

CODING FORM FOR SRC INDEXING

REVISED 10/15/86

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| Submitting Organization CONFIDENTIAL | | |
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| Contractor | | |
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| Document Title A SUBCHRONIC DIETARY ORAL TOXICITY STUDY OF DI(ISONONYL) PHTHALATE (DRAFT) WITH COVER LETTER (SANITIZED) | | |
| | | |
| Chemical Category DI(ISONONYL) PHTHALATE | | |

17 pp.

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SEHQ-0191-1150 S JOURNAL
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OTS DOCUMENT RECEIPT 0191
91 JAN -8 PM 2:55
OTS DOCUMENT RECEIPT 0191
91 JAN -8 PM 2:55

CONFIDENTIAL INFORMATION HAS BEEN SANITIZED

January 2, 1991

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

Dear Sir or Madam:

RE: Draft Report on A Subchronic (4-week) Dietary Oral Toxicity
Study of Di(isononyl) phthalate in B6C3F1 Mice,

is submitting a copy of the subject report, which is in an unaudited rough draft form. Although we do not believe the information in the enclosed study indicates a substantial risk to human health or the environment, we are submitting this information in accordance with EPA guidance on 8(e).

In the enclosed study, "male (10) and female (10) B6C3F1 mice were exposed to Di(isononyl)phthalate (INP) [DINP, CAS No. 28553-12-0] in the diet for approximately four weeks at each of the following dose groups: Group 1 (Untreated diet), 0 ppm; Group 2 (low), 3000 ppm; Group 3 (mid-low), 6000 ppm; Group 4 (mid) 12,500 ppm; Group 5 (high) 25,000 ppm".

As noted in the report, "all animals were examined grossly, and each animal was weighed prior to necropsy. Sacrifice was by exsanguination under sodium pentobarbital anesthesia. The most recent clinical observations were reviewed at necropsy, and all grossly observed abnormalities were entered, as encountered, directly into the computerized data capture system. Liver, kidneys, and testes with epididymides were weighed at the time of necropsy". Samples of certain organs, as outlined in the report, were then preserved in 10% neutral buffered formalin.

The following is a summary of some of the results:

Mean absolute body weight values were significantly depressed in both males and females of Group 5 compared to Group 1 at the weighings that occurred during weeks 3, 4 and 5 of the study.

Significant, dose related decreases in absolute mean organ weight were seen in kidneys and testes of males of Groups 3,4, and 5. In this case the decreases in testicular weight were large enough to strongly suggest a direct effect of compound exposure in Groups 3, 4, and 5. Mean liver weights, both absolute and relative, were significantly increased in response to INP exposure in males of Groups 2, 3, 4, and 5 and females of Groups 3, 4, and 5, with histologic correlates.

Histologic findings are provided in detail in the report. Of particular note are the reproductive effects, which provide both indirect evidence of the test substance affecting spermatogenesis in the male and arrest of ovulation in the female. In Group 5 females, the ovaries were observed to be smaller than the other groups. Histologically, a virtual absence of corpora lutea was observed in the ovaries of Group 5, with an attendant effect in the size of the uteri and a virtual absence of glands in the endometrium.

The discussion of the report indicates the finding of testicular damage is not a surprise, as such damage has been reported in response to both straight chain and branched alkyl phthalates, while noting "this effect is not seen with all phthalate esters, however, and is dependent on certain structural characteristics shared by those exerting the effect".

We will notify all customers of these results and submit additional information to EPA as it becomes available.

As we have claimed our company identity as Confidential Business Information, we have provided both Confidential and Sanitized versions of this document, including the cover letter.

Sincerely,

Enclosure

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December 14, 1990

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Dear

Re: A Subchronic (4-Week) Dietary Oral Toxicity Study of Di(isononyl)phthalate
in B6C3F1 Mice, HWA Study No. 2598-100.

Enclosed find a draft pathology report and draft histopathology incidence summary
for the above mentioned study.

Please contact me if you require additional information.

