and barley grain were toxicologically supported by our memorandum dated August 31,1983. This was based on a NOEL of 25 ppm from a 13-week rat feeding study and a safety factor of 2000.

Comments:

Reviews of studies submitted with this action are attached. These studies are summarized in the one liners.

A summary of support for proposed tolerances, which contains comments is attached.

Conclusions:

The major concern is the lack of a adequate MTD from the mouse oncogenicity study. This should be adressed before tolerances are granted.

Less urgent but diserving of attention is the neurologic effect seen in the rabbit and rat teratology study.

Another study, the 21-day rabbit dermal toxicity study should be supplemented. Not enough animals per group were used for adequate interpretation. No statistical dose related trend was demonstrated, but there were instances of testicular damage. Because of the lack this effect in other studies, it is not apparent that this was a meaningfull observation.

The two latter concerns should be adressed within a limited time,but would not be considered sufficient for a delay in issuance of tolerances.

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2-Generation, 4-Litter Reproduction - rat	Reproduction NOEL 5000 ppm(HDT) Fetoxic NOEL>5000 ppm(HDT) Maternal NOEL= 500 ppm Maternal LEL= 5000 ppm (decreased weight gain)
Mutagenic - salmonella typhimurium	Test for Histidine producing revertants in strains TA 1535, TA 1537, TA 98, and TA 100. All results were negative.
Mutagenic - chromosomal aberrations (CHO) in vitro	Aberrations in Chinese hamster chromosomes were caused, with and without S-9 activation.
Mutagenic - unscheduled DNA synthesis - rat	Negative. Not mutagenic.
Metabolism - rat	Rapid elimination of radioactivity. 91% or over in 96 hours.

2. Desirable data which is lacking.

a) Although no statistically significant toxicological effects were noted in the mouse oncogenicity study, there were some indications of decreased body weight gain at the highest level tested. Additional justification is needed to support the adequacy of dose levels used in the mouse oncogenicity study.

b) In the dog feeding study, contrary to the view of the contract reviewer, there appear to be dose related serum lactic dehydrogenate decreases at the highest and mid disage levels which indicate that 50 ppm is the highest certain NOEL. This NOEL could possibly be amended if historical control data from the same laboratory were furnished.

c) The rabbit teratology study showed that at the 300 and 700 mg/kg/day treatment levels caused decreased motor activity and impaired righting reflex. This is not interpreted as a "delayed" neurotoxicity effect but as another effect on the central nervous system which deserves clarification. The effect appeared to be slight at the lowest dosage level.

3. Actions needed.

Items a) and c) of 2. above should be satisfactorily addressed without delay.

4 & 5. Other tolerances.

This is the first tolerance request for this new pesticidal chemical.

6. ADI, MPI and TMRC.

Shown in the attached print-out of acceptable daily intake data are the following results:

The 1-year dog feeding NOEL was 50 ppm=1.25 mg/kg/day. The safety factor of 100 resulted in an ADI of 0.0125 and an MPI for 60 kg of 0.7500. The TMRC was 0.0455 mg/kg (1.5 kg) and % ADI of 6.06.

7. Pending regulatory actions.

None.

8. Relevant considerations in setting tolerance.

Special consideration should be given the equivocal results from the mouse oncogenicity study as indicated in items 2.a) and 3 above.

The neurologic effects found by the rabbit teratology study should be addressed in the near future preferrably after discussion with EPA. It is anticipated that clarification of neurologic effects found in the rabbit study will also clarify the slight effects noted at the LDT in the rat teratology study.

NO CFR NUMBER ● OPP-16376 ● 10/4/85 004722

unverified Printout 00472D472-2

ACCEPTABLE DAILY INTAKE DATA DRAFT

LOG mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
1.250	50.00	100	0.0125	0.7500

NOEL may change as recorded per

Current Action 453127

CROP	Tolerance	Food Factor	mg/day(1.5kg)
barley(8)	0.050	0.03	0.00002
wheat(170)	0.050	10.35	0.00777
meat, req(90)	0.100	10.81	0.01622
milk&dairy products(93)	0.050	28.62	0.02146

MPI	TMRC	% ADI
0.7500 mg/day(60kg)	0.0455 mg/day(1.5kg)	6.06

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TOXICOLOGY BRANCH

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).

EPA Evaluation Reriew. N Thomas Edwards 9-9-85
Thomas Edwards Date

Review Section Approval. Clint Skinner 9-9-85
Clint Skinner Date

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 ($p < .001$)

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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.

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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-triazion-2-yl)amino]carbonyl]amino]sulfonyl]-benzoate. (DPX-T6376, 92.9%, Technical)

EPA Evaluation Reriew. Thomas Edwards (Thomas Edwards) 9-9-85 (Date)

Review Section Approval. C T Skinner (Clint Skinner) 9-9-85 (Date)

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.

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

004722

EPA: 68-01-6561
TASK: 121
September 9, 1985

DATA EVALUATION RECORD

DPX-T6376

90-Day/18-Month Feeding Study in Mice

STUDY IDENTIFICATION: Stadler, J. J. Ninety-day and long-term feeding study in mice with benzoic acid, 2[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]methyl ester (INT-6376). (Unpublished study No. 463-84 by Haskell Laboratory for Toxicology and Industrial Medicine, E.I. duPont de Nemours and Company, Newark, DE; dated November 7, 1984.) Accession Nos. 073071-2.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 1-9-85

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1. CHEMICAL: DPX-T6376; benzoic acid, 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]methyl ester; INT-6376.

2. TEST MATERIAL: INT-6376 technical (Agricultural Chemical Notebook 8660-5) was a milled, white solid with a stated purity of 92.9 percent.

3. STUDY/ACTION TYPE: Subchronic and chronic toxicity/oncogenicity study in mice.

4. STUDY IDENTIFICATION: Stadler, J. C. Ninety-day and long-term feeding study in mice with benzoic acid, 2[[[[(4-methoxy-6-methyl-1,-3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]methyl ester (INT-6376). (Unpublished study No. 463-84 by Haskell Laboratory for Toxicology and Industrial Medicine, E.I. duPont de Nemours and Company, Newark, DE; dated November 7, 1984.) Accession Nos. 073071-2.

5. REVIEWED BY:

Kumar D. Mainigi, Ph.D.
Principal Author
Dynamac Corporation

Signature: Kumar D. Mainigi
Date: 9-9-85

William L. McLellan, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: William L McLellan
Date: Sept. 9, 1985

6. APPROVED BY:

I. Cecil Felkner, Ph.D.
Chronic Toxicity/Oncogenicity
Technical Quality Control
Dynamac Corporation

Signature: I Cecil Felkner
Date: 9-9-85

W. T. Edwards
EPA Reviewer

Signature: W Thomas Edwards
Date: 9-10-85

Clint Skinner
EPA Section Head

Signature: Clint Skinner
Date: 9-10-85

7. CONCLUSIONS:

A. Under the conditions of the study, 5, 25, 500, or 5,000 ppm of INT-6376 was not oncogenic when fed to male or female CD-1 mice for 18 months. There were no toxic signs/effects of importance, and survival was similar in dosed and control groups, which ranged from 74-96 percent at 18 months. There were no compound-related changes in hematologic parameters or total serum protein. Gross and histologic findings were similar in control and dosed groups. The only effect noted was a slight but significant decrease in mean body weights in dosed males, which was not considered compound related because there was no dose-related trend. Based on these finding, the NOEL has been set at 5,000 ppm, the highest dose level tested; a LOEL was not achieved.

B. The study is being classified Core Supplemental for both the subchronic toxicity and chronic toxicity/oncogenicity data because the highest dose level failed to induce any toxicity in the animals.

8. RECOMMENDATIONS:

It is recommended that the present study be supplemented with toxicity data at higher dose level(s). EPA guidelines require that the highest dose level for both subchronic and long-term studies elicit some signs of toxicity.

9. BACKGROUND:

To determine the dose range for long-term exposure in mice, a 90-day study using young male adult rats of undefined source, strain, age, and body weights was conducted. Rats were fed 0, 100, 1,000, or 7,500 ppm of INT-6376. The compound-related toxicity was observed at the highest dose level; therefore, the NOEL was established at 1,000 ppm.

Item 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOL): (See Appendix A for details.)

A. Materials and Methods:

1. In this combined 90-day (subchronic) and 18-month (545-day) (chronic and oncogenicity) study, mice were fed diets containing technical grade INT-6376 compound. Lot, batch number, date of receipt, and storage conditions for the test compound were not reported.

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[1]Only items appropriate to this DER have been included.

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2. Diets were prepared weekly by homogenizing the milled, white solid test material with certified Purina Laboratory Chow #5002. Homogeneity/concentration/stability of the test compound in the diets were determined prior to study initiation at three intervals of approximately 100 days and at the end of the study.

3. Male and female CRL:CD-1 (ICR) BR mice (Charles River Breeding Laboratories, Inc., Kingston, NY), approximately 6 weeks old, were adapted to the animal facility for 13 days and then randomly distributed into experimental groups. Six groups of 90 males (29.6-30.0 g) and 90 females (21.9-22.6 g) were fed diets containing 0, 5, 25, 500, 2,500, or 5,000 ppm of INT-6376. All mice were weighed at weekly intervals for 6 months and biweekly thereafter; food consumption was determined weekly. Animals were observed twice daily for signs of toxicity and mortality, and the animals received detailed weekly examinations (including palpations for tissue masses) for the first 6 months and biweekly thereafter. Blood was collected at 1, 2, 3, 6, 12, and 18 months from 10 mice/sex/group for hematologic determinations and measurement of total serum protein.

4. Ten mice/sex/group were sacrificed for pathological evaluation after 90 days. The groups receiving 2,500 ppm were terminated at 12 months. The remaining animals in each treatment group were continued on their respective diets for 18 months, after which all surviving animals were sacrificed and examined grossly. Mice sacrificed in extremis or found dead during the study were also examined.

5. The following organs were weighed at the 90-day, 18-month, and in extremis sacrifices: brain, heart, liver, kidney with adrenals, and testes with epididymides. Approximately 35 tissues from each animal were processed for histopathology. All tissues from mice found dead or sacrificed in extremis and all tissues from the control and 5,000-ppm treatment groups that were sacrificed at 90 days or at termination were examined microscopically. In addition, lungs, livers, kidneys, and all gross lesions were examined from mice in the 5-, 25-, and 500-ppm groups at terminal sacrifice.

