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Chemical Category	DIISONONYL PHTHALATE		

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Aristech Chemical Corporation
600 Grant Street
Pittsburgh, PA 15230-0250
412/433-2747
Telex: 6503608865
Answer Back: 6503608865MCI UW

ARISTECH



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Attention: 8(e) Coordinator
Office of Toxic Substances
U. S. Environmental Protection Agency
401 M Street, S.W.
Washington, D. C. 20460

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Dear Sir:

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Subject: Follow-up submission to Toxic Substances Control Act Section 8(e) Notice 8EHQ 0794-13083 Preliminary Results of the Oncogenicity Study in Rats with Di(isononyl) phthalate.

In accordance with the Toxic Substance Control Act, Aristech Chemical Corporation of Pittsburgh, Pa. is submitting follow-up information in addition to the July 13, 1994 submission regarding the 2-year dietary testing of Di(isononyl)phthalate (DINP) in rats.

In July, it was reported that, at terminal sacrifice, results of the gross pathology examination suggested that high-dose animals had an increased incidence of liver masses. At that time, the masses were not histopathologically characterized. Aristech committed to providing EPA with histopathology data on the study once it became available. Although Aristech has not received a draft study report, information is now available on the histopathological analysis of tissues from the test and control animals. Pertinent aspects of this information are summarized below.

Di(isononyl)phthalate was administered to male and female F-344 rats in the diet for at least 104 weeks. There were seven groups of animals on study (no. of animals/group):

Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
Oppm	500ppm	1500ppm	6000ppm	12000ppm	12000ppm-R	+Cntrl
(85)	(70)	(70)	(85)	(85)	(55)	(15)

A recovery high-dose group, Group 6, received DINP in the diet for the first 78 weeks of the study and then were maintained on normal diet and not test material. The positive control group, Group 7, received 1000ppm of WY 14643, a known liver peroxisome proliferative agent. For weeks 1 to 78, the average daily does of DINP consumed by rats is calculated to be: 29.2, 88.3, 358.7 and 733.2mg/kg/day for low to high-dose males, respectively and 36.4, 108.6, 442.2 and 885.4mg/kg/day, respectively, for low to high-dose females.



Survival was unaffected by treatment through week 78 and exceeded 90%. At week 104, the survival experience was reduced in a dose-related fashion and ranged from 74% in control males to 58% in the high-dose males and from 76% in control females to 70% in the high-dose females.

Histopathological characterization and incidence data of the liver masses reported in July is given below.

HEPATOCELLULAR TUMORS - MALES

TEST GROUP NO. OF ANIMALS EXAMINED	1	2	3	4	5	6
HEPATOCELLULAR ADENOMA	4	4	2	6	10	5
CARCINOMA	1	0	0	1	11	2
MULTIPLE NEOPLASMS	0	0	0	1	4	0

HEPATOCELLULAR TUMORS - FEMALES

TEST GROUP NO. OF ANIMALS EXAMINED	1	2	3	4	5	6
HEPATOCELLULAR ADENOMA	0	1	0	1	3	1
CARCINOMA	1	0	0	1	5	2
MULTIPLE NEOPLASMS	0	0	0	0	0	1

Treatment-related lesions were increased in the kidneys of mid- and high-dose male rats. The lesions consisted of mineralization of the renal papilla, renal tubule cell pigment deposition and renal carcinomas. The incidence of the renal carcinomas was:

KIDNEY TUMORS - MALES

TEST GROUP NO. OF ANIMALS EXAMINED	1	2	3	4	5	6
MALIGNANT TUBULE CELL CARCINOMA	0	0	0	0	2	4
MALIGNANT TRANSITIONAL CELL CARCINOMA	0	0	0	1	0	0

Due to the low incidence and inverse-dose response relationship, the renal carcinomas are not considered by Aristech to test related.

Mononuclear cell leukemia, also known as large granular lymphocyte leukemia, occurred in rats of all test and control groups. The incidence of this lesion is presented below along with historical control data.

MONONUCLEAR CELL LEUKEMIA

STUDY TEST GROUP	1	2	3	4	5	6
MALES ON STUDY (%)	34	46	42	49	46	62
FEMALES ON STUDY (%)	26	32	18	44	46	48
LABORATORY HISTORIC						
CONTROL - MALES						38.9% (range 36.2-46%)
- FEMALES						30.3% (range 13.3-40%)
CHARLES RIVER LABORATORY						
PUBLISHED SPONTANEOUS						
RATE - MALES (% AND RANGE)						16.5% (0-31.3)
- FEMALES (% AND RANGE)						10.4% (0-26.4)

The spontaneous incidence of monocellular leukemia in the performing laboratory for this study is substantially elevated in the populations of animals historically used and in those used in the present investigation. There is a 2.3-fold increase for males and 2.9-fold increase for females in the leukemia experience of the historical control animals in the performing laboratory versus that which has been reported by the animal breeder. Because of this point and the two following:

- 1) that except for groups 4 and 6 (males) and groups 4, 5 and 6 (females), the range of leukemias occurring in treatment groups falls within the historical range of spontaneous leukemias for this testing facility; however, the incidence of leukemia in both male and female treatment groups is not dose-related at any points along the dose-response curve. Group 6 is not the high test dose but a recovery group that received less test compound than group 5 animals and group 4 animals received a greater dose of test material than group 5 animals;
- 2) and that because of food consumption/body weight differences female animals on test received approximately a 25% greater dose of test material than males in the same dosing group but there is no manifestation of this in the incidence of leukemia in test animals;

it is the position of Aristech Chemical Corporation that the leukemia seen in this study is not the result of test material administration.

The statistical significance and the biological significance of the data issuing from this study are not yet known. Accordingly, Aristech does not believe that information on the occurrence of kidney carcinomas or leukemia in this study is reportable under Section 8(e) of TSCA, but given the EPA's broad interpretation of information it wishes to receive under Section 8(e), Aristech is submitting these data.

A copy of the final test report for this study will be forwarded to you when it becomes available.

Sincerely,

John R. Bankston II / sta

John R. Bankston II
Supervisor, Product Regulation
(412) 433-7686