Sincerely,

/rpi-f

Enclosures

ROUGH DRAFT

November 29, 1990

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Pathology Report
Subchronic (4-Week) dietary Oral Toxicity Study of
Di(isononyl)phthalate in B6C3F1 Mice
Project Number

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Male (10) and female (10) B6C3F1 mice were exposed to Di(isononyl)phthalate (INP) in the diet for approximately four weeks at each of the following dose groups: Group 1 (untreated diet), 0 ppm; Group 2 (low), 3000 ppm; Group 3 (mid-low), 6000 ppm; Group 4 (mid) 12,500 ppm; Group 5 (high) 25,000 ppm.

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Methods

All animals were examined grossly, and each animal was weighed prior to necropsy. Sacrifice was by exsanguination under sodium pentobarbital anesthesia. The most recent clinical observations were reviewed at necropsy, and all grossly observed abnormalities were entered, as encountered, directly into the computerized data capture system. Liver, kidneys, and testes with epididymides were weighed at the time of necropsy.

After gross examination, samples of the following organs were preserved in 10% neutral buffered formalin:

lesions
brain with brainstem
(medulla/pons, cerebellar
cortex, and cerebral cortex)
Aorta (thoracic region)
pituitary
thyroid (parathyroids)
thymus
lungs
trachea
heart

bone marrow (femur)
salivary glands (mandibular)
gall bladder
kidneys
adrenals
pancreas
testes with epididymides
ovaries
uterus
liver
spleen

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aorta
esophagus
stomach
duodenum, jejunum, ileum

colon, cecum, rectum
urinary bladder
mesenteric lymph node
sciatic nerve

Each lobe of the liver was incised several times to enhance penetration of the fixative, and each kidney was bisected-left longitudinally, right transversely. The lungs were inflated with formalin via the trachea, and contracted bladders were inflated with formalin. After fixation, bony tissues were decalcified prior to processing. Tissues to be examined histologically were embedded in paraffin, sectioned at approximately 5 microns, and stained with hematoxylin and eosin. Histopathological evaluations were performed on those tissues listed above from all animals of Groups 1 and 5. The liver, kidneys, spleen, and testes with epididymides, and gross lesions were also examined from all animals of the remaining groups. During the initial histologic examination of tissues, additional target organs were defined which included, thymus, ovaries, and uterus. As required by the protocol, these tissues were then examined histologically from all remaining animals in which they were present.

Gross and Related Findings

Gross findings are summarized in detail in the accompanying tables.

All animals survived until the scheduled terminal sacrifice during which there were few observed abnormalities. Of interest were descriptions of altered hepatic size (enlargement) and color which were applied mostly to males or females of Groups 3, 4, and 5. These findings appear to have been manifestations of histological alterations that will be described later in this report.

"Dark areas" were described a number of times in the mucosa of the glandular stomach, but without relation to exposure level.

All other gross abnormalities were of singular occurrence and unrelated to exposure level.

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Mean absolute body weight values were significantly depressed in both males and females of Group 5 compared to Group 1 at the weighings that occurred during weeks 3, 4, and 5 of the study. Group 5 animals of both sexes also lost body weight as a function of time on study. All other groups gained weight as the study progressed.

The possible role of food consumption in weight depressions is not clear, and, although there are definite groupwise differences, with a couple of exceptions they are unrelated to dose. In females, food consumption was clearly depressed in Group 5 for most of the study, which may help to explain why that group lost weight. Group 5 males, on the other hand, consumed more food than any but Group 3 starting at about 2 weeks and more than any other group from 3 weeks until the end of the study; and yet Group 5 males still lost weight as described, so that the role of caloric intake is not clear.

Overnight fasting prior to necropsy caused large decreases in mean body weights of all the groups which are reflected in both the terminal body weight figures and the relative organ weight values calculated on the basis of terminal (post fasting) absolute body weights.

Significant, dose related decreases in absolute mean organ weight were seen in kidneys and testes of males of Groups 3, 4, and 5. Expressed as organ to terminal body weight ratios, significantly decreased values are still present for kidneys of Groups 2 and 3 males; however, the kidneys of Group 5 show a significant increase in value. This is likely the result of the disproportionally large loss of body weight that occurred in this group and are not the result of any direct effect of the high dose on the kidneys.