6. Tissues (brain, liver, kidney, spleen, muscle, testis, and fat) and blood samples were collected at the terminal sacrifice, pooled by test group, frozen, and sent to the Agricultural Chemicals Department for residue analyses.

Statistical Analysis: Analysis of variance (ANOVA) was performed on all continuous data measurements (body weights, body weight gains, organ weights, and clinical chemistry determinations). Differences between controls and treatment groups were analyzed either by the least significant-

difference (LSD) test or Dunnett's test for multiple comparisons. Bartlett's test was used to establish homogeneity of variance before the ANOVA was performed. The level of significance was 0.05.

B. Protocol: Materials and Methods are submitted in lieu of protocol, see Appendix A.

Quality Control Information is not included

12. REPORTED RESULTS:

Dietary Analysis: The mean concentrations of INT-6376 in freshly frozen samples taken at five different intervals were within ±12 percent of the nominal concentrations. Although the percent recovery for the active ingredient was fairly constant (92.7 percent), an [redacted] material applied to the column was recorded. No attempt to identify this impurity was made. However, on a weight-to-weight basis, correct amounts of the active ingredients were added to the test diets.

Analysis of samples taken from different levels of the mixing vessel showed that INT-6376 was homogeneously distributed in the diet. Similarly, samples stored at different temperatures (frozen, refrigerated, room temperature) from 24 hours to 10 days had at least 80 percent of the INT-6376 concentration found in freshly frozen samples.

Clinical Observations and Mortality: During the subchronic study, a high incidence of ruffled fur was observed in all the males receiving INT-6376 except for those receiving 25 ppm (Table 1). This clinical condition persisted through the chronic/oncogenicity study, but was not considered to be compound related; its biological significance remained unexplained. Other observations occurred at a low incidence and were not increased in the dosage groups when compared to the control groups. During the entire 18-month study, a total of six masses, three in each sex and no more than one in each dosage group, were observed.

By the end of the 90-day study, none of the male or female dosage groups had more than two unscheduled deaths. The number of deaths at the end of the long-term study ranged from 15 to 24 per group. No dose-response trend was apparent; therefore, none of the mortalities were considered to be compound related (Table 2).

Body Weights: At the end of the 90-day study, mean body weights in both the 500- and 5,000-ppm female groups were significantly ($p < 0.05$) lower than controls. By the end of the 18-month study, mean body weights for all male groups on the test diets were significantly ($p < 0.05$) lower than controls. The mean weights for females were lower only in the 500- and 5,000-ppm groups. In all male groups fed INT-6376 diets, mean body weight gains over the 545 (18 months) days of the study were slightly (5-8 percent) lower than

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TABLE 1. Incidence of Ruffled Fur in Male and Female Mice Fed Diets Containing Different Levels of INT-6376 for 90 Days[a]

	Concentration (ppm)					
	0	5	25	500	2500	5000
Males	4(28)[b]	14(28)	6(49)	13(28)	16(36)	10(28)
Females	1(45)	1(42)	2(39)	4(43)	0	0

[a] There were 90 mice in each group at the start of the study.

[b] The number outside the parentheses indicates the number of mice within each group that exhibited the clinical condition and the number within the parentheses indicates the median days-on-test when the clinical sign was first observed.

TABLE 2. Incidence of Mortality in Mice Fed Diets containing Different Levels of INT-6376 for 545 Days

Dietary Group (ppm)	Number of unscheduled deaths (% mortality)[a]			
	Males		Females	
	0-90 days	91-545 days	0-90 days	91-545 days
0	1/90(1%)	17/79(22%)[b]	1/90(1%)	20/79(25%)
5	2/90(2%)[b]	15/78(19%)	2/90(2%)	20/78(26%)
25	0/90(0%)	24/80(30%)	2/90(2%)	20/78(26%)
500	0/90(0%)	17/80(21%)	1/90(1%)	18/79(23%)
2,500	1/90(1%)	3/79(4%)[c]	2/90(2%)	7/78(9%)[b,c]
5,000	0/90(0%)	22/80(28%)	1/90(1%)	22/79(28%)

[a] % mortality = (number of unscheduled deaths during interval/number of survivors at start of interval) x 100.

[b] Includes one mouse killed accidentally.

[c] Unscheduled deaths prior to group sacrifice at 12 months.

the controls. However, the smallest gain, but not significantly different, was in the 25-ppm group (Table 3). The reduced body weights and weight gains were not considered compound related; there was no indication of a dose-related trend, and the values that were significantly lower than controls were not consistent with time but occurred sporadically.

Food Consumption: During the subchronic phase of the study, the mean daily food consumption by males in various dose groups differed from controls. In comparison, it was slightly higher in the 500- and 5,000-ppm groups and lower in the 5-, 25-, and 2,500-ppm groups of males. In all the female treatment groups, consumption was slightly lower than in the controls. The report stated that the differences were not significant. However, because of lack of individual data and statistical analysis of group data, this statement cannot be verified. In conclusion, no dose-response trend for food consumption was evident (Table 4).

Hematology and Biochemistry: Hematologic parameters and total serum protein were measured from blood samples taken from each mouse at 1, 2, 3, 6, 12, and 18 months. Several data were found to be statistically significant when compared to the controls, but these differences were found to be within the normal ranges of biological variation. No compound-related hematologic effects were observed in either of the sexes. The 5,000-ppm dietary concentration of INT-6376 was interpreted to be the NOEL for the hematologic and total serum protein measured under the conditions of this study.

Organ Weights: After the subchronic study, 10 males and 10 females from each dietary group were necropsied, and various organs were collected for gross and histopathological examinations. In males the absolute liver weights in the 5- and 25-ppm groups and of testes with epididymides from the 5-, 25-, and 500-ppm groups were higher than controls (Table 5). The relative weights of male livers in the 5-ppm group and relative weights of testes in the 5- and 25-ppm groups were significantly ($p < 0.05$) higher than their respective controls (Table 6). None of the organ weights in the the females were significantly different from controls. In males on long-term feeding, none of the mean absolute organ weights were statistically different from controls. The mean relative brain weights for all treatment groups were significantly ($p < 0.05$) higner than controls, but no dose-response relationship existed. No significant changes in absolute or relative organ weights were observed in females.

Gross Pathology and Histopathology: At necropsy all the mice were observed for gross abnormalities. All the mice from control and 5,000-ppm groups were examined histologically. In other groups, only the dead animals and those sacrificed in extremis were examined histologically. No gross or histopathologic changes were attributed to dietary intake of INT-6376.

TABLE 3. Mean Body Weights (g) at Selected Intervals in Mice Fed INT-6376 for 545 Days

Group/dose (ppm of INT-6376)	Day 0	7	28	91	182	365	545
MALES							
0	30.0(1.7)[a]	31.4(1.67)	33.6(2.77)	37.3(3.10)	39.1(4.77)	43.5(6.28)	45.1(6.30)
5	29.8(1.[illegible])	30.7(2.01)	33.3(2.81)	36.4(2.51)	38.2(3.69)	42.2(4.52)	42.2*(5.44)
25	29.6(1.88)	31.2(1.75)	34.4(2.57)	37.0(2.76)	38.9(3.70)	42.2(4.33)	41.4*(3.31)
500	29.8(1.75)	31.4(1.87)	32.6(3.13)	36.9(3.10)	38.7(4.45)	42.5(5.22)	42.7*(5.62)
2,500	29.9(1.68)	31.3(2.10)	33.2(1.91)	36.5*(2.61)	38.7(3.47)	-[b]	-[b]
5,000	29.9(1.87)	31.5(2.39)	32.5(3.22)	36.3(2.55)	38.2(3.84)	41.3(4.24)	42.2*(4.74)
FEMALES							
0	22.6(1.94)	23.7(1.55)	25.9(1.75)	28.9(2.65)	29.9(3.06)	35.3(3.59)	35.9(4.37)
5	22.5(1.70)	23.7(1.52)	25.7(1.90)	28.4(2.89)	30.9(3.26)	34.1(3.77)	34.7(3.53)
25	22.0(1.85)	23.5(2.05)	25.4(2.37)	28.3(3.46)	30.3(3.74)	33.9(4.50)	34.5(4.70)
500	21.9(1.91)	23.4(1.65)	25.7(1.73)	27.9*(2.89)	27.6*(4.87)	33.1*(4.02)	34.2*(5.74)
2,500	22.0(2.00)	23.3(1.91)	25.1(2.38)	28.2(2.74)	27.8*(4.64)	-[b]	b
5,000	22.1(1.81)	23.6(1.76)	25.2(1.95)	27.6*(2.55)	29.9(3.33)	32.5*(3.65)	33.5*(4.77)

*Statistically different from control at $p < 0.05$.

[a]Values in parentheses are standard deviations.

[b]Animals sacrificed prior to day 350.

TABLE 4. Mean Daily Food Consumption (g) of Mice Fed Various Levels of INT-6376 for 545 Days

Group/Dose (ppm)	Interval on Test (Days)			
	0-7	0-91	0-182	0-545
Males				
0	6.0	5.5	5.3	5.3
5	5.7	5.3	4.8	4.9
25	5.7	5.2	4.9	5.1
5000	5.8	5.6	5.4	5.2
2,500	6.2	5.4	5.1	—[a]
5,000	7.3	5.6	5.3	5.2
Females				
0	5.0	5.4	5.1	5.5
5	4.8	5.0	4.9	5.1
25	4.9	4.9	4.8	5.2
500	5.0	4.9	4.6	5.0
2,500	5.2	4.7	4.6	—[a]
5,000	5.1	4.9	4.8	5.1

*Animals sacrificed prior to 355 days.

TABLE 5. Mean Absolute Organ Weights (g) of Male Mice Fed Various Levels of INT-6376 for 90 Days

Concentration (ppm)	Liver	Testis/Epididymides
0	1.855 (0.177)[a]	0.390 (0.107)
5	2.118 (0.217)*	0.493 (0.054)*
25	2.067 (0.257)*	0.548 (0.067)*
500	1.858 (0.188)	0.502 (0.067)*
2,500	1.766 (0.151)	0.400 (0.099)
5,000	1.718 (0.148)	0.437 (0.117)

* Significantly different ($p < 0.05$) from control group by LSD and Dunnett's test.

[a] Values in parentheses are standard deviations.

