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

007264

JUL -5 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Company Response to Review of Toxicology Data Submitted in Support of Registration of DPX-L5300 (EPA Reg. Nos. 352-LNO and 352-LRU) and Tolerances in/on Wheat and Barley (Petition No. 7F3540).

TO: Richard Mountfort, Product Manager #23
Registration Division (H7505C)

FROM: Roger Gardner, Toxicologist Roger Gardner 6-29-89
Review Section 1, Toxicology Branch
Insecticides/Rodenticides Support
Health Effects Division (H7509C)

THRU: Edwin R. Budd, Section Head 6/29/89
Review Section 1, Toxicology Branch
Insecticides/Rodenticides Support Actions
Health Effects Division (TS-769) 7/3/89

Tox. Chem. No. 419S
Tox. Proj. Nos. 8-1173 and 9-0661

Actions Requested

Consideration of the following:

1. Historical control data on the incidence of mammary tumors in female rats,

2. Adequacy of the dose levels tested in female mice in an 18-month feeding study,

3. Additional histopathology data from a two-generation reproduction study with DPX-L5300 in rats, and

4. Information missing from a previously submitted mutagenicity assay with DPX-L5300 in Salmonella typhimurium.

Recommendations and Conclusions

1. There are adequate Toxicology data to support the proposed tolerances for Express® on wheat and barley.

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Recommendations and Conclusions (continued)

2. The historical control data were considered and accepted in the Agency's Peer Review. The additional data confirmed that a significantly increased incidence of mammary gland adenocarcinomas was observed at the highest dose tested in the chronic feeding study with rats.

3. The mouse oncogenicity study was also considered in the Agency's Peer Review as adequate with respect to the dose levels evaluated. Therefore, the classification of the study should be upgraded to "Minimum."

4. There were adequate additional data submitted from the multigeneratior reproduction study to support the conclusions of the investigators that there were no treatment-related effects in F_0 generation rats.

5. The revised report of a mutagenicity assay in Salmonella typhimurium included information on the composition of the test substance and cytotoxicity data not previously submitted. There is adequate information in the revised report to upgrade the classification of the study from "Unacceptable" to "Acceptable." The study indicated that the test material is not mutagenic in Salmonella typhimurium with or without metabolic activation.

6. Technical grade Express® has moderate acute toxicity by inhalation and dermal routes (Category III) and slight acute oral toxicity (Category IV). Limited irritation and sensitization studies on the technical grade material and available data on the 75% DF formulation (see point 6. below) suggest that Express® is slightly irritating to the eyes and skin (Toxicity Category IV), and the herbicide is not a skin sensitizer.

7. The 75% DF formulation has moderate acute toxicity (Category III) by the oral and dermal routes. No acute inhalation toxicity study is needed because <0.5% of the granules are less than 105 um in diameter, and the formulation is not respirable. The formulation is a moderate eye irritant (Toxicity Category III) and causes no skin irritation or skin sensitization.

8. Toxic effects observed in a 90-day rat feeding study included decreases in food consumption, body weight gain, food efficiency, and absolute weights for the heart, brain, liver, and kidneys. Relative organ weights for the heart, liver, kidneys, testes, and spleen were increased because of the decreased body weights observed. Serum glucose, globulin, and cholesterol concentrations were also decreased, but there were no treatment-related histopathological effects. The LOEL is 1750 ppm (highest dose tested), and the NOEL is 100 ppm.

9. The NOEL is probably >2500 ppm (highest dose tested) in dogs based on results from a 90-day feeding study.

Recommendations and Conclusions (continued)

10. A NOEL was established at 25 ppm (0.625 mg/kg/day), and the LEL was 250 ppm in a one-year dog study based on elevated blood levels of bilirubin and aspartate aminotransferase (AST), increased urinary volume and decreased body weight gain in males, and elevated bilirubin, AST, creatinine and globulin levels along with decreased body weight gain in females. The highest dose tested was 1500 ppm.

11. Based on reduced body weight and body weight gain in treated male and female rats, a NOEL was established in the chronic feeding study at 25 ppm (1.25 mg/kg/day). There was also a statistically significantly increased incidence of mammary gland adenocarcinomas observed in treated female rats. The highest dose tested was 1250 ppm.

12. Based on the increased incidence of seminiferous degeneration and oligospermia in mice from a long-term feeding study, the NOEL was 20 ppm (3 mg/kg/day), and the LEL was 200 ppm (30 mg/kg/day). Under the conditions of the study, Express® was not oncogenic.

13a. Maternal toxicity in a rat teratology study at 125 mg/kg and higher included: decreased body weight gain and food consumption, increased liver-to-body weight ratios, and excess salivation in some animals. Fetuses from dams given toxic doses of 500 or 125 mg/kg had reduced body weights. Increased resorptions, fetal deaths, and incomplete ossification were observed at the 500 mg/kg dose (highest dose tested). These results indicate that the NOEL for maternal and developmental toxicity was 20 mg/kg/day, and the LOEL is 125 mg/kg/day.

13b. A developmental toxicity study in rabbits indicated that the NOEL for maternal toxicity was 20 mg/kg/day based on statistically significantly decreased feed consumption and increased incidence of abortions. The LEL for maternal toxicity was 80 mg/kg/day (highest dose tested). The LEL for fetal effects (reduced fetal weight) was also 80 mg/kg/day, and the NOEL is 20 mg/kg/day. There were no fetal malformations or variations associated with administration of the test substance in pregnant rabbits.

14. In a two-generation reproduction study, no effects were seen on fertility, gestation, or lactation at dietary levels as high as 1000 ppm (highest dose tested). Effects associated with Express® included reduced group mean body weight for the adult females and offspring and reduced spleen weight in the second litter of the final generation. The NOEL was established at 25 ppm, and the LEL was 250 ppm.

15. No mutagenic activity was observed in Chinese Hamster Ovary cells *in vitro* or in bacteria (*Salmonella typhimurium*); no cytogenetic effects were seen in bone marrow cells from treated rats; no induction of micronuclei were found in normochromatocytes from treated mice; and no unscheduled DNA sysnthesis was induced in primary hepatocytes from treated rats.

Recommendations and Conclusions (continued)

16a. Orally administered Express® is readily absorbed by male and female rats. The excretion half-life (time required for excretion of half of the dose) for a low dose was 26 to 33 hours. At high single doses the excretion half-life for male rats was 51 to 54 hours, and that value for female rats was 69 to 96 hours. The major route of excretion in rats was the urine.