The fact that kidney weights were decreased in a dose related pattern in three groups, two of which showed no evidence of body weight loss, suggest that those decreases occurred as a direct result of exposure to the test substance. Histologic findings tend to corroborate this observation.

Testicular weights are usually quite stable and do not respond quickly to losses of body condition. In this case the decreases in

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testicular weight were large enough to strongly suggest a direct effect of compound exposure in Groups 3, 4, and 5.

Mean liver weights, both absolute and relative, were significantly increased in response to INP exposure in males of Groups 2, 3, 4, and 5 and females of Groups 3, 4, and 5. Histologic correlates will be described.

Histologic Findings

Histologic findings are summarized in detail in the accompanying tables.

There were a number of observed histologic alterations which seem to be related to INP exposure.

Hepatocellular enlargement was present in the livers of males of Groups 3, 4, and 5 and females of Groups 2, 3, 4, and 5 with a clear dose response relative to incidence and severity. The change, which correlates nicely with organ weight data, was generally diffuse; but in some less developed cases it was more centrilobular in distribution. Affected hepatocytes were swollen with dense, hypereosinophilic cytoplasm. The normal, trabecular architecture was somewhat obscured by the swollen hepatocytes. In many cases, particularly in Group 5 males and also, though less commonly Groups 4 and 5 females, focal areas of coagulative necrosis, mostly devoid of inflammatory reaction, accompanied these cytoplasmic changes; and, in addition, separate chronic inflammatory foci were also seen in these groups. These latter changes, particularly the presence of hepatocellular necrosis, may explain an increase in serum levels of alanine aminotransferase that was also reported in the Group 5 males and females.

The kidneys of all Group 5 males and females showed compound-related changes characterized by areas of atrophic tubules, sometimes dilated, and often containing granular proteinaceous material which sometimes contained cellular debris. Degenerative cytoplasmic changes, and often regenerative foci were present; but tubular necrosis was not characteristic. Although these lesions did not as a whole appear

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morphologically to be very severe, morphologic appearance is not necessarily an accurate indicator of functional impairment. It is, therefore, possible that significantly elevated BUN values reported for Group 5 males did occur as a result of renal damage. BUN values were not significantly evaluated for females, and that may or may not be a reflection of histologic lesions that were of a less severe nature than in males.

A single Group 4 male had a small renal lesion compatible with those described, but one which could just as easily be attributed to early chronic progressive nephropathy, a spontaneous kidney disease of mice. The Group 4 level would appear to be a no observable effect level (NOEL) relative to described renal effects, but that is not conclusive without further study.

Some compound related effect on the lymphoreticular system is suggested by the finding, in several males and females of Group 5, of distinct hypocellularity in the interfollicular areas of the spleen with little or no evidence of extramedullary hematopoiesis. This finding was termed atrophy. Seen also, in most females of all groups but primarily in Groups 4 and 5 of the males was an increase in the necrosis of lymphocytes in the thymus. In the most mild cases this was seen as an increase in the number of debris-laden macrophages, but in the more severely affected animals there was a great deal of karyorrhectic debris besides that in phagocytes. There was no noticeable change in the bone marrow. Any conclusions drawn between these observations and their possible relationship to INP exposure would be tenuous; however, there were some rather vague but suggestive changes to hematologic parameters which support the suggestion that the hematopoietic system should be carefully watched in any further work with this compound. Below the Group 4 level there is no suggestion of effect; at the Group 4 level the suggestion of effect is very slight.

The testes are interesting in that while there were no histologic alterations to the testes themselves suggestive of a correlation with the dose related decrease in organ weight, and while spermatogenesis seemed

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not to have been affected as evidenced only by subjective histologic observations of the numbers of spermatozoa in testes and epididymides, there was a clear increase in the amount of cellular debris present in the tail of the epididymides of all Group 5 males. The testes are the presumed origin of this detritus which serves as indirect evidence that spermatogenesis was, somehow affected by the test substance, and that the viability of some spermatogenic cells was somehow compromised. The limitation of this finding to Group 5 correlates nicely with organ weight data which also showed a much larger effect on Group 5 males. Taken together, however, the data suggest that organ weights are, in this case, a more sensitive indicator of testicular effect than histopathology by itself.