TABLE 6. Mean Relative Organ Weights (% Body Weight) of Male Mice Fed Various Levels of INT-6376 for 545 Days

Concentration (ppm)	Liver (90 Days)	Testes/ Epididymides (90 Days)	Brain (545 Days)
0	5.053 (0.375)[a]	1.065 (0.286)	1.176 (0.151)
5	5.477 (0.462)[b]	1.281 (0.175)[c]	1.226 (0.148)[c]
25	5.235 (0.408)	1.389 (0.117)[b]	1.286 (0.130)[b]
500	4.613 (0.315)	1.247 (0.145)	1.252 (0.166)[b]
2,500	4.689 (0.336)	1.064 (0.263)	—[d]
5,000	4.706 (0.519)	1.193 (0.314)	1.230 (0.104)[c]

[a] Values in parentheses are standard deviations.

[b] Significantly different ($p < 0.05$) from control group by LSD and Dunnett's test.

[c] Significantly different ($p < 0.05$) from control group by LSD.

[d] Animals sacrificed prior to 355 days.

A variety of neoplastic lesions were observed in all the dietary groups in both sexes (Table 7). Metastatic lymphomas were the major type of neoplasms observed (Appendx B). However, no lesions attributable to INT-6376 treatment were observed in this study.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The author concluded that exposure of male and female mice to INT-6376 in the diet resulted in no compound-related lesions; all lesions and/or observations were interpreted to be the result of intercurrent disease and/or spontaneous age-related changes. The author also concluded that the decreased body weights observed in all compound-treated mice were not related to dietary intake of INT-6376; no dose-response trend was evident and no other adverse effects were observed during this study. Therefore, the author concluded that the NOEL for the dietary administration of INT-6376 to male and female mice for 90 days and 18 months is 5,000 ppm, which was the highest dose tested.

B. A signed but undated quality assurance statement was presented.

14 REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

Under the conditions of the study, INT-6376 was not oncogenic. This conclusion was based on the well-documented histopathologic records. The experimental protocol, however, was not adequate to evaluate the chronic/oncogenicity testings. A 90-day rat study to find the dose range was conducted. The compound-related effects (reduced body weights and total serum protein and decreased liver weights) were observed at the highest concentration of 7,500 ppm. For the long-term exposure the highest dose level was reduced to 5,000 ppm. No rationale for this change was given in the report. The species of mouse used for the long-term study failed to exhibit any toxic effect(s) due to the test compound. In males, the mean body weight gains over the 545 days of INT-6376 feeding were slightly (5-8 percent) lower than the controls. The lowest gain was recorded in the 25-ppm group. Apparently, this minor change in body weight was not a dose-related effect. We agree with the study author's conclusion that 5,000 ppm is the NOEL. However, the LOEL remains undetermined. It is suggested that the sponsor provide supplementary toxicity data at the higher dose level(s). EPA guidelines require that the highest dose level for both subchronic and long-term studies elicit some signs of toxicity.

Under Materials and Methods it was mentioned that tissues and blood samples were sent to the Agricultural Chemicals Department (Biochemicals Department) for residue analysis and that the department was to report the results of such analysis. No such results were found in the report.

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TABLE 7. Incidence of Neoplastic Lesions in Mice Fed Different Levels of INT-6376 for 545 Days

	Males Dose level (ppm)					Females Dose level (ppm)				
	0	5	25	500	5000	0	5	25	500	5000
Liver	79[a]	78	80	80	78	79	77	78	76	78
Hepatocellular adenoma	9	6	3	4	6	0	0	1	0	0
Carcinoma	5	3	2	2	4	0	2	0	0	0
Lung	79[a]	78	80	80	79	79	77	78	78	77
Alveolar/Bronchiolar Adenoma	3	5	6	6	4	4	4	5	2	1
Alveolar/Bronchiolar Carcinoma	3	0	1	0	2	2	1	2	2	0
Ovary						77[a]	38	38	35	76
Theca-granulosa cell tumor						2	0	0	0	4
Mammary Gland						77[a]	23	27	20	77
Adenocarcinoma						0	2	0	0	0
Adenoma						0	0	1	0	1
Uterus						79[a]	53	59	47	78
Endometrial stromal sarcoma						1	1	0	0	0
Fibrosarcoma						0	0	1	2	0
Leiomyoma						2	0	1	1	4
Leimyosarcoma						0	0	0	1	0
Multiple Tissues	79[b]	78	80	80	79	79	19	78	78	77
Metastatic lymphomas	3	1	7	1	2	5	6	5	3	7

[a]The number of organs examined for each group is underlined.

[b]The number of animals examined for each group is underlined.

The total serum protein was the only biochemical determination made. However, the text gave the impression that multiple clinical chemistry determinations were being made.

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Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 16-23.

004722

APPENDIX A

Materials and Methods
(pp. 4-13)

Pages 26 through 28 contain detailed registration data submitted by the registrant. These pages are not included.

004722

EPA: 68-01-6561
TASK: 121
August 20, 1985

DATA EVALUATION RECORD

DPX-T6376 (H-14453)

Chronic Feeding Study in Rats

STUDY IDENTIFICATION: Burdock, G. A., Hamada, N. N., Dudeck, L. E., Alsaker, R. D., Hastings, T. F., Burns, J. M., and Mistretta, L. H. Chronic feeding study with concurrent two-generation reproduction study in rats. Chronic phase H-14453. (Unpublished study No. 201-562 prepared by Hazleton Laboratories of America, Inc., Vienna, VA, for E. I. duPont de Nemours and Co., Inc., Wilmington, DE; dated January 31, 1985.) Accession Nos. 073333-073345.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 8-20-85

004722

1. CHEMICAL: DPX-T6376.

2. TEST MATERIAL: H-14453, technical, benzoic acid 2[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) amino]carbonyl]amino]sulfonyl]-methyl ester, INT 6736, had a purity of 93-95.8 percent.

3. STUDY/ACTION TYPE: Chronic feeding and oncogenicity phase of a combined chronic feeding and oncogenicity and two-generation reproduction study in rats.

4. STUDY IDENTIFICATION: Burdock, G. A., Hamada, N. N., Dudeck, L. E., Alsaker, R. D., Hastings, T. F., Burns, J. M., and Mistretta, L. H. Chronic feeding study with concurrent two-generation reproduction study in rats. Chronic phase H-14453. (Unpublished study No. 201-562 prepared by Hazleton Laboratories of America, Inc., Vienna, VA, for E. I. duPont de Nemours and Co., Inc., Wilmington, DE; dated January 31, 1985.) Accession Nos. 073333-073345.

5. REVIEWED BY:

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Signature: Ina Cecil Dehmer for
Date: 8-20-85

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6. APPROVED BY:

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Date: 8-20-85

W. Thomas Edwards
EPA Reviewer

Signature: W. Thomas Edwards
Date: 9-1-85

Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 9-9-85

7. CONCLUSIONS:

A. Under the conditions of this study, H-14453 was not carcinogenic in Sprague-Dawley rats when fed for 2 years at levels of 5, 25, 500, or 5000 ppm in the diet. Mean body weights in males and females receiving 5000 ppm were significantly lower than controls and mean weight gains between weeks 0-13 or 0-52 were lower in rats receiving 5000 ppm than in controls. There were no toxicologically important effects as determined from hematology, clinical chemistry, or urinalysis testing, and no increase in any gross or histologic lesion occurred when dosed groups were compared with controls. At terminal sacrifice, brain-to-body weight ratios in males receiving 500 and 5000 ppm and the kidney-to-brain weight ratio in males receiving 500 ppm were increased compared to controls. However, absolute organ weights were similar in dosed and control groups and increases in relative organ weights may have been caused by decreased body weights. There were increases in organ weights at the 12-month sacrifice, but they are of doubtful toxicologic significance. The LOEL for systemic chronic toxicity is considered to be 5000 ppm based on body weights; the NOEL has been determined to be 500 ppm. The group receiving 2500 ppm was not considered when setting these values because these animals were terminated at 61-62 weeks.

B. This study was adequately designed and conducted to ascertain the chronic toxicity/oncogenicity phase of a chronic feeding study with a concurrent two-generation reproduction study in rats. The results of the reproduction phase of the study were not included in this report.

Items 8 through 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods:

The test material was 93-95.8 percent pure according to analysis received from the supplier. Groups of 90 male and 90 female Sprague-Dawley rats were fed diets containing the test material at levels of 0, 5, 25, 500, or 5000 ppm for 2 years or at 2500 ppm for 61 or 62 weeks. Twenty animals/sex/group were removed from the chronic study at 11 weeks for the reproductive phase of the study and put back into the chronic phase at week 32. Animals were examined twice daily for moribundity and mortality. Toxic signs and abnormal behavior were recorded weekly through week 26 of the study and every other week thereafter. Body weights were recorded every 3 days during quarantine, at initiation, weekly through week 26, biweekly during weeks 28-52, and monthly thereafter. Food consumption was recorded each week through week 26, every second week until week 52, and monthly thereafter. Each animal was also examined and palpated for tissue masses and abdominal distension weekly through week 26 and every other week thereafter.

[1] Only items appropriate to this DER have been included.

Clinical pathology determinations were performed during weeks 5, 14, 27, 53, 79, and 105 on 10 rats per sex per dose. All blood samples were obtained by orbital sinus puncture following an overnight fast. Overnight individual urine samples were collected using metabolism cages. During urine collections, the rats were deprived of food, but not water. Ten animals were sacrificed after 13 and 52 weeks of treatment, and the remaining rats were sacrificed after 104 weeks of treatment. (All remaining animals in the 2500-ppm group were sacrificed during weeks 61 and 62.) All animals were subjected to a gross necropsy, some organs (brain, heart, kidneys, testes, and liver) were weighed, and a complete set of tissues from all groups of animals was preserved in formalin. At the 13-week sacrifice, livers were examined histologically; for each rat found dead, sacrificed in extremis, or sacrificed at 52 weeks, all tissues were examined microscopically; at terminal sacrifice, all tissues of the control and high-dose groups and gross lesions, tumors, target organs, lungs, livers, and kidneys from other groups were examined histologically. Appropriate statistical analyses were performed on all the data.

B. Protocol:

Materials and Methods are submitted in lieu of protocol; see Appendix A.