16b. Tissue levels of Express® and its metabolites increased with dose, but there was no concentration of radioactivity in any particular organ or tissue.

16c. Major metabolites in the urine and feces included metsulfuron methyl, saccharin, and O-demethyl triazine amine. There was no evidence of glucuronide of sulfate conjugation.

17a. DPX-L5296 (4-methoxy-N,6-dimethyl-1,3,5-triazin-2-amine) is a moderately persistent soil metabolite and a possible minor rat metabolite of Express®.

17b. Its acute oral LD_{50} for male and female rats is 410 mg/kg, and its dermal LD_{50} is greater than 2000 mg/kg in rats (highest dose tested). The metabolite did not cause skin irritation in male rabbits, and it caused slight eye irritation (conjunctival reactions) that reversed in 3 days in rabbits. No delayed dermal sensitization reactions were observed in guinea pigs treated with DPX-L5296.

17c. In a four-week oral toxicity study, an LEL was established at 40 mg/kg/day, and the effects associated with the test substance included reduced body weight and weight gain, decreased blood glucose levels, and reduced platelet counts. These effects were also observed in males and females given the highest dose tested (200 mg/kg/day). In addition, the high dose group females exhibited decreased spleen-to-body weight ratios and increased white blood cell counts. High dose group males and females also had decreased potassium, increased SGPT, and an increased incidence of myocardial degeneration (often associated with fibrosis) in the ventricular apex. The 200 mg/kg dose group males also had elevated total serum protein. Based on these results, the suggested NOEL is 8 mg/kg/day.

17d. DPX-L5296 did not increase the frequency of reverse mutations with or without metabolic activation in Salmonella typhimurium or cause structural or numerical chromosome aberrations in human lymphocytes in vitro.

18a. Express® has been classified as a Category C oncogen because of a statistically significant dose-related increase in the incidence of malignant tumors (mammary gland adenocarcinomas) in female rats. The increased incidence exceeded the historical control range, and there was evidence of a structure-activity relationship to Atrazine which also causes mammary tumors in rats.

Recommendations and Conclusions (continued)

18b. A quantitative risk assessment for Express® is not appropriate because the increased incidence of mammary gland tumors was observed in female rats treated at dose levels exceeding the Maximum Tolerated Dose (MTD), there was no evidence of genetic toxicity shown in several studies, and other structural analogs of Express® were not associated with oncogenic responses in rats and mice.

19. Using a NOEL of 25 ppm (0.625 mg/kg/day) established in a one-year dog study and a Safety Factor of 100, a Reference Dose (RfD) of 0.0063 mg/kg/day is derived. This value has been verfied by the ADI Committee.

I. Background

A. General Information

Express® (chemical name: benzoic acid, 2-[[[[N-4-methoxy-6-methyl-1, 3, 5-triazin-2-yl)-N-methylamino]carbonyl]amino]-sulfonyl]-, methyl ester) is proposed as a herbicide for use on wheat and barley. It is to be formulated for that purpose as a dry flowable (75% active ingredient). The formulation's inert ingredients have been cleared for food use.

The formulation, which is called Express® Herbicide, is applied at rates of 1/6 to 1/3 oz. active ingredient per acre according to the label, and the application is to be made between the 2-leaf and boot stages of winter or spring wheat and spring barley. The herbicide will be mixed with water, and the mixture is to be sprayed by air (1 gal/A) or ground equipment (5 gal./A) in the spring.

The proposed tolerances are 0.05 ppm in/on wheat and barley grain and 0.1 ppm in/on wheat and barley straw.

B. Summary of Previously Submitted Data

Appendix I. below contains Toxicology "One-Liners" for all the toxicity studies on Express® discussed in this section.

1. Acute toxicity

a. Technical grade Express®

The results of acute toxicity studies on technical grade Express® are summarized as follows:

Route of administration	Species	Sex	LD_{50} or LC_{50}	Toxicity Category
Oral	Rat	Both	>5,000 mg/kg	IV
Inhalation	Rat	Both	>6.7 mg/L*	III
Dermal	Rabbit	Both	>2,000 mg/kg	III

*Four hour exposure.

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

Technical grade Express® is not a dermal sensitizer.

b. Express® Herbicide (75% a. i.)

Acute toxicity results are summarized as follows:

Route of administration	Species	Sex	LD_{50} or LC_{50}	Toxicity Category
Oral	Rat	Female	5,700 mg/kg	IV
		Male	4,800 mg/kg	III
Dermal	Rabbit	Both	>2,000 mg/kg	III

In the listing of toxicity studies provided with a previous submission, the Registrant stated that an acute inhalation toxicity study with the formulation was not conducted because <0.5% of the water-dispersible granules in the formulation are smaller than 105 um.

Most of the deaths observed in the acute oral toxicity study occurred 2 to 3 days after treatment, and some were noted as long as 9 days after dosing. Gross lesions observed at necropsy were not organ-specific. Signs of toxicity noted during post-dosing observation included staining of the face and perineum, chromodacryorrhea, and body weight loss.

An eye irritation study indicated that mean irritation scores for unwashed eyes 24, 48, and 72 hours after treatment were 14, 6, and 6, respectively. At 4 and 7 days after instillation the mean scores were 4 and 0. The results were sufficient to classify Express® Herbicide® into Toxicity Category III for eye irritation.

The Primary Irritation Score for dermal irritation was 0 which places the formulation into Toxicity Category IV.

No dermal sensitization was observed in guinea pigs.

2. Subchronic toxicity

In a three-month feeding study, groups of rats were given diets containing 0, 100, 1750, or 5000 ppm Express®. The 100 ppm dietary level had no effect (NOEL). The two higher levels caused significant dose-related decreases in food consumption, body weight gain, and lower food efficiency. There were also significant decreases in absolute weights for the heart, brain, liver, and kidneys at the two highest dietary levels, and relative organ weights for the heart, liver, kidneys, testes, and spleen were increased significantly because of the decreased body weights observed. Serum glucose, globulin, and cholesterol concentrations were decreased in the mid and high dose groups, but there were no treatment-related histo-

pathological effects. These effects were described by the investigators as indications of cachexia. The LOEL is 1750 ppm.

In another 90-day feeding study, Express® was given to dogs in their diet at levels of 0, 50, 500, or 2500 ppm. The highest dose tested caused no clearly treatment related effects so these results suggest a NOEL >2500 ppm in dogs.

