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Submitting Organization

ARISTECH CHEM CORP

Contact

AMER COLL OF VETERINARY PATHOL

Document Title

SUPPLEMENT: 13-WEEK SUBCHRONIC DIETARY ORAL TOXICITY STUDY WITH DI(15)NONOYL PHTHALATE IN MICE WITH COVER LETTER DATED 070892 AND ATTACHMENTS

Chemical Category

DI(15)NONOYL PHTHALATE

ARISTECH

CONTAINS NO CBI

8-PP

Aristech Chemical Corporation
800 Grant Street
Pittsburgh, PA 15230-0250
412/433-2747
Telex: 4503608865
Answer Back: 4503608865MCI UW

8EHQ-0792-1150
88910000065:DDCN

SUPP

July 6, 1992

OTS Document Processing Center (TS-790)
(Attn: Section 8(e) Coordinator)
Office of Toxic Substances
U.S. Environmental Protection Agency
401 "M" Street, S.W.
Washington, DC 20460

92 JUL 13 AM 11:56

OTS DOCUMENT RECEIPT OFF

RE: 8EHQ-0191-1150 8



:DCN

89920000303

Dear Sir or Madam:

As a followup to subject 8(e) filing, Aristech Chemical Corporation provides a copy of the following information: A draft summary of a subchronic (13-week) Dietary Oral Toxicity Study of Di(isononyl)phthalate in B6C3F1 Mice. This study was referenced in our March 21, 1991 reply to your "EPA Information Request" following your initial review of our 8(e) filing. The findings in this study are not new information, but rather corroborative of information already submitted to the 8(e) Coordinator under the above-mentioned case number. A copy of the final report for this study will be submitted to your office upon our receipt.

Please incorporate this information into your file on this subject.

If you have any questions regarding this matter, please contact me.

Sincerely,

John R. Bankston II

John R. Bankston II
Sr. Regulatory Specialist
(412) 433-7686

Enclosure

cc: J. A. Santory
J. J. Pottmeyer III



ROUGH DRAFT

May 4, 1992

3

Pathology Report
A 13-Week Subchronic Dietary Oral Toxicity Study in Mice
with Di(isononyl)phthalate including ancillary hepatocellular
proliferation and biochemical analyses
Project No. 2598-103

Second Interim Sacrifice

Hematoxylin-and-eosin-stained sections of liver (three lobes) and duodenum were examined microscopically from mice of Groups 1, 4, and 6 sacrificed on Day 31 of study. The mice had received the control diet (Group 1), Di(isononyl)phthalate (DINP) at 10,000 ppm (Group 4, test article), or WY 14,463 at 1,000 ppm (Group 6, positive control).

Compound-related histomorphologic alterations were noted in mice of both sexes in Groups 4 and 6. Moderate diffuse hepatocellular enlargement was noted in mice of Groups 4 and 6. Focal liver necrosis occurred with increased frequency (Groups 4 and 6) and increased severity (Group 6) compared to mice of the control group. Also, individual cell degeneration/necrosis was observed in mice of Group 6.

In conclusion, dietary administration of Di(isononyl)phthalate at 10,000 ppm or WY 14,463 at 1,000 ppm to B₆C₃F₁ mice for 31 days resulted in diffuse hepatocellular enlargement of moderate degree and increased incidence/severity of focal necrosis. Individual cell degeneration/necrosis was also noted in mice of Group 6.

Pathologist:


 Richard W. Voelker, D.V.M., Ph.D.,
 Diplomate, American College of Veterinary
 Pathologists
 Life Sciences Division

5-4-92
 Date

2598-103.12

PTS Table Output	
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Yes	<u>5-4-92 RW</u> date / initials
Pending <input type="checkbox"/>	(call pathologist)

high-dose mice (one male, three females). In mid-high-dose mice, hepatocellular enlargement occurred as a centrilobular to midzonal change, and there was no evidence of pigment accumulation or individual cell degeneration/necrosis. Histomorphological changes noted in liver sections of high- and mid-high-dose mice correlated with increased liver weights in these groups. Liver weights (absolute and relative) were also increased in the mid-low-dose (4,000 ppm) group, but there was no histomorphologic correlate for this finding.