12. REPORTED RESULTS:

A. Dietary Analysis: Three lots of test material were used during the study; the lots used between weeks 1-34 and 35-45 were 93 percent pure and the lot used between weeks 46-106 was 95.8 percent pure. Concentrations of test material in diet preparations, stability of test material, and homogeneity in diets were determined at several intervals during the study. Mean levels in the diet were about 70 percent for two intervals (weeks 52 and 60), 80 percent at six intervals (weeks 13, 15, 25, 62, 65, and 78), and greater than 90 percent at three intervals (weeks 1, 37, and 91). Analytical data indicated that the material was homogeneous in the diets and stable for up to 1 week at room temperature. Fresh diets were prepared weekly.

A summary of the purity of each of the three batches of the test material used in this study is found in Appendix A, page 5.

B. Clinical Observations and Mortality: "Clinical observations were of the type commonly observed for rats of this age and strain at the laboratory" and therefore, were considered unrelated to compound administration. Palpable tissue masses were observed in a similar number of rats in the control and treated groups. The incidence of clinical signs was small and of similar numbers in all groups.

Cumulative survival data are presented in Table 1. Survival was similar in all groups and ranged from 53-64 percent at 24 months.

C. Body Weight: Table 2 summarizes selected mean body weight and weight gain data. Body weight data were analyzed statistically (by the study authors) at weeks 13, 52, and 104. Mean body weights in males were significantly lower than controls for the group receiving 5000 ppm at weeks 13, 52, and 104 and at 13 weeks for the 2500-ppm group. Mean body weights in females were significantly lower than controls for the group receiving 5000 ppm at weeks 13 and 52 (but not week 104) and in the group receiving 2500 ppm at week 13. Body weight gains were significantly lower than controls in both males and females receiving 5000 ppm in the 0-13 and 0-52 week intervals and in males and females receiving 500 and 2500 ppm at the 0-13 week interval only.

D. Food and Water Consumption: Food consumption was noticeably decreased for both sexes in the 2500- and 5000-ppm groups during the first 8 weeks and continued through week 26 for the females in the 5000-ppm group. The food consumption values in dosed animals were comparable to the controls thereafter. The authors assessed that the decreased food consumption may have been caused by unpalatability of the test substance. Other groups of both sexes exhibited variable degrees of food consumption with sporadic instances of significantly increased or decreased consumption when compared to controls.

Water consumption was not measured in this study.

E. Clinical Pathology: Occasional statistically significant ($p \leq 0.05$) changes from the controls were noted for the various hematological and clinical chemistry parameters in the different groups at the various sampling intervals. However, these changes occurred sporadically and were not consistent with a dose-related trend or time. Mean corpuscular hemoglobin (MCH), hematocrit, and erythrocyte count were decreased in females receiving 5, 25, and 500 ppm at week 53. MCH was decreased in males receiving 25 and 2500 ppm at week 53; white cells were increased in males receiving 500 and 5000 ppm at weeks 53 and 79. There were also sporadic increases in platelet counts in females. Serum glutamic oxaloacetic transaminase was increased in males receiving 25 and 2500 ppm at week 79.

F. Organ Weights: At the 13-week sacrifice, mean liver weights in males receiving 5000 ppm and females receiving 2500 and 5000 ppm were significantly lower than in corresponding controls; liver-to-body weight ratios in females receiving 2500 and 5000 ppm were also significantly lower than controls. The weights of other organs were not determined at 13 weeks.

TABLE 1. Survival Data for Rats Fed H-14453 for 2 Years

Dietary Level (ppm)	Percent Survival at Week			
	Males		Females	
	52[a]	104[b]	52[a]	104[b]
0	96	99	63	59
5	99	99	56	53
25	99	99	64	61
500	96	98	63	56
2500	99	96	--[c]	--[c]
5000	98	94	59	61

[a]Based on 79-80 animals/group.

[b]Based on 68-70 animals/group.

[c]The groups receiving 2500 ppm were sacrificed between 61-62 weeks.

TABLE 2. Mean Body Weights and Weight Gains in Rats Fed H-14453 for 2 Years

Dietary Level (ppm)	Mean Body Weight (g) at Week[a]			Mean Weight Gain (g/rat) in the Interval[b]	
	13	52	104	0-13 Weeks	0-52 Weeks
Males					
0	502±48.8	617±62.5	627±62.1	278±44.2	393±57.5
500	494±36.7	608±55.4	583±83.0*	270±31.7*	382±51.5
2500	476±34.2*	599±55.5	—[c]	254±3..8*	377±51.3
5000	465±30.5*	581±54.6*	570±78.4*	244±27.6*	360±53.6*
Females					
0	277±25.3	364±51.9	414±69.4	118±18.6	205±47.4
500	271±21.2	370±49.3	402±93.5	112±17.2*	211±44.9
2500	266±20.8*	359±50.2	—[c]	108±16.9*	201±47.0
5000	259±18.7*	337±42.2*	392±83.2	101±14.9*	178±39.4*

*Statistically different from control value ($p < 0.05$).

[a] From Table 1, pp. 33-56 of final report (CBI).

[b] From Table 2B, p. 81 of final report (CBI).

[c] The groups receiving 2500 ppm were sacrificed at weeks 61 and 62.

At the 52-week sacrifice, there were significant increases, relative to control groups, in mean brain weights in males and females receiving 2500 and 5000 ppm. There were also increases in brain-to-body weight ratios (Table 3). Significant increases in absolute brain weights but no corresponding effect on relative brain weights in males receiving 25 and 100 ppm were observed when compared to controls. Mean heart weights were also significantly higher than controls in males and in females receiving 2500 and 5000 ppm and there were corresponding increases in heart-to-body weight ratios in males at 2500 and 5000 ppm and in females at 5000 ppm. Kidney-to-body weight ratios were significantly increased in males receiving 2500 and 5000 ppm.

At the terminal sacrifice, organ weights were similar for all groups but there were significant increases in brain-to-body weight ratios in males receiving 500 and 5000 ppm and kidney-to-body weight ratios in males receiving 500 ppm.

G. Gross Pathology: Gross lesions were consistent with those commonly found in rats of the same age and strain. There was no evidence for a dose-related trend in any of the gross observations.

H. Histopathology: Summary incidence tables for histopathologic findings in the final report separately tabulated findings for (a) decedents from weeks 1-52, (b) decedents from weeks 52-104, (c) animals sacrificed at week 13, (d) animals sacrificed at week 52, and (e) animals sacrificed after week 104. For animals at terminal sacrifice, a full complement of tissues were examined for the control and 5000-ppm groups; only liver, kidney, lungs, and grossly observed tumors were examined for animals in other groups. For animals at the 13-week sacrifice, only the livers were examined histologically. Animals that died or were sacrificed moribund had complete histologic examinations. No summary table of neoplasms was presented.

There were no increases in neoplasms when the high-dose animals were compared to controls. Table 4 summarizes tumor incidence in control and high-dose animals. Table 5 summarizes neoplasms for lung, liver, kidneys, mammary glands, and pituitary for all dose groups.

The incidence of nonneoplastic lesions was similar among control and dosed groups. The authors concluded that there were no microscopic lesions attributable to compound administration.

The authors noted an increased incidence of chronic progressive nephropathy in males receiving 2500 ppm (5/10) that were sacrificed at 52 weeks compared to controls (0/10) and an increase in focal hepatic alteration in males receiving 5000 ppm (4/10 versus 1/10 for controls) at the 52-week sacrifice. They did not consider these changes compound related. Nonneoplastic hepatic changes, however, were not increased in animals that died or in those sacrificed at termination.

TABLE 3. Mean Organ Weights and Organ-to-Body Weight Ratios at 52 Weeks[a]

	Males/Dose Level (ppm)			Females/Dose Level (ppm)		
	0	2500	5000	0	2500	5000
Brain						
grams	2.25±0.16	2.69±0.12*	2.67±0.14*	2.03±0.08	2.45± 0.11*	2.46±0.10*
% x 10^2	39.8± 5.4	47.8± 5.4*	50.3± 2.3*	60.1± 8.2	74.1±10.9*	76.3± 6.4*
Heart						
grams	1.54±0.20	1.85±0.13*	1.87±0.22*	1.02±0.14	1.33± 0.13*	1.45±0.37*
% x 10^2	27.1± 3.5	32.9± 2.9*	35.1± 3.9*	28.2± 3.9	27.4± 4.2	43.7± 8.3*
Kidneys						
grams	3.40±0.58	3.76±0.32*	3.57±0.24	2.55±0.45	2.40± 0.30	2.38±0.33
% x 10^2	59.5± 7.6	66.6± 4.6*	67.1± 5.2	75.7±15.2	71.5±10.1	74.0±13.9

*Significantly different from control value ($p < 0.05$).

[a]Mean of 10 animals/sex/group.

TABLE 4. Incidence of Primary Neoplasms in Rats Administered H-14453 for 2 Years[a]

Organ/Neoplasm	Males/Dose Level (ppm) 0	Males/Dose Level (ppm) 5000	Females/Dose Level (ppm) 0	Females/Dose Level (ppm) 5000
Brain	(77)[b]	(78)	(76)	(75)
Glioma	3	5	0	0
Adrenal	(76)	(78)	(78)	(74)
Pheochromocytoma	13	11	2	3
Pheochromocytoma (M)	1	1	0	0
Cortical adenoma	1	2	0	0
Pancreas	(77)	(77)	(78)	(74)
Carcinoma, islet cell	4	0	4	1
Thyroid	(73)	(76)	(74)	(72)
C-cell adenoma	8	5	4	5
C-cell carcinoma	0	3	2	1
Follicular adenoma	1	1	0	0
Follicular carcinoma	1	0	0	1
Testis	(77)	(78)		
Interstitial cell tumors	6	1		
Uterus			(78)	(75)
Endometrial stromal polyp			1	3
Leiomyosarcoma			1	0
Cervix			(78)	(75)
Squamous carcinoma			0	2
Skin	(77)	(78)	(78)	(75)
Lipoma	7	2	0	1
Squamous papilloma	3	2	1	0
Basal cell carcinoma	1	0	0	0
Keratoacanthoma	6	6	0	0
Zymbal gland	(43)	(39)	(41)	(42)
Squamous papilloma	0	0	1	0
Squamous carcinoma	2	1	0	0

[a]Includes animals sacrificed at 52 and 104 weeks and decedents from week 52.

[b]Numbers in parenthesis are the number of tissues examined histologically.

