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

JUN 12 1989

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Registration and Tolerances for Sethoxydim (Poast®) for Use on Peas and Beans; Review of a 1-Year Chronic Dog Study; Redefining of the Defined Doses in a 6-Month Dog Study.

EPA No. 8F-3640, 8H-5557, 7969-58 Project No. 8-0993
Record No. 221871, 221870, 227708 Tox. Chem. No. 72A
40 CFR § 180.412

TO: Robert J. Taylor, PM #25
Registration Division (H7505C)
and
Jay S. Ellenberger, Acting Chief
Generic Chemical Support Branch
Registration Division (H7505C)

FROM: John E. Whalan, DABT, Toxicologist
Section I, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

John E. Whalan 5-11-89

THRU: Edwin R. Budd, Section Head
Section I, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

Budd 5/19/89

This memorandum discusses two points, the issuance of tolerances for peas and beans, and the redefining of the RfD.

Registration Action:

The Registrant, BASF Corporation, has requested the issuance of tolerances for the herbicide Poast® (2-[1-(ethoxyimino)butyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one) and its metabolites to control grassy weeds in peas and beans at the following residue levels:

| | |
|---|---|
| Peas (dry and succulent) | 40 ppm |
| Beans (dry and succulent) | 15 ppm |
| Pea forage and hay | 40 ppm |
| Bean forage and hay | 40 ppm |

Poast Herbicide will be applied as a single 0.5-2.0 pints/acre (0.3-0.5 lbs a.i./A) postemergence application to crops and annual grassy weeds. Perennial grasses will be treated with a maximum of 2.5 pints/acre with a repeat application at a rate of 1.5 pints/acre. A maximum of 4 pints/acre/season may be applied. All applications will be by ground equipment, and will include 2 pints of oil concentrate/acre. There will be preharvest intervals (PHI) of

15 days for succulent peas and beans, and 30 days for dry peas and beans. The inert ingredients have been cleared for use. There are no pending regulatory actions against the registration of this pesticide product, and it is not being presumed against by the Special Review Branch. The existing toxicity data base is sufficient to support this registration. The Toxicology Branch has no objection to granting these tolerances, RCB considerations permitting. The dietary impact of the proposed tolerances will be addressed by the Dietary Exposure Branch. The supplemental label is acceptable provided it includes the "Danger" signal word. An Eight-Point Summary is attached.

Redefining of the RfD:

On June 5, 1987, Jack Graham (representing BASF) met with Bob Taylor (Registration Division) and John Whalan (Toxicology Branch) to discuss the way an RfD (reference dose, formerly called the ADI) was calculated for sethoxydim. At the time of this meeting, sethoxydim was already at 94% of the RfD, so there was little prospect of receiving any more crop tolerances.

John Whalan explained that two 6-Month Dog studies were considered in defining the RfD, one from Hazleton Laboratories (Report No. C14; March 25, 1986) and the other from IRDC (Report No. 449-004; March 9, 1981). Archived reports of both studies were reviewed anew in order to establish their credibility. The study performed at Hazleton (the one with the lower NOEL) was of such poor quality, that it was considered totally unreliable. It did, however, suggest the potential for serious kidney toxicity as manifest by findings of cystitis and/or urinary calculi, bloody urine, and decreased PSP clearance (phenosulfonphthalein excretion, an indicator of renal toxicity).

The other 6-Month Dog study was performed at IRDC (Report No. 449-004; March 9, 1981) and was of good quality. The defined doses from the IRDC study were based on PSP changes at 600 ppm (LEL). Anomalous PSP values were the only suggestion of renal toxicity. Because of the Hazleton study, the PSP changes could not be dismissed, although they were not supported by any other clinical or pathologic findings. The NOEL (60 ppm) was used to calculate the RfD. The RfD was supported by the Branch and Agency RFD Committees, and was admittedly conservative.

Jack Graham then produced a 1-Year Dog study (Report No. 88/5026; March 14, 1984) performed at IRDC. He was not prepared to leave it with us, but said he would soon submit it. The report's summary suggested that the NOEL would be higher than in the previous IRDC study, and there was no evidence of kidney toxicity. John Whalan skimmmed the report summary and expressed interest in reports of hemosiderosis. Presumably in response to this observation, a blind evaluation of the hematology data, and evaluations of spleen and bone marrow sections were conducted at Xenos.