Tubular nephrosis occurred as a slight to moderate change in the kidneys of high-dose mice, with the exception of minimal nephrosis in female mouse A39871, which was an accidental death during Week 5. Although the mean weight of testes with epididymides was significantly reduced in high-dose mice, the testes were normal histologically with no apparent effect on seminiferous tubules. Minimal to slight numbers of immature/abnormal sperm forms were present in the epididymal ducts, indicative of a subtle effect on spermatogenic activity. Lymphoid depletion was noted in spleen sections from 4 high-dose mice and in the thymus of 13 high-dose mice.

Sections of female reproductive tract revealed uterine hypoplasia and absence of corpora lutea (anovulatory) in high-dose mice and in mid-high-dose mouse A39856, which died during Week 2 of the study. Compound-related histomorphological alterations were not observed in tissues examined from mice of the low- and mid-low-dose groups. A variety of spontaneous disease lesions and incidental findings occurred without relationship to treatment.

Conclusion

Administration of Di(isononyl)phthalate to B₆C₃F₁ mice at dietary levels of 1,500, 4,000, 10,000 and 20,000 ppm for at least 90 days resulted in compound-related histomorphological alterations in mice of the high-dose (20,000 ppm) and mid-high-dose (10,000 ppm) groups. Hepatocellular enlargement occurred as a moderate to moderately severe diffuse change in high-dose mice and was accompanied by pigment accumulation in Kupffer cells and bile canaliculi, individual cell degeneration/necrosis, and a low incidence of focal necrosis.

Centrilobular to midzonal hepatocellular enlargement was present in mid-high-dose mice. Other changes which occurred in high-dose mice were tubular nephrosis in the kidneys, immature/abnormal sperm forms in the epididymides, lymphoid depletion in the spleen and thymus, hypoplasia in the uterus, and absence of corpora lutea in the ovaries. Compound-related alterations were not observed in tissue sections from mice at the low- and mid-low doses.

Pathologist:


Richard W. Voelker, D.V.M., Ph.D.,
Diplomate, American College of Veterinary
Pathologists
Life Sciences Division

6-17-92
Date

2598-103.M

7

OSLETON LABORATORIES, INC.
Draft Clinical Pathology Report

Proj. No.: 2500-103

Int.: Week 14

Date: May 27, 1992

Study Dir.: Ivett

Path.: Vealier

Coord.: Doyle

pending M:E ratios

Summary

The test material, Di(isooctyl)phthalate, was administered to mice at dietary levels of 0, 1500, 4000, 10000, and 20000 ppm (Groups 1-5, respectively). Blood and urine were collected at Week 14 for evaluation by routine hematologic and biochemical methods and urinalysis. There were significant elevations in the activities of alanine aminotransferase and aspartate aminotransferase in Group 5 males, findings which support hepatocellular injury caused by the administration of the test material.

Results and Discussion

Hematology - There were significant decreases in the mean values for mean cell volume in Group 4 males and Group 5 animals and for mean cell hemoglobin in Group 5 animals without concurrent changes in the erythrocyte parameters (erythrocyte count, hemoglobin, and hematocrit). The mean value for erythrocyte count was significantly decreased in Group 3 females, but the change was not of great enough magnitude to significantly affect the erythrocyte indices (mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration). The mean value for segmented neutrophil count was significantly decreased in Group 3 females, but the magnitude of the change was not great enough to significantly affect the mean values for total and corrected leukocyte counts. The differential leukocyte counts and cellular morphology were generally comparable between control and treated groups.