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TABLE 5. Incidence of Primary Neoplasms in Rats Administered H-14453 in the Diet for 2 Years

Organ/Neoplasm	Males/Dose Level (ppm)					Females/Dose Level (ppm)				
	0	5	25	500	5000	0	5	25	500	5000
Liver	(77)[a]	(78)	(78)	(76)	(78)	(78)	(78)	(79)	(77)	(75)
Hepatocellular carcinoma	2	0	2	0	2	1	1	0	0	0
Neoplastic nodule	0	0	2	3	4	1	0	2	0	2
Mammary Gland						(77)	(65)	(67)	(66)	(75)
Adenoma						0	0	1	0	5
Fibroadenoma						22	23	19	29	22
Adenocarcinoma						12	9	11	11	12
Pituitary	(76)	(60)	(54)	(52)	(76)	(78)	(75)	(73)	(74)	(75)
Adenoma	32	18	38	32	26	48	43	37	42	44
Carcinoma	1	5	5	3	3	12	9	11	10	13
Multiple Organs	(77)	(79)	(79)	(76)	(78)	(78)	(79)	(79)	(78)	(76)
Lymphomas/leukemias	2	0	2	1	3	0	1	1	1	1

[a] Numbers in parenthesis are the number of tissues examined. It includes animals sacrificed at 52 and 104 weeks and decedents from week 52.

A high incidence of chronic nephropathy was seen in all groups including controls, ranging from 46 to 69 percent in male groups and 69 to 91 percent in female groups (all sacrifices and deaths were included). These findings were not compound related.

In summary, no test compound-related inflammatory, degenerative, or neoplastic processes were observed in rats of either sex after they received up to 5000 ppm H-14453 as a dietary admixture for up to 104 weeks.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

The authors concluded that under the conditions of this study, H-14453 was not carcinogenic in rats when administered in the diet for 104 weeks at levels up to and including 5000 ppm. The NOEL and LOEL values reported for this study were 500 and 2500 ppm, respectively. The LOEL was based on reduced body weight, reduced food consumption, and possibly increased absolute brain and heart weights at the 52-week sacrifice. In the absence of corroborative effects, the toxicological relationship between H-14453 and the increased organ weights is not clear.

A signed and dated Quality Assurance Statement was included in the report.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

From the data presented, there was no indication that the test compound was oncogenic. The background incidence of tumors was similar to historical control values for the study laboratory. There was a slight increase in the incidence of neoplastic nodules of the liver and pituitary carcinomas in dosed males as compared to controls (Table 5). However, the highest incidences seen in this study were within the normal historical ranges (3-14 percent, with an average of 6.6 percent, for neoplastic nodules, and 0-8 percent, with an average of 5.0 percent, for pituitary carcinoma). There were no toxicologically important increases in nonneoplastic lesions.

The increases in organ weights at the 52-week sacrifice are of doubtful toxicologic importance. These may have been caused by decreased mean body weights; they did not persist at the terminal sacrifice. The toxicologic importance of the increased relative brain weights in males receiving 500 ppm and 5000 ppm and relative kidney weights in males receiving 500 ppm at the terminal sacrifice (Table 3) are not clear. There were no effects on clinical pathology parameters or on clinical observations.

The authors set the NOEL at 500 ppm based on body weight data; they interpreted the depression in weight gain in animals receiving 500 ppm (at 13 weeks) to be the effect of unpalatability and of no toxicologic

importance (see Table 2). Food consumption was lower than controls only at weeks 5-9 in males receiving 500 ppm; values in females receiving 500 ppm did not differ from controls. Our interpretation of these data differs from that of the study authors. The weight gains (weeks 0-13) were significantly lower in males and females receiving 500 ppm but only 3 and 5 percent lower than controls. The mean body weights in females receiving 500 ppm were not significantly lower than controls at weeks 13, 52, or 104; in males receiving 500 ppm, mean body weights were only significantly lower (7 percent) at week 104. We do not consider these differences toxicologically important. A LOEL for chronic systemic toxicity based on body weights is considered to be 5000 ppm and the NOEL to be 500 ppm; the groups receiving 2500 ppm were terminated at weeks 61-62 and should not be considered in selecting NOEL and LOEL values.

The report did not contain summary tables of neoplasms nor did it contain a composite table of histologic findings including animals that died and those that were sacrificed. Although the histologic finding of animals at the 13-week and 52-week sacrifices and the decedents were discussed in the report, findings at terminal sacrifice were not discussed. The protocol was unusual because 20 animals/sex/group were withdrawn from the study at week 10 for mating in a two-generation reproduction study and were reinstated in the chronic study at week 32. We were unable to identify these animals. With these exceptions, the design, conduct, and reporting of the study were acceptable.

Item 15--see footnote 1.

16. CBI APPENDIX:

Appendix A, Materials and Methods, CBI pp. 5-16.

APPENDIX A

Materials and Methods

(CBI pp. 5-16)

Pages 43 through 54 contain detailed registration data submitted by the registrant. These pages are not included.

004722

EPA: 68-01-6561
TASK: 121
September 11, 1985

DATA EVALUATION RECORD

DPX-T6376

A Combined 3-Month and 1-Year Feeding Study in Dogs

STUDY IDENTIFICATION: Burdock, G. A., Hagen, W. H., Voelker, R. W., Alsaker, R. D., and Spicer, K. M. A combined three-month and one-year feeding study in dogs--H-14453. (Unpublished study No. 201-571 prepared by Hazleton Laboratories America, Inc., Vienna, VA, for E. I. du Pont de Nemours & Co., Inc., Wilmington, DE; dated July 17, 1984.) Accession No. 07274.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I Cecil Felkner

Date: 9-10-85

J4722

1. CHEMICAL: DPX-T6376 metsulfuron methyl; H-14453.

2. TEST MATERIAL: H-14453, a white powder, was received from the sponsor in 3 batches: lot No. 19,751A, March 12, 1982 (93.0 percent pure); lot No. 19,7518, September 24, 1982 (93.0 percent pure); lot No. 19,751C, January 11, 1983 (95.8 percent pure).

3. STUDY/ACTION TYPE: A combined 3-month and 1-year feeding study in dogs.

4. STUDY IDENTIFICATION: Burdock, G. A., Hagen, W. H., Voelker, R. W., Alsaker, R. D., and Spicer, K. M. A combined three-month and one-year feeding study in dogs--H-14453. (Unpublished study No. 201-571 prepared by Hazleton Laboratories America, Inc., Vienna, VA, for E. I. du Pont de Nemours & Co., Inc., Wilmington, DE; dated July 17, 1984.) Accession No. 07274.

5. REVIEWED BY:

Alan C. Levy, Ph.D.
Principal Reviewer
Dynamac Corporation

Signature: James B. Black for A
Date: September 10, 1985

Nicolas P. Hajjar, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: Nicolas P. Hajjar
Date: September 10, 1985

6. APPROVED BY:

Robert Weir, Ph.D.
Oncogenicity and Chronic Effects
Technical Quality Control
Dynamac Corporation

Signature: Robert Weir
Date: September 10, 1985

W. Thomas Edwards
EPA Reviewer

Signature: W. Thomas Edwards
Date: 9-11-85

Clint Skinner, Ph.D.
EPA Section Head

Signature: _____
Date: _____

7. CONCLUSIONS:

A. When beagle dogs were fed 50, 500, or 5000 ppm of H-14453 by dietary admix, suggestions of a systemic effect were a slight decrease in food consumption among high-dose males and a consistent decrease in serum lactate dehydrogenase in all groups of both sexes. There was also a possible compound-induced dermal irritation noted at the time of the 13-week interim sacrifice. This observation was not borne out in the six surviving dogs/sex/group at the time of terminal sacrifice.

However, it appears that the dogs would have tolerated a higher concentration of test material; consequently, a maximum tolerated dose was not achieved in this study.

B. This study provides supplementary data on the toxicity of H-14453 in dogs.

Item 8--see footnote 1.

9. BACKGROUND:

The oral approximate lethal dose (ALD) in young male rats was greater than 25,000 mg/kg. When administered in divided doses, the test compound produced salivation on the day of dosing at 11,000, 17,000, and 25,000 mg/kg, chromodacryorrhea for 1 day after 25,000 mg/kg, and transient weight loss at 670, 2,250, 7,500, 11,000, and 25,000 mg/kg.

When 10 dosages of 3,400 mg/kg of body weight per day were administered over a 2-week period to a group of six young adult male rats, the test compound produced a slight weight loss during the dosing period, but no mortalities. Gross pathological and histopathological examination of the test animals revealed no changes that could be clearly attributed to the test compound.

Item 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS): (Complete details of Materials and Methods can be found in Appendix A.)

A. Materials and Methods:

1. Purebred beagles, 18-22 weeks of age, were obtained from Hazleton Research Animals, Cumberland, VA. Groups of 20 dogs,

---

[1]Only items appropriate to this DER are included.

10 of each sex, were placed on diets containing 0 (control diet), 50, 500, or 5,000 ppm of test material. All dogs were observed twice daily for mortality and moribundity and once daily for appearance, behavior, fecal elimination, and signs of toxic and pharmacologic effects. Individual food consumptions were recorded daily, and individual body weights were reported weekly. Hematologic, serum chemistry, and urinalysis examinations were performed twice prior to treatment and during study weeks 4, 8, 13, 26, 39, and 52.

2. Four dogs/sex/group were sacrificed after 13 weeks, and the remaining six/sex/group were sacrificed after 52 weeks. Following necropsy the weights of the following organs were determined: brain, heart, liver, thyroid with parathyroids, kidneys, testes with epididymis, ovaries, adrenals, and pituitary. More than 40 tissues from each dog were preserved. All of the preserved tissues from the control and high-dose (5,000 ppm) dogs and sections of tissues with gross lesions from the low- (50 ppm) and mid-dose (500 ppm) dogs at week 13 as well as all of the preserved tissues of the animals sacrificed at study termination were examined microscopically.