3. Chronic Toxicity

a. Non-rodents

Groups of 5 male and 5 female beagle dogs were given diets containing 0, 25, 250, or 1500 ppm Express® for one year. Effects associated with Express® treatment included elevated blood levels of bilirubin and aspartate aminotransferase (AST), increased urinary volume and decreased body weight gain in males. Treated females exhibited elevated bilirubin, AST, creatinine and globulin levels along with decreased body weight gain. A NOEL was established for these effects at 25 ppm (0.625 mg/kg/day) and the LEL was 250 ppm (6.25 mg/kg/day).

b. Rodents

Groups of 72 male and 72 female Sprague-Dawley rats were given diets containing 0, 25, 250, or 1,250 ppm Express® for up to 24 months.

Effects attributed to the test substance included decreased body weight and increased incidences of masses located on the shoulder, side, and under body regions in high dose group female rats. The masses were associated with the statistically significantly increased incidence of mammary gland adenocarcinomas observed in the high dose group females (see next Section below). There was no significant effect on survival in treated animals.

By the end of the study, the mid and high dose group weight gains for males were 10.8 and 36.4% less than that for the control group. In female rats the mid dose group had a body weight gain that was 26.6% less than that for the control group at the end of the study, and the high dose group's weight gain was 53.8% less than controls.

Organ weights in treated animals reflected the observed decreases in body weight (i. e., significant increases in the majority of relative organ weights in the male and female rats at the 1,250 ppm dose level and female rats at the 250 ppm dose level along with statistically significantly decreased absolute organ weights).

In male rats given the high dose level, the incidence of polyarteritis in the pancreas, decreased secretion in seminal vessicles, lymphoid depletion in the spleen, and mineralization of the aorta and stomach were statistically significantly increased above control group incidences. The latter two lesions were associated with an increase in severity of glomerulonephropathy in the high dose group males. The incidence of dilatation of the

renal pelvis, dilatation of the uterine horns, and retinal degeneration was statistically significantly increased in females given the highest dose level.

Based on the reduced body weights in treated male and female rats, a NOEL was established in the study at 25 ppm (1.25 mg/kg/day).

4. Oncogenicity

a. Rats

In the rat chronic feeding study discussed above, the incidence of mammary gland adenocarcinomas and combined mammary tumors in female rats given the 1250-ppm dose level was statistically significantly increased. The mammary gland tumor results are summarized as follows:

Observations	Dose level (ppm) 0	25	250	1250
Fibroadenoma	16/70+	12/61	7/59	6/71
	(23)	(20)	(20)	(13)
p++ =	0.0578	0.4103	0.4492	0.0862
Adenoma	1/46	1/44	2/47	2/47
	(2)	(2)	(4)	(4)
p =	0.2921	0.5054	0.3832	0.3832
Adenocarcinomas	10/70	9/61	13/59	26/71
	(14)	(15)	(22)	(37)
p =	0.0002**	0.6283	0.1802	0.0020**
Combined (all three types)	24/70	19/61	22/59	34/71
	(34)	(31)	(37)	(48)
p =	0.0172*	0.4233	0.4319	0.0706

( ) Percentage incidence.

+ Number of tumor bearing animals/number of animals at risk, excluding those that died before observation of the first tumor.

++ Cochran-Armitage Trend Test ("p =" under the 0 ppm group column) and Fisher's Exact Test ("p =" under each dose group column).

* Statistically significant at $p \leq 0.05$.

** Statistically significant at $p \leq 0.01$.

b. Mice

Diets containing 0, 20, 200, or 1500 ppm Express® were given to male and female Charles River Crl:CD-1(ICR) BR strain mice for 18 months.

By the end of the study the highest dose tested caused minimal effects on body weight (6 and 5% less than control group means for males and females, respectively), and body weight gain (24% and 20% less than controls for males and females, respectively) were observed. At 13 weeks, there was approximately a 10% decrease in body weight gain for the high dose group males, and female mice in that group gained the same amount of weight as the control group females.

Although mortality was not statistically significantly increased at the highest dose in male mice, it was 65% in the 1500 ppm dose group compared to 51% in the control group. The incidence of amyloidosis was statistically significantly increased in male and female mice at the highest dose level ($p < 0.01$; Fisher's Exact Test), and the incidence of bilateral seminiferous degeneration (atrophy) and oligospermia was statistically significantly increased in 200 and 1500 ppm group males. Amyloidosis was also increased in females from the 1500 ppm dose group. Thyroid inflammation was statistically significantly increased in both sexes at the highest dose.

Based on the increased incidence of bilateral seminiferous degeneration and oligospermia in mid dose group male mice, the suggested NOEL was 20 ppm (3 mg/kg/day), and the LEL was 200 ppm (30 mg/kg/day). The minimal body weight reductions in female mice in the 1500 ppm dose group suggests that the NOEL for females is 200 ppm (30 mg/kg/day).

Under the conditions of the study, Express was not oncogenic.

5. Developmental toxicity

a. Rats

Doses of 0, 20, 125, or 500 mg Express® per kg body weight were administered to groups of pregnant rats on gestation days 6 through 16.

The mid and high doses were found to cause maternal toxicity (decreased maternal body weight gain and food consumption, increased liver-to-body weight ratios at the highest dose, and excess salivation).

Fetuses from dams given the two highest doses also had reduced body weights. The highest dose caused resorptions, fetal deaths, and incomplete ossification.

These results indicated that the NOEL's and LOEL's for maternal and developmental toxicity are 20 and 125 mg/kg/day, respectively.

b. Rabbits

Groups of 22 pregnant New Zealand White rabbits were given daily doses of 0, 5, 20, or 80 mg Express® by gavage on gestation days 7 through 19.

Based on statistically significantly decreased feed consumption and increased incidence of abortions at the highest dose, the LOEL for maternal toxicity was 80 mg/kg/day. The NOEL was 20 mg/kg/day.

The LEL for fetal effects (10% reduction in fetal weight without statistical significance) was also 80 mg/kg/day, and the NOEL is 20 mg/kg/day. There were no fetal malformations or variations associated with administration of the test substance in pregnant rabbits.

6. Reproduction toxicity

In a two-generation reproduction study, male and female rats were given diets containing 0, 25, 250, or 1000 ppm Express®.

There was no effect on fertility, gestation, or lactation, and effects associated with the test substance included reduced group mean body weight for the adult females and for offspring, reduced spleen weight in the second litter of the final generation in the study. The NOEL was established at 25 ppm, and the LEL was 250 ppm.