More than a year later, the 1-Year Dog study report was submitted to the Agency (the study review is attached). Anemia was found at 600 and 3600 ppm in males, and mild hepatotoxicity was evident in both sexes at 3600 ppm. There was no evidence of renal toxicity or carcinogenicity, and the findings of hemosiderosis were of doubtful significance. The study was classified Core Guideline.

It is reasonable to believe that the major indicators of renal toxicity in the Hazleton study were iatrogenically induced during PSP sampling with catheters. PSP anomalies seen in the 6-Month IRDC Dog study were probably artifactual since there were no other indicators of renal toxicity, and the One-Year Dog study had no evidence of renal toxicity. The liver and bone marrow, rather than the kidney, appears to be the major target organ in dogs. Thus, the defined doses have been redefined for the 6-month IRDC study as follows (a copy of the One-Liners is attached):

NOEL = 600 ppm (20.0 mg/kg/day, M/F)
LEL = 6000 ppm (177/223 mg/kg/day, M/F) - Nonspecific anemia, liver effects.

The HED RfD Workgroup agreed with using the 1-Year Dog to redefine the RfD. In the course of reevaluating the available studies, however, the following two studies were compared:

1. Subacute Feeding Study of NP-55 in Rats. MRID No. 00045859
   Nisso Institute for Life Sciences; Report No. C13; October 18, 1978.
   Doses tested: 0, 33, 100, 300, 900, and 2700 ppm
   NOEL = 300 ppm; LEL = 900 ppm (liver pathology)

2. 104 Week Chronic Dietary Study of NP-55 in Rats. MRID No. 00100526
   Hazleton Laboratories, America, Inc. Report No. C25; December 1981
   Doses tested: 0, 40, 120, and 360 ppm]
   NOEL $\geq$360 ppm (HDT)

It became apparent that the chronic study was performed at a dose that was essentially nontoxic, and may not have been sufficient to elicit oncogenic response. Unless the Registrant can justify the doses used, the Toxicology Branch is requesting that the Chronic Rat study be repeated at doses that attain an MTD level.

cc HED RfD Workgroup

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SUMMARY OF TOXICITY DATA
and
EIGHT POINT FREE-STANDING SUMMARY

1. Summary of selected toxicology data considered for these actions:

| STUDY | RESULTS | TOXICITY CATEGORY | CLASSIFICATION |
|---|---|---|---|
| Data on Technical NP-55 (sethoxydim): | | | |
| Acute Oral $LD_{50}$, Rat | 3125 mg/kg (males)<br>2676 mg/kg (females) | III | Guideline |
| Acute Dermal $LD_{50}$, Rat | >5000 mg/kg (males and females) | III | Guideline |
| Acute Inhalation $LC_{50}$, Rat (4 hours) | 6.03 mg/l (males)<br>6.28 mg/l (females) | III | Guideline |
| Primary Eye irritation, Rabbit | No irritation | IV | Guideline |
| Primary Dermal Irritation Rabbit | No irritation | IV | Guideline |
| Dermal Sensitization, Guinea Pig | Negative | | Minimum |
| 1-Year Feeding, Dog | NOEL = 8.86/9.41 mg/kg/day (M/F; 300 ppm)<br>LEL = 17.5/19.9 mg/kg/day (M/F; 600 ppm - Equivocal anemia in males. Not oncogenic at $\leq$110/129 mg/kg/day (M/F; 3600 ppm) | | Guideline |
| 2-Year Chronic Feeding/ Oncogenicity, Mouse | NOEL = 18 mg/kg/day (120 ppm)<br>LEL = 54 mg/kg/day (360 ppm - non-neoplastic liver lesions). Not oncogenic in $BDF_1$ mice at $\leq$162 mg/kg/day | | Guideline [Chronic feeding]<br>Guideline [Oncogenicity] |