3. Mean body weight changes for weeks 1 through 13, 26, 39, and 52, total food consumption for weeks 1-13, 1-26, 1-39, and 1-52, clinical pathology data (excluding differential leukocyte counts, erythrocyte morphology, and qualitative urinalysis data), and organ weight data were analyzed statistically. Box's test for homogeneity of variances was performed and if the variances proved to be homogeneous, the data were analyzed by one-way classification analysis of variance (ANOVA). If the variances proved to be heterogeneous, a rank transformation of data was performed that was followed by Box's test and ANOVA. If ANOVA of untransformed or transformed data was significant, Dunnett's t-test was used for control versus compound-treated group mean comparisons. If ANOVA was not significant, the analysis was complete. Tests for homogeneity of variances and ANOVA were evaluated at 5.0 percent one-tailed probability level. Control versus compound-treated group mean comparisons of the above data were evaluated at the 5.0 percent two-tailed probability level.

B. Protocol: See Appendix B.

12. REPORTED RESULTS:

Test Material Analyses: The concentration, stability, and homogeneity analyses for the control and test diets were performed by the sponsor at weeks 1, 15, 38, and 53 of the study. The data indicated that the concentrations of test material in the diet were within 15 percent of the nominal levels.

Clinical Observations and Mortality: There were no mortalities. Sporadic instances of dermal irritation of the ears, ear "sores," and alopecia of the ears were noted among some treated animals during the first 13 weeks of the study. Similar lesions were noted in some control animals throughout the study. These lesions were not considered related to compound administration.

Body Weights: There were no significant differences or compound-related trends noted for the mean body weights of control and dosed animals. However, the mean body weight of males receiving the mid and high doses were slightly lower than the control values from weeks 14-53 of the study (Table 1).

Food and Compound Consumption: There were no significant differences or compound-related trends noted for test material consumption. Mean total food consumption values for high-dose males were slightly lower than controls (Table 2).

Hematology: There were no significant differences noted in hematology parameters among control and dosed animals, except for significant increases ($p < 0.05$) in mean corpuscular hemoglobin concentrations of females receiving the low (34.7 ± 0.24), mid (34.7 ± 0.25), and high (34.6 ± 0.19) doses when compared to controls (34.2 ± 0.27) at final sacrifice. There were a few isolated differences noted in other parameters, but these were not dose related and did not show any apparent trends.

Clinical Chemistry: There were no significant differences noted in clinical chemistry except for lactate dehydrogenase activity (Table 3). A statistically significant decrease in lactate dehydrogenase in high-dose males at week 4 and in all treated male groups at weeks 8, 13, 26, 39, and 52 was noted. In females, lower lactate dehydrogenase values were noted for all treated female groups at weeks 13 and 39 and for high-dose females at week 52. There were a few other isolated differences noted in other parameters, but these were not dose related and did not show any trends.

Urinalysis: There were no significant differences noted among control and dosed animals.

Gross Examination: Thickening, alopecia, and/or crusting of the pinna(ae) were noted in dosed animals at the interim and final sacrifices (Table 4). However, the data in a summary table for the gross lesions found at final sacrifice were identical to those data presented for interim sacrifice in the study report. Consequently, the summary data were not presented for final sacrifice. Other postmortem findings included dark, raised margins of the spleen in a number of control and treated animals at both sacrifices and raised focal areas in the stomach of some animals at interim sacrifice. With the possible exception of the findings in the pinnae, no other findings were considered compound related.

TABLE 1. Mean Body Weight of Dogs Fed Diets Containing H-14453 For 1 Year

Dose/Group (ppm)	Mean Body Weight (kg) at Week[a]			
	1	13	26	52
Males				
Control	8.73±1.0	11.01±1.5	11.85±1.9	12.48±1.5
50	8.72±1.2	11.55±1.9	11.35±2.3	12.50±2.6
500	8.61±1.4	10.92±1.8	10.68±2.3	11.50±2.0
5000	8.50±1.1	11.10±1.3	11.02±1.1	11.65±1.2
Females				
Control	6.91±0.9	9.09±0.8	9.38±1.1	10.45±0.9
50	7.10±1.0	9.59±1.2	9.85±0.9	10.62±1.3
500	6.85±0.9	9.04±1.6	10.05±2.3	10.82±2.5
5000	6.55±0.9	8.89±1.3	9.92±2.0	10.38±2.0

[a]Mean body weight ± standard deviation.

TABLE 2. Mean Food Consumption of Dogs Fed Diets Containing H-14453 For 1 Year

Dose/Group (ppm)	Mean Food Consumption at Week[a]				
	1	13	26	38	52
Males					
Control	2.26±0.4	2.10±0.3	1.82±0.3	2.18±0.3	2.37±0.3
50	2.44±0.6	2.07±0.4	1.67±0.3	2.00±0.4	2.03±0.2
500	1.88±0.4	2.01±0.3	1.43±0.2	2.07±0.3	2.00±0.3
5,000	2.15±0.4	2.08±0.3	1.47±0.2	1.77±0.1	1.92±0.3
Females					
Control	1.55±0.3	1.65±0.2	1.50±0.3	1.98±0.3	1.75±0.5
50	2.01±0.3	1.77±0.3	1.33±0.2	1.58±0.3	1.77±0.5
500	1.72±0.3	1.76±0.3	1.27±0.3	1.73±0.4	1.67±0.5
5,000	1.66±0.2	1.60±0.2	1.63±0.3	1.58±0.4	1.85±0.3

[a]Food consumption is the mean ± standard deviation expressed as kg/dog/week.

TABLE 3. Mean Lactate Dehydrogenase Activities in Dogs Fed Diet Containing H-14453 For 1 Year

Group/Dose (ppm)	Lactate Dehydrogenase Activity (IU/L) At Weeks						
	-2[a]	4[b]	8[a]	13	26	39	52[a]
Males							
Control	104±43	109±64	105±37	81±34	139±41	105±31	107±35
50	71±25	83±26	66±31*	48±15*	82±47*	56±24*	57±17*
500	81±33	67±25	64±30*	40±13*	69±21*	34±11*	46±20*
5,000	56±10*	51±22*	53±12*	37±11*	46±15*	33±10*	29±79*
Females							
Control	77±21	101±49	92±32	80±22	131±48	106±39	69±27
50	65±19	71±37	79±54	47±22*	92±31	53±12*	54±14
500	87±21	68±20	75±26	58±21*	75±36	39±14*	44±18
5,000	56± 8	60±26	67±18	42±16*	106±55	41±11*	29±13*

[a] Rank transformed data analyzed for males and females.

[b] Rank transformed data analyzed for males.

* Significantly different from control, $p \leq 0.05$.

TABLE 4. Summary of Gross Pathologic Findings in Dogs Fed Diet Containing H-14453 For 13 Weeks

Lesion		Males				Females			
		0	50	500	5,000	0	50	500	5,000
Pinna	N[a]	4	4	4	4	4	4	4	4
Thickened		0	0	0	1	0	0	0	0
Focal areas		0	0	0	0	0	0	1	0
Alopecia		0	0	0	0	0	0	1	1
Crusting		0	0	0	0	0	0	0	1
Spleen	N	4	4	4	4	4	4	4	4
Dark, raised margins		2	4	1	4	4	3	2	3
Stomach	N	4	4	4	4	4	4	4	4
Focal areas		1	1	1	0	0	1	1	0

[a]Number of tissues examined.

Histopathology: No histologic evidence of systemic toxicity was observed in the tissues examined at interim sacrifice (Table 5). There was topical irritation on the pinnae of the ears in two mid- and two high-dose females and one high-dose male. Two of these females also exhibited either precapsular lymph node or nictitating membrane lesions.

At final sacrifice, compound-related histomorphologic alterations were not observed in the tissues examined. A variety of spontaneous disease lesions and incidental findings were noted (Table 6). Histologic examinations of the ears of four control, two low-dose, and two mid-dose dogs that exhibited thickening and/or reddening of the inner surface indicated that chronic-active dermatitis was present with acanthosis, hyperkeratosis, and mononuclear cell infiltration.

Organ Weights: At interim sacrifice, there was a significant increase in the mean testes weights of animals receiving the high dose (23.4 g) when compared to controls (15.6 g) and a significant decrease in the mean pituitary-to-body weight ratio in animals receiving the mid-dose (0.0006 percent versus 0.0009 percent for the controls). There were no significant changes in organ weights or organ to body weight ratios among control and dosed animals at final sacrifice.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study authors concluded that the only evidence of a systemic effect associated with the administration of 50, 500, or 5,000 ppm H-14453 as a dietary admix to dogs was a slight decrease in food consumption among high-dose male dogs. There was a consistent decrease in serum lactate dehydrogenase in all groups of both sexes at two or more intervals, but because all mean values of both control and treated groups were within the historical control range, the biological significance of this finding was uncertain.

A suspected compound-induced dermal irritation, "postulated at the time of the interim sacrifice, was not borne out by subsequent clinical observations or by histopathological examination of the terminal sacrifice animals."

Based on the available results, it was concluded that the NOEL was 500 ppm in males and 5,000 ppm in females.

B. Quality assurance inspections/reviews were performed during the course of the first 13 weeks of the study according to the 13-week interim report. No indication was found in the final report that inspections/reviews were made during the last 9 months of the in-life portion of the study.

TABLE 5. Summary of Most Frequently Observed Nonneoplastic Lesions in Dogs Fed Diets Containing H-14453 For 13 Weeks

Organ/Lesion		Number of Animals Affected							
		Males				Females			
		0	50	500	5000	0	50	500	5000
Lung	N[a]	4	0	0	4	4	0	1	4
Interstitial pneumonitis		2	0	0	4	4	0	1	3
Focal mononuclear infiltration		0	0	0	2	1	0	1	1
Kidney	N	4	0	0	4	4	0	0	4
Mineralization		4	0	0	2	4	0	0	3
Liver	N	4	0	0	4	4	0	0	4
Focal mononuclear infiltration		2	0	0	4	3	0	0	3
Urinary bladder	N	4	0	0	4	4	0	0	4
Focal mononuclear infiltration		0	0	0	0	0	0	1	1
Pinna	N	0	0	0	1	0	0	2	2
Dermatitis		0	0	0	0	0	0	1	1
Hyperkeratosis		0	0	0	1	0	0	1	1
Acanthosis		0	0	0	1	0	0	2	1
Mononuclear infiltration		0	0	0	1	0	0	2	1

[a]Number of tissues examined.