As part of the subchronic feeding study in rats, a one-generation reproduction experiment was conducted. Six male and six female rats from each group were mated to produce the litters. Decreased pup viability and pup weights were observed in the 5000 ppm dose group. These results were consistent with the decreased body weights and generally poor condition of the dams given the highest dose level in the subchronic experiment.

7. Mutagenicity

a. Gene mutation assays

No increase in the frequency of reverse mutations was observed in Salmonella typhimurium strains TA1535, TA97, TA98, and TA100 when exposed to levels as high as 500 ug/plate without metabolic activation or as much as 2000 ug/plate with metabolic activation.

No mutagenic activity was observed in Chinese Hamster Ovary cells exposed in vitro to concentrations of 0.5 to 5.0 mM Express®-20 with and without activation.

b. Structural chromosomal damage assays

Single oral doses of 50, 500, or 5000 mg Express® per kg body weight had no effect on the incidence of chromosomal aberrations or mitotic index of bone marrow cells in male and female rats.

A single oral dose of 5000 mg Express® per kg body weight was shown to be cytotoxic (reduced polychromatic/normochromatic erythrocyte ratio) in mice. However, that dose did not increase the incidence of polychromatic erythrocytes with micronuclei in treated mice.

c. Other genotoxicity

Under the conditions of an in vitro unscheduled DNA sysnthesis (UDS) assay, Express® did not induce UDS in rat primary hepatocytes at concentrations of 0 to 2500 uM.

8. Metabolism studies

A series of limited experiments suggested that orally administered Express® is readily absorbed by male and female rats. The excretion half-life (time required for excretion of half of the dose) for a low dose (20 mg/kg) was 26 to 33 hours. Half-life values were similar in male and female rats and in rats given repeated daily doses (100 ppm for 21 days followed by a single 20 mg/kg dose on day 22). At high single doses (1700 to 2000 mg/kg) the excretion half-life for male rats was 51 to 54 hours, and that value for female rats was 69 to 96 hours.

The major route of excretion in rats was the urine. Urine samples collected over a 168-hour period following a single 1700 mg/kg dose contained two to four times more of the administered radioactivity than the feces.

Tissue levels of Express® and its metabolites increased with dose, but there was no concentration of radioactivity in any particular organ or tissue.

Major metabolites in the urine and feces included metsulfuron methyl, saccharin, and O-demethyl triazine amine. There was no evidence of glucuronide or sulfate conjugation.

Results from the single low dose indicated that approximately 35 to 40% of the recovered radioactivity in urine and feces samples collected during the 96 hours following dosing was associated with saccharin and approximately 15 to 20% was associated with metsulfuron methyl. Forty to 50% of the radiolabel recovered in excreta was unidentified.

The O-demethyl triazine amine was identified in the excreta of rats given the high dose, and it represented 40% of the recovered radioactivity in feces and urine from males and approximately 15% in female rats. Metsulfuron methyl accounted for approximately 20% of the radioactivity recovered during the 168 hours after the high dose in male and female rats. Approximately 25% of the radioactivity in excreta of males and 40% of that in females was not identified.

9. Toxicology Data on DPX-L5296

DPX-L5296 is described by the Registrant (LuPont) as a moderately persistent soil metabolite of Express®. Its chemical name is 4-methoxy-N, 6-dimethyl-1,3,5-triazin-2-amine, and it has been identified as one of the possible minor metabolites in rats (see Section I. B. 8. above).

a. Acute toxicity

The acute oral LD_{50} in rats for both sexes combined was 410 mg/kg. The LD_{50} for males alone was 394 mg/kg, and that values for females was 427 mg/kg. Signs of toxicity included lethargy, decreased motor activity, hunched posture, ataxia, irregular breathing, colored occular discharges, stained snout, and closed eyes. Survivors recovered from these signs during the first 4 days after dosing.

The results of an acute dermal toxicity study indicated that the dermal LD_{50} is greater than 2000 mg/kg in rats. No toxicity was observed in the treated animals, and 2000 mg/kg was the highest dose tested.

DPX-L5296 did not cause skin irritation in male rabbits. The metabolite caused slight eye irritation (conjunctival reactions) that reversed in 3 days in rabbits.

No delayed dermal sensitization reactions were observed in guinea pigs treated with DPX-L5296 in a Maximization test.

b. Subchronic toxicity - rats

In a four-week study, groups of male and female rats were given daily doses of 0, 8, 40, or 200 mg DPX-L5296 per kg body weight by gavage. The LEL was established at 40 mg/kg/day, and the effects associated with the test substance included reduced body weight and weight gain, decreased blood glucose levels, and reduced platelet counts. These effects were also observed in males and females given the highest dose tested. In addition, the high dose group females exhibited decreased spleen-to-body weight ratios and increased white blood cell counts. High dose group males and females also had decreased potassium, increased SGPT, and an increased incidence of myocardial degeneration (often associated with fibrosis) in the ventricular apex. The 200 mg/kg dose group males also had elevated total serum protein. Based on these results, the suggested NOEL is 8 mg/kg/day.

c. Mutagenicity

DPX-L5296 did not increase the frequency of reverse mutations with or without metabolic activation in Salmonella typhimurium at concentrations up to 5000 ug/plate (a toxic dose level).

There were no structural or numerical chromosome aberrations induced by DPX-L5296 in human lymphocytes in vitro at concentrations up to toxic levels (100 ug/ml).

C. Regulatory Considerations

1. Oncogenic Potential of Express®

On December 14, 1988, the Health Effects Division Peer Review Committee considered the oncogenic potential of Express®. The Committee's weight-of-evidence analysis and classification of the chemical as a Group C oncogen was presented to the Scientific Advisory Panel (SAP) on May 9, 1989, and Express® was reconsidered along with the comments from the SAP by the Peer Review Committee on June 1, 1989. In a draft document, the Peer Review Committee stated:

> The Committee upheld its classification of Express® as a Category C oncogen because of a statistically significant and dose-related increase in the incidence of malignant tumors (mammary gland adenocarcinomas) in female rats. In addition, the increased incidence exceeded the historical control

range, and there was evidence of a structure-activity relationship to Atrazine which also causes mammary tumors in rats.