| STUDY | RESULTS | TOXICITY CATEGORY | CLASSIFICATION |
|---|---|---|---|
| 2-Year Chronic Feeding/ Oncogenicity, Rat | NOEL 18 mg/kg/day (>360 ppm - HDT)<br>Not oncogenic at ≤18 mg/kg/day | | Guideline [Chronic feeding]<br>Guideline [Oncogenicity] |
| Teratology, Rat | Maternal NOEL = 40 mg/kg/day<br>Maternal LEL = 100 mg/kg/day (significantly decreased adrenal weight)<br>Teratogenicity NOEL >250 mg/kg/day (HDT) | | Guideline |
| Teratology, Rabbit | Maternal NOEL = 160 mg/kg/day.<br>Maternal LEL = 480 mg/kg/day (HDT, severe weight loss, 5/16 deaths, 6/16 abortions, and reduction in the number of litters and viable fetuses)<br>Teratogenic NOEL = 160 mg/kg/day.<br>Teratogenic LEL = 480 mg/kg/day (HDT, increased number of a variety of random effects including skeletal and visceral abnormalities, reduced fetal weight, and changes in male/female ratios, considered due to extreme toxicity in dams) | | Minimum |
| Two-Generation Reproduction, Rat | Reproductive NOEL = 54 mg/kg/day (1080 ppm)<br>Systemic NOEL = 18 mg/kg/day (360 ppm) [LEL was not defined] | | Guideline |
| Mutagenicity Studies: | | | |
| 1. Gene Mutation Test: | | | |
| Mouse Host-Mediated Assay, S. typhimurium | Negative at up to 2500 mg/kg bw/day of chemical. | | Minimum |
| 2. Structural Chromosome Aberration Test: | No data available | | |

| STUDY | RESULTS | TOXICITY CATEGORY | CLASSIFICATION |
|---|---|---|---|
| Tests for Other Genotoxic Effects: | | | |
| Rec-Assays and Forward Mutations, B. subtilis, E. coli, S. typhimurium | Negative at concentrations of chemical to 100% | | Minimum |
| Metabolism, Rat | Tissue accumulation of chemical negligible and excretion extremely rapid, assuming DMSO vehicle does not affect storage or excretion of the chemical. | | Guideline |
| Data on Hydroxymetabolite 5-OH-MSO2 (MU-1): | | | |
| 90-Day Feeding, Rat | NOEL >1080 ppm (70.2 mg/kg/day for males; 74.0 mg/kg/day for females) [HDT]. | | Minimum |
| Teratology, Rat | Teratogenic NOEL >250 mg/kg/day [HDT]<br>Fetotoxic NOEL >250 mg/kg/day.<br>Maternal NOEL >250 mg/kg/day. | | Minimum |
| Mutagenicity Studies: | | | |
| 1. Gene Mutation Test: | | | |
| CHO-HGPRT Forward Mutation Assay in Chinese Hamster Ovary Cells | Not mutagenic with or without S-9 activation at doses of 2.0-10.0 mg/ml. | | Acceptable |
| 2. Structural Chromosome Aberration Test: | | | |
| Chinese Hamster Bone Marrow Cytogenetic Assay | Not mutagenic at oral doses as high as 10,000 mg/kg. | | Acceptable |

| STUDY | RESULTS | TOXICITY CATEGORY | CLASSIFICATION |
|---|---|---|---|
| 3. Tests for Other Genotoxic Effects: | No data available | | |
| Data on Hydroxymetabolite MeMSO (Nor-MSO): | | | |
| Acute Oral $LD_{50}$, Rat | >5000 mg/kg in males. | IV | Minimum |
| Mutagenicity Studies: | | | |
| 1. Gene Mutation Test: | | | |
| Ames Assay | Negative in nonactivated and activated systems. | | Acceptable |
| 2. Structural Chromosome Aberration Test: | No data available | | |
| 3. Tests for Other Genotoxic Effects: | No data available | | |
| Metabolism, Rat | Radiolabelled MeMSO represented 2.1% of the radioactivity in urine at an unspecified time. | | Minimum |

2. Summary of Data Considered Desirable but Lacking for This Action:

A protocol to evaluate unscheduled DNA synthesis in rat liver primary cell cultures was reviewed by the Toxicology Branch (ref. M. Sochard memorandum, 7-9-84); the final report has not yet been received.