Serum and Urine Biochemistry - The high incidence of low-volume (quantity not sufficient, QNS) serum samples very likely affected the statistical analysis of the individual values for many of the biochemical analytes. The mean values for alanine aminotransferase and aspartate aminotransferase activities were significantly increased in Group 5 males, findings which are suggestive of ongoing hepatocellular injury. There were significant decreases in the mean values for urinary sodium, urinary

chloride, and urinary creatinine in the Group 5 animals. In addition, the mean value for urine volume was significantly elevated for Group 5 males. The cause of the changes in the aforementioned urinary analytes is not readily apparent, but the changes are not dose related.

The mean value for glucose concentration was significantly decreased in Group 5 females. There were significant increases in the mean values for globulin concentration in Group 2 males and albumin concentration in Group 5 males, but neither change was of a magnitude great enough to significantly affect the mean values for total protein concentration.

Urinalysis - Urinalyses were generally comparable between control and treated groups, with the exception of an decreased incidence of protein in the Group 4 and 5 animals.

Clinical Pathologist:

RCP

6-22-72

Renee C. Pearson, M.S., D.V.M.
Life Sciences Division

Date

ROUGH DRAFT

June 17, 1992

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Pathology Report
A 13-Week Subchronic Dietary Oral Toxicity Study
in Mice with Di(isononyl)phthalate Including Ancillary
Hepatocellular Proliferation and Biochemical Analyses
Project No. 2598-103

Main Study

Methods

This narrative summarizes pathology findings in B₆C₃F₁ mice from a 13-week subchronic study of Di(isononyl)phthalate when administered at dietary levels of 1,500, 4,000, 10,000 and 20,000 ppm (Groups 2, 3, 4, and 5, respectively). Group 1 served as the control group.

Following at least 90 days of treatment, the mice were necropsied and tissues were preserved in 10% neutral-buffered formalin. Hematoxylin-and-eosin-stained sections of protocol tissues were examined from mice of the control and high-dose groups. In addition, gross lesions, liver, kidneys, spleen, testes with epididymides (males), and uterus (females) were examined microscopically from mice of Groups 2, 3, and 4. The quantity and quality of tissues examined were adequate for a meaningful evaluation.

Results

Compound-related histomorphological alterations were observed in the liver, kidneys, epididymides, spleen, thymus, ovaries, and uterus of high-dose (Group 5) mice and in the liver of mid-high-dose (Group 4) mice.

Liver changes in the high-dose mice consisted of moderate to moderately severe diffuse hepatocellular enlargement, pigment in Kupffer cells and bile canaliculi, and degeneration/necrosis of individual cell (minimal or slight). Focal hepatocellular necrosis was noted in four

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ROUGH DRAFT

April 8, 1992

Pathology Report
A 13-Week Subchronic Dietary Oral Toxicity Study in Mice
with Di(isononyl)phthalate including ancillary hepatocellular
proliferation and biochemical analyses
Project No. 2598-103

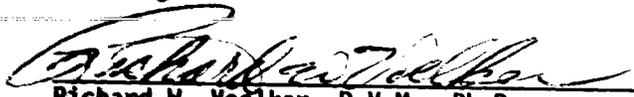
First Interim Sacrifice

Hematoxylin-and-eosin-stained sections of liver (three lobes) and duodenum were examined microscopically from mice of Groups 1, 4, and 6 sacrificed on Day 4 of study. The mice had received the control diet (Group 1), Di(isononyl)phthalate (DINP) at 10,000 ppm (Group 4, test article), or WY 14,463 at 1,000 ppm (Group 6, positive control).

Compound-related histomorphologic alteration noted in mice of both sexes in Groups 4 and 6 consisted of diffuse hepatocellular enlargement. The degree of hepatocellular enlargement was essentially comparable in mice which received the test article or positive control.

In conclusion, dietary administration of Di(isononyl)phthalate at 10,000 ppm or WY 14,463 at 1,000 ppm to B₆C₃F₁ mice for 3 days resulted in diffuse hepatocellular enlargement of comparable degree.

Pathologist:


Richard W. Voelker, D.V.M., Ph.D.,
Diplomate, American College of Veterinary
Pathologists
Life Sciences Division

4-8-92
Date

2598-103

RECEIVED

JUN 23 1992

HAZLETON - WASHINGTON

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