The oncogenic response observed may be associated with a hormonal imbalance that may not occur at doses below an MTD. The Peer Review Committee concluded that a quantitative risk assessment for Express® is not appropriate because the increased incidence of mammary gland tumors was observed in female rats treated at dose levels exceeding the Maximum Tolerated Dose (MTD), there was no evidence of genetic toxicity shown in several studies, and other structural analogs of Express® were not associated with oncogenic responses in rats and mice.

2. Reference Dose (ADI)

Using a safety factor of 100 and the NOEL of 25 ppm (0.625 mg/kg/day) established in the one-year dog feeding study, the Acceptable Daily Intake (ADI) is calculated as follows:

$$\frac{0.625 \text{ mg/kg/day}}{100} = 0.0063 \text{ mg/kg/day}$$

This ADI has been verified by the Agency.

II. New Information

The Registrant (Du Pont) noted that historical control data were submitted to the Agency on August 30, 1988 (see Section I. C. 1. above and Appendix II).

According to the Registrant, the initial review of an 18-month feeding study in mice classified the study as "Supplementary" on the basis of inadequate dose levels tested in the females. The response to the Toxicology Branch review pointed out:

The EPA expressed concern that the...study in mice...did not achieve a Maximum Tolerated Dose at the high dose level used for the female mice. This concern is based on the calculation of a 5% decrease in mean body weight for the females at the high dose. This calculation is...not correct because it is based on the body weights at test day 266. The high-dose at the end of the study (test day 546) was 10% less (statistically significant) than the control mice.

In addition, the body weight gain was 20% less than the control at the high-dose level. These effects on body weight and body weight gain meet the criteria of an MTD as defined in the Toxicity Potential (Guidance for Analysis and Evaluation of Subchronic and Chronic Exposure Studies) (EPA-540/9-85-020).

The Registrant also included additional histopathology data from a two-generation reproduction study and a complete report of a mutagenicity assay in Salmonella typhimurium in the submission (see Sections III. B. and C. and Appendices III and IV below).

III. Discussion

A. Historical control data

The historical control data were considered and accepted in the Peer Review Document (see Section I. B. above). The additional data confirmed that a significantly increased incidence of mammary gland adenocarcinomas was observed in the 1250-ppm dose group female rats.

B. Adequacy of dose levels in the mouse study

As indicated in Section I. B. above, the mouse study is considered by the Peer Review Committee to be adequate with respect to dose levels evaluated in female mice. Therefore, the classification of the mouse oncogenicity study should be upgraded from "Supplementary" to "Minimum."

C. Additional histopathology data from a reproduction study

There were adequate data presented to support the conclusions of the investigators that there were no treatment-related effects in F_0 generation rats in a two-generation reproduction study with Express (see Appendix III below).

D. Additional information on a mutagenicity study

The revised report of a mutagenicity assay in Salmonella typhimurium included information on the composition of the test substance and cytotoxicity data not previously submitted. There is adequate information in the revised report to upgrade the classification of the study from "Unacceptable" to "Acceptable." The study indicated that the test material is not mutagenic in Salmonella typhimurium with or without metabolic activation (see Appendix IV below).

IV. List of Appendices

APPENDIX I: Toxicology "One-Liners" for Express (Tox. Chem. No. 419S)
APPENDIX II: Historical Control Data for a Rat Chronic Feeding/Oncogenicity Study with Express Herbicide
APPENDIX III: Additional Data from MRID 409272-09.
APPENDIX IV: Additional Data from MRID 409272-10.

Express science review

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Pages 15 through 21 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

X A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

___ FIFRA registration data

___ **The document is a duplicate of page(s) _____**

___ **The document is not responsive to the request**

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

APPENDIX I

Toxicology "One-Liners" for
Express (Tox. Chem. No. 419S)

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Reproduction-1 generation Species: rat Haskell Lab 413-83; 6/6/85	DPX-L5300 tech 96.8% ai	073790	Developmental NOEL = 2500 ppm, Developmental LEL = 5000 ppm (decrease pup viability and weight gain) . No final conclusion can be drawn because there were only 3 to 6 dams with liters available for analysis. Adult toxicity NOEL and LEL (see feeding phase of this study, Report no. 413-85, below) Doses tested: 0, 100, 2500, & 5000 ppm in the diet		Supplementary 004943
Teratology Species: rat Argus Research Labs hlo-513-85; 8/16/85	DPX-L5300 tech 96.8% ai	073790	Maternal NOEL = 20 mg/kg, Maternal LEL = 125 mg/kg (decreased body weight gain and food consumption, increased liver to body weight ratio), Developmental NOEL = 20 mg/kg, Developmental LEL = 125 mg/kg decreased body weight, at the HDT increased resorptions and fetal deaths, incomplete ossification. A/D ratio = 125/125 = 1. Doses tested = 0, 20, 125, and 500 mg/kg on gestations days 6-16		Guideline 004943
Teratology Species: rabbit Haskell Lab 150-86; 4/8/86	Expreus tech 94.2% ai	402455-14	Maternal toxicity: NOEL = 20 mg/kg, LEL = 80 mg/kg (HDT) (decreased food consumption, increased abortions). Developmental toxicity: NOEL = 20 mg/kg, LEL = 80 mg/kg (HDT) (10% decrease in body weight compared to controls - difference was not statistically significant). No terata were associated with treatment. Doses tested: 0,5,20, and 80 mg/kg/day.		Minimum 006833
Reproduction-2 generation Species: rat Haskell Lab 193-86; 4/14/86	Express tech	402455-15	Paternal systemic toxicity : NOEL = 25 ppm (1.25 mg/kg), LEL = 250 ppm. (decreased body weight gain in F1 females). Reproductive toxicity: NOEL = 25 ppm, LEL = 250 ppm (decreased body weight gain during lactation for F1b and F2b pups). Developmental toxicity: NOEL = 25 ppm (decreased absolute spleen weights in F2b pups). Doses tested: 0, 25, 250, and 1250 ppm.		Minimum 006833
Feeding-1 year Species: dog Haskell Lab 565-86; 10/10/86	Express tech	402455-12	NOEL (M) = 25 ppm (0.625 mg/kg), LEL(M) = 250 ppm (elevated serum bilirubin and AST levels, increased urinary volume); NOEL(F) = 250 ppm (6.25 mg/kg), LEL(F) = 1500 ppm (increased serum creatinine, bilirubin, AST, and globulin, decreased body weight gain [18.2%]). Doses tested: 0, 25, 250, and 1500 ppm.		Minimum 006833
Feeding/oncogenic-2 year Species: rat Haskell Lab 61-87; 3/10/87	Express tech 96.8% ai	402455-11	NOEL = 25 ppm (1.25 mg/kg), LEL = 250 ppm (decreased body weight gain in males and females). Oncogenic positive (statistically significant increase in mammary gland adenocarcinomas in female rats at 1250 ppm). Doses tested: 0, 25, 250, and 1250 ppm.		Minimum 006833
Feeding/oncogenic-18 month Species: mice Haskell Lab 60-87; 3/6/87	Express tech 96.8% ai	402455-13	NOEL = 200 ppm (3 mg/kg), LEL = 1500 ppm (HDT) (increased incidence of seminiferous degeneration and oligospermia, 10% decrease in body weight gain at 90 days), LEL (F) > 1500 ppm. Oncogenic negative (no increase in tumor incidence). Doses tested: 0, 20, 200, and 1500 ppm Inadequate for testing oncogenic potential in female mice. Doses were male and		Supplementary 006833 Minimum 007264