TABLE 6. Summary of Most Frequently Observed Nonneoplastic Lesions in Dogs Fed Diets Containing H-14453 For 52 Weeks

Organ/Lesion		Number of Animals Affected							
		Males				Females			
		0	50	500	5000	0	50	500	5000
Pituitary	N[a]	6	6	6	6	6	6	6	6
Cysts		0	0	0	0	0	3	2	1
Parathyroids	N	4	6	6	6	4	6	6	6
Cysts		0	0	1	1	1	0	2	2
Lung	N	6	6	6	6	6	6	6	6
Focal mononuclear infiltration		5	6	6	6	5	6	6	6
Interstitial pneumonitis		4	2	2	1	3	3	4	1
Spleen	N	6	6	6	6	6	6	6	6
Congestion		4	5	4	6	4	5	6	5
Liver	N	6	6	6	6	6	6	6	6
Focal mononuclear infiltration		6	5	6	6	6	6	6	6
Kidney	N	6	6	6	6	6	6	6	6
Mineralization		6	6	6	6	6	6	6	6
Mononuclear infiltration		1	3	1	2	1	0	1	3
Thymus	N	6	6	6	6	6	6	6	6
Cysts		3	2	0	1	1	5	1	2
Tonsils	N	6	6	6	6	6	6	6	6
Focal neutrophil infiltration		5	3	2	1	3	3	3	1
Pinna	N	3	1	1	1	1	1	1	0
Dermatitis		3	1	1	0	1	1	1	0
Mononuclear infiltration		3	1	0	1	1	1	1	0
Hyperkeratosis		2	1	1	0	1	0	1	0

[a]Number of tissues examined.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. We agree with the conclusions of the study authors that the only evidence of a systemic effect as a result of compound administration was a slight, but not statistically significant, decrease in food consumption among high-dose males and a consistent decrease in serum lactate dehydrogenase in all groups of both sexes at two or more intervals. Although the authors stated that all mean lactate dehydrogenase values for both control and dosed dogs were within the historical control range, historical control values were not provided. However, there is agreement that the biological significance of this serum chemistry finding is uncertain since toxic effects are associated with elevated and not decreased values. There was a suspected compound-induced dermal irritation noted at the 13-week interim sacrifice, but this did not appear to be substantiated by clinical observations or by histopathological examination of animals at terminal sacrifice. None of the following parameters indicated a compound-related toxicologic effect: survival, physical signs (other than ears), body weight, hematology, urinalysis, organ weights, gross necropsy findings, or microscopic pathology. It is apparent that a maximum tolerated dose was not achieved in this study.

A few deficiencies in reporting the data were noted; however, they do not compromise the conclusions. Table 9B (CBI, p. 81) should contain data on gross findings for animals at terminal sacrifice; however, it contains the same data as Table 9B, gross finding at interim sacrifice. Table 10C (CBI; p. 96) presents means for terminal body weights, but the number of animals/sex/group is four rather than six; however, means and standard deviations correspond to those calculated by our reviewers from weights recorded on the individual necropsy sheet for animals at the terminal sacrifice (six dogs/sex/group). A few typographical errors and errors in the text referring to table numbers were also noted.

B. There are no differences between the conclusions reported by the study authors and those of the reviewers except for the fact that the dogs could have tolerated a higher dietary level (> 5,000 ppm).

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 4-13 and Appendix B, Protocol, CBI pp. 124-145.

APPENDIX A

Materials and Methods

Pages 69 through 78 contain detailed registration data submitted by the registrant. These pages are not included.

APPENDIX B

Protocol
(pp. 124-145)

Appendix 1
Project Protocol, Protocol Addenda, and Amendments
A Combined Three-Month and One-Year Feeding Study of H-14453 in Dogs

Pages 81 through 101 contain detailed registration data submitted by the registrant. These pages are not included.

004722

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: 2-Generation, 4-litter reproduction, rat

Accession Number: 073332

MRID Number:

Sponsor: DuPont, HLR No. 524-85

Contracting Lab:

Date: January 21, 1985

Test Material: DPX-T6376 technical (INT-6376)

EPA Evaluation Review. [signature] Thomas Edwards — Date [illegible]

Review Section Approval. [signature] Clint Skinner — Date 1-13-[illegible]

Protocol: See attached procedures.

Results:

Diets were analysed and found to not vary in concentration more than 10%.

There were no remarkable or dose-related clinical effects reported for any dosage group.

After 90 days of feeding at the highest dosage (5000 ppm), in the F_0 groups and also in the F_{1B} groups the body weights of males and females were significantly less than respective controls (Tables 2,3,6,7; Figures 1,2,3,4).

There were no treatment related deaths and none during the F_0 or F_{1B} feeding phases.

There was only one suggestion of fetal effect. The decrease in litter size of the F_2A group as shown in Table 29 was statistically significant but apparently not biologically significant.

There were no biologically significant histopathological lesions in the weanlings.

Conclusions

No effects on reproduction or fetal effect at 5000 ppm (HDT).

Maternal NOEL: 500 ppm
Maternal LEL: 5000 ppm (decreased weight gain)

Core Classification:

Minimum

Pages 104 through 125 contain detailed registration data submitted by the registrant. These pages are not included.

004722

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: 21-Day Primary Dermal Toxicity Study, Rabbit

Accession Number: 072765 (6)

MRID Number:

Sponsor: DuPont, Haskell Lab No. 137-83

Contracting Lab:

Date: May 2, 1983

Test Material: DPX-T6376, Benzoic acid, 2-[[[[(4-methoxy-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-,methyl ester, 92.9%, technical

EPA Evaluation Review. Thomas Edwards 4-7-83
Thomas Edwards Date

Review Section Approval. C. Skinner 4-7-83
Clint Skinner Date

Protocol:

"Four groups of 5 male and 5 female adult New Zealand White rabbits fitted with plastic collars were clipped free of hair over the back and trunk areas twice a week. Proper doses of the test material, as an aqueous paste, were applied to the intact skin on the back of each rabbit under one 3" x 8-1/2", 12-ply gauze pad. Dose levels were either 125, 500 or 2000 mg/kg day for 21 consecutive days; an additional group of rabbits served as controls and was treated with water only. The trunk of each rabbit was then wrapped with a layer of plastic wrap, stretch gauze bandage and elastic adhesive tape. After a 6-hour exposure period, the wrappings were removed, the backs washed with water and wiped with a dry towel and the rabbits returned to their cages. The rabbits were weighed and observed daily and weighed weekly during a 14-day recovery period (no additional treatment). Blood samples were taken for clinical pathologic examination 2 days prior to dosing, 1 day after the last dose and on the 14th recovery day. Six rabbits (3 of each sex) from each group were sent to Pathology the day after the last dose for histologic examination and the 4 remaining rabbits (2 of each sex) in each group were sent to Pathology for histologic examination on the 14th recovery day."

Results:

The two deaths which occurred were not found to be compound related.

No clinical signs or weights changes attributed to treatment were found.

Histopathological changes found in the testes are shown in the attached excerpt from Table III. Although the testicular effects were not believed by the report writer to be treatment related, there is a possible relationship. The distrubution of lesions was 3/5 in the high-dose level, 1/5 in the low. Two of the lesions were observed after the recovery period in the high dosage group.

All other microscopic findings were considered "incidental" or result of "intercurrent disease."

Conclusions:

The author concluded that, "a mild testicular degeneration or atrophy, possibly resulting from a secondary effect of the test compound, was detected in the male rabbits at any of the dose levels."

Because of the deficient number of animals killed one day after last dose, a "lack of dose-response relationship" is not clearly credible.

The number of animals was not enough to establish valid conclusions.

Core Classification:

Supplemental

HN-14418
63
4492

TABLE III: INCIDENCES OF NON-NEOPLASTIC LESIONS
SPECIES: RABBIT COMPOUND: INT-6376-22
DERMAL SUBACUTE

004722

MALES

TISSUE/LESION:	GROUP DESIGNATION:	I	I-R	IV	IV-R	III	III-R	II	II
	DOSE (MG/KG):	0.00	0.00	125.00	125.00	500.00	500.00	2000.00	2000
	NUMBER IN GROUP:	3	2	3	2	3	2	3	3
MESENTERIC LYMPH NODES		1	1	1	0	2	1	3	-
PANCREAS		3	2	3	2	3	2	3	-
ACCESSORY SPLEEN		-	-	-	-	1	-	-	
SKIN (TREATED)		3	2	3	2	3	2	3	-
SKIN (UNTREATED)		3	2	3	2	3	2	3	-
SPLEEN		3	2	3	2	3	2	3	-
STERNEBRAE W BONE MARROW		3	2	3	2	3	2	3	-
STOMACH		3	2	3	2	3	2	3	-
TESTES		3	2	3	2	3	2	3	-
DEGENERATION OF SPERMATOGONIA, SEMINIFEROUS TUBULES		-	-	2	-	1	-	1	
TESTICULAR ATROPHY, FOCAL & LOBULAR (SEGMENTAL)		-	-	-	-	-	-	-	
TESTICULAR DEGENERATION, FOCAL, UNILATERAL		-	-	-	-	-	-	-	
THYMUS		3	2	3	2	3	2	3	-
ATROPHY/DEPLETION OF LYMPHOCYTES		-	-	-	-	-	-	-	
THYROID GLANDS		3	2	3	2	1	2	3	-
CYSTS OF ULTIMOBRANCHIAL-DUCT REMNANT		-	-	-	-	-	1	-	
ECTOPIC SKELETAL MUSCLE (CHORISTIA), UNILATERAL		-	-	1	-	-	1	-	
TRACHEA		3	2	3	2	3	2	3	-
URINARY BLADDER		3	2	3	2	3	2	3	-

NOTES:
o THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.

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004722

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Primary Dermal Irritation, Rabbit

Accession Number: 072765 (3)

MRID Number:

Sponsor: DuPont

Contracting Lab: Hazelton No. 201-708

Date: March 9, 1984

Test Material: DPX-T6376 60% Dry Flowable (Haskell No. 15,273).

EPA Evaluation Review. Thomas Edwards (Thomas Edwards) 9-9-85 (Date)

Review Section Approval. Clint Skinner (Clint Skinner) 9-9-85 (Date)

Protocol:

"Prior to treatment, the dorsal areas of each rabbit was clipped free of hair, and four sites were chosen for application of Haskell No. 15,273. The skin of two sites of all animals was abraded with minor incisions which were sufficiently deep to penetrate the stratum corneum, but not deep enough to produce bleeding. Two sites remained intact. A 0.5 gram aliquot of the test material was introduced to skin premoistened with water under an approximate one-inch square patch which was secured in place with transparent tape. The trunk of each rabbit was wrapped with impervious rubber damming. The rabbits were then immobilized in stocks for 24 hours without food and water.