Reproductive system effects were not limited to the male, however. The ovaries of all Group 5 females appeared smaller (they were not weighed); and, interestingly, the main distinguishing histologic feature was the virtually complete absence of corpora lutea. Normal follicles were plentiful, but the lack of luteinization would suggest an arrest of ovulation. This finding was termed "atrophy" for purposes of this report. The uteri of all Group 5 females were also affected by INP-exposure. They were smaller than normal in cross-sectional area; and the endometrium was virtually devoid of glands.

Discussion

The finding of hepatocytomegaly is not surprising, as phthalate esters have, for some time, been recognized to induce proliferation of specific cytoplasmic organelles called peroxisomes in liver cells resulting in the enlargement of those cells and the liver itself.¹

Similarly, testicular damage has been reported in rodents in response to certain phthalate esters.^{2,3,4} This effect is not seen with all phthalate esters, however, and is dependent on certain structural characteristics shared by those exerting the effect.^{3,4} In this study, testicular damage per se was not seen histologically; but an effect was clearly demonstrated by decreases in testicular weight and by the presence

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of increased amounts of cellular debris in the tail of the epididymides. While it is important to note that the epididymidal finding was present only in Group 5 animals that had been exposed to an extremely high level of INP, it should also be mentioned that mice have been shown to be less sensitive to the testicular effects of some phthalate toxicities than rats; consequently, rats exposed to equivalent levels of this compound might be expected to exhibit a more severe response.

The apparent anovulatory effect and uterine atrophy/hypoplasia observed in the female reproductive tract were surprises. Although only in animals exposed to the highest level of the test substance, these changes have not, to my knowledge, been reported in previous toxicity studies of this class of compounds and are potentially very important.

Renal tubular nephrosis was seen with certainty only at the highest dose level; however it will be important to study the kidneys under conditions of longer term exposure to lesser dose levels of this compound.

Effects on the lymphoreticular system were suggested as a result of exposure to INP; however the changes were not consistent enough to draw clear conclusions.

Pathologist:

12/6/90

Date

REFERENCES

1. Warren JR, Labwan ND, Reddy JK: Phthalate esters as peroxisome proliferator carcinogens. Environmental Health Perspectives 45:35-40, 1982.
2. Gangoli SD: Testicular effects of phthalate esters. Environmental Health Perspectives 45:77-84, 1982.

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REFERENCES - Continued

3. Foster PMD, Thomas LV, Cook MW, Gangoli SD: Study of the testicular effects and changes in zinc excretion produced by some n-alkyl phthalates in the rat. Toxicology and Applied Pharmacology: 54:392-398, 1980.
4. Curto KA, Thomas JA: Comparative effects of diethylhexyl phthalate or monoethylhexyl phthalate on male mouse and rat reproductive organs. Toxicology and Applied Pharmacology: 62:121-125, 1982.

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SUBCHRONIC (4 WEEK) DIETARY ORAL TOXICITY STUDY OF DI(ISONONYL) PHTHALATE IN B6C3F1 MICE
DRAFT EXPANDED HISTOPATHOLOGY INCIDENCE SUMMARY *DRAFT*

PRINTED: 28-NOV-84
PAGE: 1

STUDY NUMBER:

--- NUMBER OF ANIMALS AFFECTED ---

TABLE INCLUDES:

SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

SEX: -----MALE----- -----FEMALE-----

GROUP: -1- -2- -3- -4- -5- -1- -2- -3- -4- -5-

ORGAN/TISSUE EXAMINED

NUMBER: 10 10 10 10 10 10 10 10 10 10

** TOP OF LIST **

| ORGAN/TISSUE EXAMINED | NUMBER EXAMINED | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
|------------------------|------------------|----|----|----|----|----|----|----|----|----|
| BRAIN W/STEM | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| PITUITARY | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 9 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 9 | 0 | 0 | 10 |
| ADRENAL, CORTEX | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| ADRENAL, MEDULLA | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| THYROID | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| PARATHYROID | NUMBER EXAMINED: | 8 | 0 | 0 | 0 | 9 | 9 | 0 | 0 | 8 |
| | NOT REMARKABLE: | 8 | 0 | 0 | 0 | 9 | 9 | 0 | 0 | 8 |
| ESOPHAGUS | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| TRACHEA | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| LUNG | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| HEART | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 10 |

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PRINTED: 28-NOV-
PAGE: 2

SUBCHRONIC (4 WEEK) DIETARY DRAL TOXICITY STUDY OF DI(ISONONYL)
PHTHALATE IN B6C3F1 MICE

DRAFT EXPANDED HISTOPATHOLOGY INCIDENCE SUMMARY *DRAFT*

STUDY NUMBER:

--- NUMBER OF ANIMALS AFFECTED ---

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=ALL

SEX: -----MALE----- -----FEMALE-----

GROUP: -1- -2- -3- -4- -5- -1- -2- -3- -4- -5-

ORGAN/TISSUE EXAMINED

NUMBER: 10 10 10 10 10 10 10 10 10 10

SPLEEN NUMBER EXAMINED: 10 10 10 10 10 10 10 10 10 10
NOT REMARKABLE: 10 10 10 10 7 10 10 10 10 7

--ATROPHY
2> 0 0 0 0 3 0 0 0 0 2
3> 0 0 0 0 0 0 0 0 0 1
TL> 0 0 0 0 3 0 0 0 0 3
MN> 0.0 0.0 0.0 0.0 2.0 0.0 0.0 0.0 0.0 2.3

LIVER NUMBER EXAMINED: 10 10 10 10 10 10 10 10 10 10
NOT REMARKABLE: 10 6 0 0 0 9 10 3 1 0

--HEPATOCYTOMEGALY
1> 0 4 9 3 0 0 0 7 3 0
2> 0 0 1 7 4 0 0 0 5 8
3> 0 0 0 0 6 0 0 0 0 2
TL> 0 4 10 10 10 0 0 7 8 10
MN> 0.0 1.0 1.1 1.7 2.6 0.0 0.0 1.0 1.6 2.2

--NECROSIS, FOCAL
1> 0 0 0 0 2 0 0 0 0 0
2> 0 0 0 0 5 1 0 0 1 1
3> 0 0 0 0 1 0 0 0 3 0
TL> 0 0 0 0 8 1 0 0 4 1
MN> 0.0 0.0 0.0 0.0 1.9 2.0 0.0 0.0 2.8 2.0

--INFLAMMATION, CHRONIC, FOCAL
1> 0 0 0 0 1 0 0 0 0 0
2> 0 0 0 0 5 0 0 0 1 0
TL> 0 0 0 0 6 0 0 0 1 0
MN> 0.0 0.0 0.0 0.0 1.8 0.0 0.0 0.0 2.0 0.0

--BILE PIGMENT, FOCAL
1> 0 0 0 0 1 0 0 0 0 0
2> 0 0 0 0 1 0 0 0 0 0
TL> 0 0 0 0 2 0 0 0 0 0
MN> 0.0 0.0 0.0 0.0 1.5 0.0 0.0 0.0 0.0 0.0

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UNAUDITED

PRINTED: 28-NOV-5
PAGE: 3

SUBCHRONIC (4 WEEK) DIETARY ORAL TOXICITY STUDY OF DI(ISONONYL)
PHTHALATE IN B6C3F1 MICE

DRAFT EXPANDED HISTOPATHOLOGY INCIDENCE SUMMARY *DRAFT*

STUDY NUMBER:

--- NUMBER OF ANIMALS AFFECTED ---

| ORGAN/TISSUE EXAMINED | NUMBER: | SEX: -----MALE----- | | | | | -----FEMALE----- | | | | |
|-----------------------|------------------|--|-----|-----|-----|-----|------------------|-----|-----|-----|-----|
| | | GROUP: -1- -2- -3- -4- -5- -1- -2- -3- -4- -5- | | | | | | | | | |
| | | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GALLBLADDER | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| KIDNEY | NUMBER EXAMINED: | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | NOT REMARKABLE: | 10 | 10 | 9 | 9 | 0 | 10 | 10 | 10 | 10 | 0 |
| --TUBULAR NEPHROSIS | 2> | 0 | 0 | 0 | 1 | 6 | 0 | 0 | 0 | 0 | 9 |
| | 3> | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 1 |
| | TL> | 0 | 0 | 0 | 1 | 10 | 0 | 0 | 0 | 0 | 10 |
| | FN> | 0.0 | 0.0 | 0.0 | 2.0 | 2.4 | 0.0 | 0.0 | 0.0 | 0.0 | 2.1 |
| --CORTICAL ATROPHY | 3> | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | TL> | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | FN> | 0.0 | 0.0 | 3.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| STOMACH, NONGL | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| STOMACH, GL | NUMBER EXAMINED: | 10 | 1 | 0 | 0 | 10 | 10 | 4 | 1 | 1 | 10 |
| | NOT REMARKABLE: | 10 | 1 | 0 | 0 | 9 | 9 | 0 | 0 | 0 | 10 |
| --EROSION, MUCOSA | 2> | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 1 | 1 | 0 |
| | TL> | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 1 | 1 | 0 |
| | FN> | 0.0 | 0.0 | 0.0 | 0.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 0.0 |
| --ULCER | 2> | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| | TL> | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| | FN> | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 2.0 | 0.0 | 0.0 | 0.0 |
| DUODENUM | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| JEJUNUM | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |

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UNAUDITED

SUBCHRONIC (4 WEEK) DIETARY ORAL TOXICITY STUDY OF DI(ISONONYL) PHTHALATE IN B6C3F1 MICE
DRAFT EXPANDED HISTOPATHOLOGY INCIDENCE SUMMARY *DRAFT*

PRINTED: 28-NOV-
PAGE: 4

STUDY NUMBER:

--- NUMBER OF ANIMALS AFFECTED ---

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=ALL

SEX: -----MALE----- FEMALE-----

GROUP: -1- -2- -3- -4- -5- -1- -2- -3- -4- -5-

| ORGAN/TISSUE EXAMINED | NUMBER: | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | |
|-----------------------|------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| ILEUM | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 9 | 10 | 0 | 0 | 0 | 10 |
| | --VILLOUS ATROPHY | | | | | | | | | | |
| | 2> | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | TL> | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | MM> | 0.0 | 0.0 | 0.0 | 0.0 | 2.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| CECUM | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| COLON | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| RECTUM | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| PANCREAS | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 |
| LN, MESENTERIC | NUMBER EXAMINED: | 8 | 0 | 0 | 0 | 7 | 10 | 0 | 0 | 0 | 10 |
| | NOT REMARKABLE: | 8 | 0 | 0 | 0 | 7 | 10 | 0 | 0 | 0 | 10 |
| TESTIS | NUMBER EXAMINED: | 10 | 10 | 10 | 10 | 10 | 0 | 0 | 0 | 0 | 0 |
| | NOT REMARKABLE: | 10 | 10 | 10 | 10 | 10 | 0 | 0 | 0 | 0 | 0 |
| EPIDIDYMIS | NUMBER EXAMINED: | 10 | 10 | 10 | 10 | 10 | 0 | 0 | 0 | 0 | 0 |
| | NOT REMARKABLE: | 10 | 10 | 10 | 10 | 0 | 0 | 0 | 0 | 0 | 0 |
| | --CELLULAR DEBRIS, INCREASED | | | | | | | | | | |
| | 1> | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 0 |
| | 2> | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 |
| | 3> | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | TL> | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 0 | 0 | 0 |
| | MM> | 0.0 | 0.0 | 0.0 | 0.0 | 1.6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |

SANITIZED

UNCLASSIFIED

SUBCHRONIC (4 WEEK) DIETARY ORAL TOXICITY STUDY OF DI(ISONONYL) PHTHALATE IN B6C3F1 MICE
DRAFT EXPANDED HISTOPATHOLOGY INCIDENCE SUMMARY *DRAFT*

PRINTED: 28-NOV-
PAGE: 5

STUDY NUMBER:

--- NUMBER OF ANIMALS AFFECTED ---

TABLE INCLUDES:
SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=ALL

SEX: -----MALE----- -----FEMALE-----

GROUP: -1- -2- -3- -4- -5- -1- -2- -3- -4- -5-

NUMBER: 10 10 10 10 10 10 10 10 10 10

ORGAN/TISSUE EXAMINED

URINARY BLADDER NUMBER EXAMINED: 10 0 0 0 10 10 0 0 0 10
NOT REMARKABLE: 10 0 0 0 10 10 0 0 0 10

UTERUS NUMBER EXAMINED: 0 0 0 0 0 10 10 10 10 10
NOT REMARKABLE: 0 0 0 0 0 10 10 10 10 0

--ATROPHY
3> 0 0 0 0 0 0 0 0 0 10
TL> 0 0 0 0 0 0 0 0 0 10
MN> 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 3.0

UTERUS NUMBER EXAMINED: 0 0 0 0 0 10 10 10 10 10
NOT REMARKABLE: 0 0 0 0 0 10 10 10 10 0

--ATROPHY
3> 0 0 0 0 0 0 0 0 0 8
4> 0 0 0 0 0 0 0 0 0 2
TL> 0 0 0 0 0 0 0 0 0 10
MN> 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 3.2

SPLEEN AND SALIVARY GL NUMBER EXAMINED: 10 0 0 0 10 10 0 0 0 10
NOT REMARKABLE: 10 0 0 0 10 10 0 0 0 10

THYMUS NUMBER EXAMINED: 9 10 10 10 8 10 10 10 10 7
NOT REMARKABLE: 8 10 10 6 1 0 3 0 5 0

--LYMPHOID NECROSIS
1> 1 0 0 4 0 1 0 1 2 0
2> 0 0 0 0 1 6 5 7 0 4
3> 0 0 0 0 2 3 2 2 2 1
4> 0 0 0 0 2 0 0 0 1 1
TL> 1 0 0 4 5 10 7 10 5 6
MN> 1.0 0.0 0.0 1.0 3.2 2.2 2.3 2.1 2.4 2.5

--LYMPHOID DEPLETION
2> 0 0 0 0 3 0 0 0 0 4
TL> 0 0 0 0 3 0 0 0 0 4
MN> 0.0 0.0 0.0 0.0 2.0 0.0 0.0 0.0 0.0 2.0

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SUBCHRONIC (4 WEEK) DIETARY ORAL TOXICITY STUDY OF DI(ISONONYL) PHTHALATE IN B6C3F1 MICE

PRINTED: 28-NOV- PAGE: 6

DRAFT EXPANDED HISTOPATHOLOGY INCIDENCE SUMMARY *DRAFT*

STUDY NUMBER:

--- NUMBER OF ANIMALS AFFECTED ---

TABLE INCLUDES:

SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=ALL

| ORGAN/TISSUE EXAMINED | SEX: | MALE | | | | | FEMALE | | | | | |
|-----------------------|------------------|--------|-----|-----|-----|-----|--------|-----|-----|-----|-----|-----|
| | | GROUP: | -1- | -2- | -3- | -4- | -5- | -1- | -2- | -3- | -4- | -5- |
| | NUMBER: | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| AORTA, THORACIC | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 9 | 0 | 0 | 0 | 10 | |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 9 | 0 | 0 | 0 | 10 | |
| NERVE, SCIATIC | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 | |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 | |
| MARROW, FEMUR | NUMBER EXAMINED: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 | |
| | NOT REMARKABLE: | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 10 | |
| MARROW, STERNUM | NUMBER EXAMINED: | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | NOT REMARKABLE: | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| EYE | NUMBER EXAMINED: | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | |
| | NOT REMARKABLE: | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | |

** END OF LIST **