007264

2

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	CORE/GRADE/ DOCUMENT#
Risk assessment Species: rat Haskell Lab 3/87	Express (INL-5300)		Two year chronic oncogenicity study. Dose levels of 0, 25, 250,and 1250 ppm of Express. Design - 72 animals in each group (M&F). Qualitative Risk Assessment : Males - no significant findings. Females - mammary gland tumors. Significant trends in adenocarcinomas and in adenomas and/or adenocarcinomas. Pair-wise comparison with controls resulted in significant differences in adenocarcinomas and in adenomas and/or adenocarcinomas in the highest dose group (1250 ppm).		006955
Feeding-3 month Species: rat Haskell Lab 413-85; 7/6/85	DPX-L5300 tech 96.8% ai	073790	NOEL = 100 ppm, LEL = 1750 ppm(decrease body weight gain & food consumption and food efficiency; decrease absolute heart, brain, liver, and kidney weights; relative organ weights for heart, liver,kidneys, testes, and spleen were increased; serum glucose, globulin & cholesterol were decreased); Doses tested: 0,100, 1750, & 5000 ppm.		Minimum 004943
Feeding-3 month Species: dog Bio/dynamics Inc. HLO-514-85; 8/85	DPX-L5300 tech 96.8% ai	073788 073789	NOEL > 2500 ppm(HDT); Doses tested: 0, 50, 500, & 2500 ppm		Minimum 004943
Feeding-3 month Species: rat Haskell Lab 112-89; 3/16/89	DPX-L5300		Doses tested: 0 and 5000 ppm. Estrogenic effects at 5000 ppm included: slightly prolonged estrus, increased cell proliferation in the uterus, increase in serum prolactin levels, increased progesterone receptor number in mammary glands, decreased estrogen-binding affinity of receptors in the uterus and mammary glands. Food consumption was significantly decreased along with body weight gain. Decrease food consumption could also affect the endocrine system which raises questions about the relationship between treatment and hormonal effects observed. A "pair-fed" control group is needed. The study wasn't conducted with an estrogenic substance (positive control		Supplementary 007264
Dissimilation chemicals	Methyl-2-[[[[N-(4-methoxy 6-methyl-1,3,5-triazin-2-yl)N-methylaminocarbonyl] amino]sulfonyl]benzoate		Caswell # 419S		
Metabolism Species: rat Haskell Lab 31-87; 4/15/87	Express Radiolabeld (14C-phenyl or 14C-triazin)(spec acti vity 20.5 uCi/mg)	402455-16	Single orally doses are readily absorbed. Excretion half-life for low single and repeated doses (20 mg/kg/day was 26 to 33 hours. At high single doses (1700 to 2000 mg/kg) the excretion half-life for males was 51 to 54 hours, and for females it was 69 to 96 hours. The major route of excretion is the urine (2 to 4 times the amount excreted in feces). Tissue levels increased with dose, but there was no accumulation in any particular organ or tissue. Major metabolites in the urine and feces included metsulfuron methyl, saccharin, and O-demethyl triazine amine. There was no evidence of glucuronide or sulfate conjugation.		Acceptable 006833

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Oncogenic risk assessment Species: rat Haskell Lab 61-87	Express (INL-5300)		2 Year Chronic/Oncogenic Rat (Sprague Dawley) Study -- Conducted by Haskell Labs (Study 61 - 87): Quantative R.A. - Unit Risk *Q1 = 446 x 10 exp -2 (mg/kg/day)-1 in human equivalents. Estimate is based upon female rat - mammary gland tumors (adenoma &/or adenocarcinoma) Used Multistage Model (Global 86-K Crump).1) No dose related survival problem; 2) mammary gland tumor rates had a significant trend & there was a significant difference between controls & the high dose group; 3) dose levels of Express were 0, 25, 250, & 1250 ppm		007146
Pharmacology/estrogen receptor Species: rat cytosol (ut&mam) Haskell Lab 112-89; 3/16/89	DPX-L5300 (96.8% a.i.)		Doses tested = 1 nM. Express and some of its metabolites can act as agonists at estrogen receptors.		Supplementary 007264
Mutagenic-Ames Species: salmonella Haskell Lab 245-83; 5/25/85	DPX-L5300 tech 96.8% ai	073790	Not mutagenic		Unacceptable 004943 Acceptable 007264
Mutagenic-point mutation Species: cho cells Haskell Lab 58-85; 5/30/85	DPX-L5300 tech 96.8% ai	073790	Not mutagenic		Acceptable 004943
Mutagenic- cytogenetic Species: rat Haskell Lab 286-85; 6/14/85	DPX-L5300 tech 96.8% ai	073790	No genotoxicity		Acceptable 004943
Mutagenic-micronucleus assay Species: mouse Haskell Lab 420-85; 7/22/85	DPX-L5300 tech 96.8% ai	073790	No genotoxicity		Acceptable 004943
Mutagenic-unscheduled DNA synt Species: rat Haskell Lab 565-84; 7/18/85	DPX-L5300 tech 96.8% ai	073790	No genotoxicity		Acceptable 004943
Mutagenic-Ames Species: bacteria Life Science Research 86/DPR007/525	L5296(metabolite of DPX-L 5300)	402455-17	Negative for induction of increase revertents w/without activation in S.typhimurium strains exposed to toxic concentration 5000 ug/plate		Acceptable 006833