"Twenty-four hours following application, the binders and patches were removed and the exposure sites were wiped with a dry towel to preclude further exposure of the animal to the test material. The test material was administered dermally because potential human exposure is by the dermal route.

"Dermal responses were graded and scored at 24 and 48 hours according to the system of Draize (1959).
All animals were observed once daily for mortality."

"After termination (48 hours postapplication) all rabbits were sacrificed and discarded without necropsy."

Results:

One male animal exibited very slight erythema at 24 hours at one of two sites.

Primary irritation score was calculated by Haskell to be 0.125 in one animal.

Conclusions:

Primary dermal irritation: slightly irritating

Dermal irritation category: IV

Core Classification:

Guideline

004722

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Metabolism in Rat

Accession No: 072765(9)

MRID No.:

Sponsor: DuPont No. AMR-108-83

Contracting Lab:

Date: June 27, 1984

Test Material: DPX-T6376, Metsulfuron methyl

EPA Evaluation Review. Thomas Edwards 9-7-85
Thomas Edwards Date

Review Section Approval. 9-9-85
Date

Protocol: See attached excerpted procedures.

Results:

Elimination of radioactivity is shown in Tables IV to VI and Figure 1. Results are comparable between groups.

Distribution of radioactivity among organ and tissue samples is shown in Tables IV to VI. Note that hides are suspected to be contaminated from the cages.

After hide, carcass, and GI tract, the liver contained the highest percent of radioactivity but this was not large percentage-wise. The highest percent being 0.014 of dose. Sex differences did not appear to be significant.

Four metabolites were found. One was identified to be saccharin. Others were numbered I, II, and III.

The proposed pathways are shown in an excerpt attached.

Distribution of elimination of parent compound and metabolites is shown in Table XV and Figure 13.

Conclusions:

Elimination of radioactivity in urine and feces was rapid and comparable in all groups. Urine contained about 10 times as much as feces. Elimination appeared to be somewhat faster in the pretreated than in the not pretreated 16 mg/kg groups. Also, in the 3000 mg/kg groups at 72 hours, elimination was slightly less fast than in the 16 mg/kg not preconditioned group. The meaning of these differences is doubtful, because of the smallness of the groups, even if expected.

The only apparent dosage effect on production of metabolites was related to saccharin. Preconditioning, and to a larger extent increased dosage, decreased the percent of saccharin found.

It is regretted that the triazine ring was not tagged. There is a suspected relationship between some triazines and teratogenicity.

Core Classification:

MINIMUM

Pages 133 through 151 contain detailed registration data submitted by the registrant. These pages are not included.

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Acute Oral Toxicity, Rat

Accession Number: 072765 (1)

MRID Number:

Sponsor: DuPont

Contracting Lab: Haskell Lab. No. 181-84

Date: April 5, 1984

Test Material: DPX-T6376 60% Dry Flowable

EPA Evaluation Review. T. Edwards (Thomas Edwards) 9-7-85 (Date)

Review Section Approval. C. Skinner (Clint Skinner) 9-7-85 (Date)

Protocol:

"The Environmental Protection Agency's Proposed Guidelines for Pesticide Registration (Federal Register, Volume 43, page 37336, August 22, 1978) were followed. Rats were fasted for 24 hours prior to dosing. Single oral doses of the test material, as a suspension in corn oil, were administered by intragastric intubation to a group of 10 rats, 5 per sex, that were 8-9 weeks old. Later in the day, the rats were checked for clinical signs of toxicity. Survivors were weighed and observed daily (weekends included when deemed necessary by rat condition) through a 14-day recovery period and then sacrificed for gross pathologic examination."

Results:

"Data

Dose (mg/kg)	Average Fasted Body Weight (g)	Suspension Concentration (mg/mL)	Average Dose (mL)	Mortality Ratio
Males				
5,000	220	250	4.39	0/5
Females				
5,000	173	250	3.47	0/5"

The reported clinical signs included for males stained and wet perineum and for females stained and wet perineum, red ocular discharge, diarrhea, and lung sounds.

Weight loss was irregular and slight to moderate.

One female rat had a dark red nodule in the spleen, which was not considered to be treatment related. No treatment related pathology was found.

Conclusions:

Acute oral LD_{50}: greater than 5000 mg/kg (HDT) for both male and female rats.

Acute oral toxicity category: IV

Core Classification:

Guideline

004722

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Acute Dermal Toxicity, Rabbit

Accession Number: 072765 (2)

MRID Number:

Sponsor: DuPont

Contracting Lab: Hazelton No. 201-707

Date: March 12, 1984

Test Material: DPX-T6376 60% Dry Flowable

EPA Evaluation Review. [signature] Thomas Edwards — Date 7/

Review Section Approval. [signature] Clint Skinner — Date 9-7-85

Protocol:

"Prior to initiation, the hair was closely clipped from the back of each rabbit. Just prior to compound application, the skin of all animals in each group was abraded with minor incisions which were sufficiently deep to penetrate the stratum corneum, but not deep enough to disturb the derma or to produce bleeding. The test material, mixed with approximately 3-5 ml tap water to form a paste, was applied to the skin of each rabbit at a dose level of 2000 mg/kg. The test material remained in contact with the skin for 24 hours by means of a nonabsorbent binder composed of rubber damming. Plastic collar restrainers were placed on the animals at time of treatment and removed on Day 7.

"Twenty-four hours following application, the binders were removed, the residual amount of the test material was estimated, and the exposure sites were wiped with gauze to preclude further exposure of the animals to the test material.

"All of the rabbits were observed for mortality and signs of toxic and pharmacologic effects once daily for 14 consecutive days. Dermal responses were graded and scored on Days 1, 3, 7, 10, and 14 according to the system of Draize (1959)."

"Individual body weights were recorded at initiation, Day 7, and at termination.

"At termination (Day 14), all surviving rabbits were sacrificed without necropsy."

Results:

There were no deaths.

Skin reactions included slight to moderate edema lasting less than three days and none to moderate erythema lasting less than seven days.

Conclusions:

Acute dermal LD_{50}: more than 2000 mg/kg

Acute dermal toxicity category: III

Core Classification:

Minimal

004722

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Eye Irritation, Rabbit

Accession Number: 072765 (4)

MRID Number:

Sponsor: DuPont

Contracting Lab: Hazelton No. 201-597

Date: 4-11-83

Test Material: DPX-T6376 60% Dry Flowable

EPA Evaluation Review: Thomas Edwards 9-9-85
Thomas Edwards Date

Review Section Approval: Clint Skinner 11-1-85
Clint Skinner Date

Protocol:

"Prior to instillation of the test material, the left eye of each rabbit was examined following staining with 2% fluorescein sodium solution (Alcon Laboratories, Inc., Fort Worth, Texas) to confirm the absence of corneal defects. Only rabbits initially free of corneal defects were used in this study. A 43 mg aliquot (weight of 0.1 ml) of the test material was placed into the conjunctival sac of the left eye of each rabbit. The eye was gently held closed for approximately one second following instillation. The treated eye was not rinsed in six rabbits and was rinsed in three rabbits. The right eye of each rabbit was not treated, and thus served as a negative control.

"Eye irritation was scored and graded at 24, 48, and 72 hours, and at Days 4 and 7 according to the system of Draize (1959)."

"At termination (seven days postinstillation), all rabbits were sacrificed and discarded without necropsy."

Results:

Corneal opacity was observed in one unwashed eye at 24 hours. It had cleared by 48 hours.

Conclusions:

Eye irritation category III

Core Classification:

Guideline

156

004722

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Dermal Sensitization, Guinea Pig

Accession Number: 072765 (5)

MRID Number:

Sponsor: DuPont

Contracting Lab: Hazelton No. 201-709

Date: 4-4-84

Test Material: DPX-T6376 60% Flowable, Haskell No. 15,273

EPA Evaluation Review. Thomas Edwards — Date 4-9-85

Review Section Approval. Clint Skinner — Date 4-9-85

Protocol:

Thirty (30) guinea pigs were divided into one test group, one positive control group, and one negative control group of 10 each and were used in testing for primary irritation and sensitization.

"Primary Irritation

Ten test guinea pigs were treated in the primary irritation phase. The dorsal skin from the shoulder to mid-back was clipped free of hair and two sites on each animal were chosen for a single application. Two concentrations (2% and 20% in saline suspension) of the test material were applied to separate test sites on each animal. The resulting irritation scores were compared to the challenge scores as determined at the end of the sensitization period.

Ten positive control animals were treated identically with two concentrations of DNCB in acetone (0.1% and 1.0% solution).

Induction of Sensitization

The same 10 test animals that were used in the primary irritation phase were treated during the induction phase. The sacral/hip area of these animals was clipped free of hair. A 0.1 ml aliquot of 1% Haskell No. 15,273 in saline was injected into the shaved area. The intradermal injections were repeated weekly for a total of four injections. The injection site was alternated between sacral/hip areas at each injection. The 10 positive control animals were injected with a 0.1 ml aliquot of 1% DNCB in acetone.

Challenge Phase

Fourteen days after the final sensitization injection was administered, the backs of all animals (both the test and control groups) were shaved. A 0.05 ml aliquot of the challenge test solution at 2% and 20% was applied to the assigned two test sites on each animal. The 10 test animals, as well as 10 naive animals, were exposed to the same challenge doses. The 10 DNCB-induced animals were challenged with 0.5 ml aliquots of DNCB in acetone solution at 0.1% and 1.0% concentrations.

Observations and Records

At 24 and 48 hours after each application in the range-finding, primary irritation, and challenge phases, the test sites were examined and scored according to the method described on page 4. After the induction phase treatments, the test sites were observed for necrosis and erythema was scored by the scale of 0 to 5 at 24 hours only.

Throughout the study, all animals were observed for mortality and signs of toxic and pharmacologic effects. At termination, all surviving animals were sacrificed with T-61 Euthanasia Solution (Taylor Pharmacal Company, Decatur, Illinois) and discarded without necropsy."

Results:

No sensitization was demonstrated in the challenge phase in treated animals.

Negative controls gave negative results.

Positive controls gave positive results.

Conclusions:

Not sensitizing to guinea pigs.

Core Classification:

Minimum