007264

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Mutagenic Species: mammalian Life Science Research 86/DPR008/525	L5296(metabolite of DPX-L 5300)	402455-17	Negative for inducing structural or numerical chromosome damage in primary human lymphocytes exposed up to toxic level (100 ug/ml)		Acceptable 006833
Acute oral LD50 Species: rat Haskell Lab 167-85; 5/5/85	DPX L5300 Tech. (96.8% a.i.)		LD50 > 5000 mg/kg for both sexes (Limit test)	4	Minimum 004943
Acute oral LD50 Species: rat Haskell Lab 280-85; 5/30/85	DPX-L5300 herbicide (75%)		LD50 = 5700 mg/kg (M). LD50 = 4800 mg/kg (F).	3	Minimum 004943
Acute Dermal LD50 Species: rabbit Hazleton HLO-21-85; 12/24/84	DPX L5300 tech. (96.8% a.i.)	073787	LD50 > 2000 mg/kg for both sexes (Limit test)	3	minimum 004943
Acute Dermal LD50 Species: rabbit Hazleton HLO-234-85; 4/11/85	DPX L5300 herbicide (75% dry flowable)	073787	LD50 > 2000 mg/kg for both sexes (Limit test)	3	Minimum 004943
Acute inhalation LC50 Species: rat Haskell Lab 431-85; 8/13/85	DPX L5300 Tech (96.8% a.i.)	073787	LC50 > 6.7 mg/L for both sexes, 4 hr. exposure. Concentration tested = 6.7 mg/L and 1.3 mg/L. Nose only exposure.	3	Minimum 004943
Acute inhalation LC50 Species: rat	DPX L5300 herbicide (75% dry flowable)	073787	Requirement waived because < 0.5% of the formulations granules are < 105 um in diameter.		004943
Primary eye irritation Species: rabbit Hazleton HLO-305-85; 5/24/85	DPX L530 herbicide (75% Dry flowable)	073787	Moderately irritating (no Primary Irritation Score given). Corneal opacity persisted for three days, redness persisted for 4 days.	3	Minimum 004943
Primary dermal irritation Species: rabbit Hazleton 233-85; 4/11/85	DPX L5300 herbicide (75% dry flowable)	073787	PIS = 0	4	Minimum 004943

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Dermal sensitization Species: guinea pig Hazleton HLO-295-85; 5/23/85	DPX-L5300 herbicide (75% dry flowable)	073787	Not a sensitizer.		Minimum 004943
Dermal sensitization Species: guinea pig Hazleton 617-68; 10/27/86	DPX-L5300	400498-03	Nonsensitizer.		Guideline 006306
Acute oral LD50 Species: rat Haskell Lab 619-86; 10/23/86	DPX L5300	400498-04	LD50 > 5000 mg/kg. Dose: 5000 mg/kg.	4	Guideline 006306
Primary dermal irritation Species: rabbit Haskell Lab 518-86; 9/10/86	DPX L5300	400498-05	At 24 hrs. 6/6 = 1 for erythema. At 72 hrs, no irritation. PIS - 0.5.	4	Guideline 006306
Primary eye irritation Species: rabbit Haskell Lab 604-86; 9/19/86	DPX L5300	400498-07	Corneal opacity and irritation cleared by 72 hrs.	3	Guideline 006306
Acute Dermal LD50 Species: rabbit Haskell Lab 689-86; 11/10/86	DPX L5300	400498-06	LD50 > 2000 mg/kg. Dose = 2000 mg/kg	3	Guideline 006306
Acute oral LD50 Species: rat Haskell Lab 115-85; 2/25/85	DPX L5300 12.5%; 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl] benzenesulfamide 62.5%	258174	LD50 (M) = 5600 mg/kg (4600-6200). LD50 (F) = 6200 (5700-6600)	4	Guideline 006289
Acute Dermal LD50 Species: rabbit Hazleton 201-805; 1985	DPX L5300 12.5%; 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl] benzenesulfoamide 62.5%	258174	LD50 > 2000 mg/kg.	3	Guideline 006289
Primary dermal irritation Species: rabbit 1/8/85 201-806	DPX L5300 12.5%; 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl] benzensulfoamide 62.5%	258174	Slight to severe erythema at 30 to 60 minutes post-treatment. At 24 hrs. slight to well-defined irritation; had cleared by 72 hrs.	3	Guideline 006289

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Primary eye irritation Species: rabbit Hazleton 201-806; 1985	DPX-L5300 12.5%; 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl] benzensulfoamide 62.5%	258174	Corneal opacity and other irritation had cleared at 72 hrs.	3	Guideline 006289
Dermal sensitization Species: guinea pig Hazleton 201-808; 3/12/85	DPX L5300 12.5%; 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl] benezensulfoamide 62.5%	258174	Nonsensitizing.		Guideline 006289
Primary eye irritation Species: rabbit Hazleton 201-616; 6/6/83	DPX L5300 tech.	403574-01	Levels tested = 10 mg instilled into the right eye of each of two rabbits redness with vessels injected more than normal were observed 1 and 4 hrs after treatment.		Supplementary 006569
Dermal sensitization Species: guinea pig Hazleton 201-617; 9/12/83	DPX L5300 Tech.	402574-02	Not a sensitizer.		Minimum 006569
Primary dermal irritation Species: guinea pig Hazleton 201-617; 9/12/83	DX L5300 tech.	403547-02	Levels tested: 7 and 70% solution in dimethyl phthalate. Study was designed to determine a dose level for the dermal irritation study rather than assessing the dermal irritation potential of the undiluted technical grade material.		Supplementary 006569

APPENDIX II

Historical Control Data for a Rat Chronic Feeding/Oncogenicity Study with Express Herbicide

THE INCIDENCE OF PRIMARY MAMMARY NEOPLASMS IN FEMALE Crl:CD®BR CONTROL RATS

FROM 2-YEAR FEEDING STUDIES AT HASKELL LABORATORY (1980-1938)

TYPE OF NEOPLASM	PATHOLOGY REPORT NUMBER											
	1-80	33-80[a]	33-80[a]	2-81[b]	30-81	20-84	43-85	75-85[b]	2-86	M-8A[c]	9-86	10-88
Adenoma	0/58[d]	0/29	0/30	0/80	1/64	0/67	1/64	2/76	6/66	1/59	0/58	3/60
Adenocarcinoma	1/58	1/29	3/30	6/80	13/64	7/67	15/64	6/76	10/66	7/59	12/58	13/60
Fibradenoma	26/58	16/29	17/30	35/80	33/64	27/67	18/64	24/76	16/66	18/59	19/58	24/60
Fibroma	0/58	0/29	0/30	0/80	0/64	0/67	0/64	0/76	1/66	0/59	0/58	0/60
Fibrosarcoma	0/58	0/29	0/30	0/80	0/64	0/67	0/64	1/76	0/66	0/59	0/58	0/60

[a] Study had two control groups

[b] Number of animals includes those from the one-year sacrifice. For the other studies, only the animals remaining on study after the one-year sacrifice are included.

[c] Gavage study

[d] Number of rats with neoplasm/number of rats with mammary tissue examined

APPENDIX III

Additional Data from

MRID 409272-09. Chiu, T. November 3, 1988. Two-Generation Reproduction Study in Rats with IN L5300: Supplemental Report to Pathology Report No. 4-86. Unpublished report no. 193-86, Proj. No. 7366 prepared by Haskell Laboratory for Toxicology and Industrial Medicine. Submitted by E. I. DuPont de Nemours and Company, Inc., Newark, DE.

TWO-GENERATION REPRODUCTION STUDY IN RATS
INL-5300

HN-15601
HC-42
MR-7366

TABLE 1
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS

GROUP DESIGNATION:	I	III	V	VII
DOSE (UNITS):	CONTROL	25 ppm	250 ppm	1000 ppm
SITE/LESION: NUMBER IN GROUP:	10	10	10	10
LUNGS				
DISCOLORATION	0	1	0	1
KIDNEYS				
SMALL	0	0	0	1
CALCULUS	0	0	0	1
DEFORMITY	0	0	0	1
RENAL PELVIS				
DILATATION	1	1	2	2
URINARY BLADDER				
DILATATION	0	1	0	0
THYMUS				
SMALL	0	0	0	1
DISCOLORATION	0	0	1	0
MANDIBULAR LYMPH NODES				
LARGE	1	1	0	1

TWO-GENERATION REPRODUCTION STUDY IN RATS
INL-5300

HN-15601
HC-42
MR-7366

TABLE 2
INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS

FEMALE

SITE/LESION:	GROUP DESIGNATION: II DOSE (UNITS): CONTROL NUMBER IN GROUP: 10	IV 25 ppm 10	VI 250 ppm 10	VIII 1000 ppm 10
SKIN				
ULCER/EROSION	1	0	0	0
ALOPECIA	0	0	1	2
LUNGS				
FOCI	1	0	0	0
DISCOLORATION	0	0	0	1
RENAL PELVIS				
DILATATION	2	1	1	0
UTERINE HORNS				
DISTENDED WITH LIQUID	1	1	0	1
PITUITARY				
LARGE	1	0	0	0
MAMMARY GLAND				
LESION, OTHER	0	0	0	1

TWO-GENERATION REPRODUCTION STUDY IN RATS
INL-5300

HN-15601
HC-42
MR-7366

TABLE 3
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

TISSUE/LESION	LESION GRADES (1,2,3,4,P)	GROUP DESIGNATION:	I	VII
		DOSE (ppm):	0	1000
		NUMBER IN GROUP:	10	10
EPIDIDYMIDES			10	10
INFLAMMATION,GRANULOMATOUS,FOCAL,FAT PAD			1 (1,-,-,-,-)	1 (1,-,-,-,-)
LYMPHOCYTIC INFILTRATE,FOCAL,INTERSTITIAL			9 (9,-,-,-,-)	1 (1,-,-,-,-)
PROSTATE			10	10
EDEMA			-	1 (-,1,-,-,-)
INFLAMMATION,SUBCHRONIC,FOCAL			3 (3,-,-,-,-)	1 (-,1,-,-,-)
TESTES			10	10
ASPERMATOGENESIS,FOCAL,UNILATERAL			-	1 (1,-,-,-,-)
LYMPHOCYTIC INFILTRATE,FOCAL,INTERSTITIAL			1 (1,-,-,-,-)	-

NOTES:
- o THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- o LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. FOR EXAMPLE: (-,1,2,-,-) MEANS NO LESIONS WERE GRADED MINIMAL, 1 LESION WAS MILD, 2 LESIONS WAS MODERATE, NO LESIONS WERE SEVERE AND "PRESENT" (NON-GRADED LESIONS).

TWO-GENERATION REPRODUCTION STUDY IN RATS
1NL-5300

HN-15601
HC-42
MR-7366

TABLE 4
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS

TISSUE/LESION	LESION GRADES (1,2,3,4,P)	GROUP DESIGNATION: DOSE (ppm): NUMBER IN GROUP:	II 0 10	VIII 1000 10
OVARIES			10	10
UTERUS-CERVIX			10	10
UTERUS-CORPUS			10	10
DILATATION,LUMINAL			1 (-,-,-,-,1)	2 (-,-,-,-,2)
VAGINA			10	10

NOTES:
- o THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- o LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. FOR EXAMPLE: (-,1,2,-,-) MEANS NO LESIONS WERE GRADED MINIMAL, 1 LESION WAS MILD, 2 LESIONS WAS MODERATE, NO LESIONS WERE SEVERE AND "PRESENT" (NON-GRADED LESIONS).

APPENDIX IV

Additional Data from

MRID 409272-10. Rickard, L. B. December 5, 1988. Mutagenicity Testing of INL-5300-9 in the Salmonella typhimurium Plate Incorporation Assay. Unpublished report no. 245-83, Proj. No. 4581-105 prepared by Haskell Laboratory for Toxicology and Industrial Medicine Submitted by E. I. DuPont de Nemours and Company, Inc., Newark, DE.

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CONCLUSIONS

INL-5300-9 was nonmutagenic in Salmonella typhimurium when tested according to the protocol described in METHODS.

Composition: 94% INL-5300-9

Synonyms: o None

Original Report

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Report by: Lauren B. Rickard 12/5/88
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TABLE I

CYTOTOXICITY OF INL-5300-9 IN SALMONELLA TYPHIMURIUM STRAIN TA1535

Concentration ug/Plate	Without Activation (Colonies/Plate)	With Activation (Colonies/Plate)
0	827, 649	1163, 1154
50	606, 686	1087, 1232
100	588, 454	1192, 1193
500	126, 188	1247, 1183
1000	84, 31	1165, 1083
5000	0, 0	314, 282
10000	0, 0	45, 62

H-14,801 = INL-5300-9
MR-4581-105