3. Action Being taken to Obtain the Lacking Information or Other Additionally Needed Information:

John Whalan (TB) asked Vickie Walters (RD) the status of the mutagenicity study. The registrant believes that the study was performed, and will ask the performing laboratory in Germany to expedite completion of the final report.

4. A Summary of Other Permanent Tolerances Granted for This Herbicide:

This information will be supplied by the Dietary Exposure Branch.

5. The dietary impact of the proposed tolerances will be addressed by the Dietary Exposure Branch.

6. The 1-Year Dog Feeding study with a NOEL of 300 ppm (8.86/9.41 mg/kg/day, M/F) was used to set the RfD. The safety factor employed was 100. The RfD is 0.09 mg/kg/day.

7. There are at this writing no pending regulatory actions against the registration of this pesticide.

8. Other Relevant Considerations in Setting These Tolerances:

None

Tox Chem No. 72A | File Last Updated 7-26-86 | Current Date 5-2-89

| Study/Lab/Study #/Date | Material | EPA Accession No. | Results: $LD_{50}$, $LC_{50}$, PIS, NOEL, LEL | TOX Category | CORE Grade/ Doc. No. |
|---|---|---|---|---|---|
| 1-Year Feeding-Dog; International Research and Development Corp.; BASF #88/5026, IRDC #449-010; 3-14-84 and 4-29-88 (attachment) and Xenos; BASF #85/5028, Xenos #XNS12D.2; 4-26-88 | Technical NP-55 (96.86% pure) | 152669 406290-01 | NOEL = 300 ppm (8.86/9.41 mg/kg/d M/F)<br>LEL = 600 ppm (17.5/19.9 mg/kg/d, M/F) - Equivocal anemia in males.<br>At 3600 ppm (110/129 mg/kg/d, M/F), toxicity included decreased female body weights (12%), anemia in males, increased alkaline phosphatase and ALT levels, slightly decreased cholesterol and albumin levels, increased liver weights, and decreased myeloid erythropoiesis in the sternal bone marrow.<br>There was no evidence of carcinogenicity at the doses tested.<br>Levels tested:<br>0 ppm (vehicle control)<br>300 ppm - 8.86/9.41 mg/kg/d<br>600 ppm - 17.5/19.9 mg/kg/d<br>3600 ppm - 110/129 mg/kg/d<br>in beagles. | | Guideline |

Tox Chem No. 72A | File Last Updated 7-23-86 | Current Date 11-18-88

| Study/Lab/Study #/Date | Material | EPA Accession No. | Results: $LD_{50}$, $LC_{50}$, PIS, NOEL, LEL | TOX Category | CORE Grade/ Doc. No. |
|---|---|---|---|---|---|
| CURRENT VERSION: | | | | | |
| 6-Month feeding - dog; International Research and Development Corp.; #449-004; 3-9-81 pp 1-222 and Appendix I-III | Technical NP-55 (96.1% purity) | | NOEL = 60 ppm (males and females), 2.0 mg/kg/day actual measurement<br>LEL = 600 ppm (males and females), 20.0 mg/kg/day actual measurement (PSP clearance decreases indicating decreased kidney output)<br>Levels tested: 0, 60, 600, and 6000 ppm in beagles. | | Guideline 002000<br>Guideline 005324 |
| REVISED VERSION: | | | | | |
| 6-Month feeding - dog; International Research and Development Corp.; #449-004; 3-9-81 pp 1-222 and Appendix I-III | Technical NP-55 (97.6% purity) | 099996 | NOEL = 600 ppm (20 mg/kg/d, meas.)<br>LEL = 6000 ppm (177/223 mg/kg/d, meas.) - liver effects and nonspecific anemia.<br>Levels tested: 0, 60, 600, and 6000 ppm in beagles. | | Guideline 002000<br>Guideline 005324<br>Guideline Doc. No. ? |

Reviewed by: John E. Wha JW 5-2-89
Section I, Tox. Branch I (IRS) (TS-769C)
Secondary reviewer: Edwin R. Budd
Section I, Tox. Branch I (IRS) (TS-769C) Budd 5/3/89



DATA EVALUATION REPORT

STUDY TYPE: Chronic Toxicity Study in Dogs

ACCESSION NUMBER: 1. 152669
2. 259488

TOX. CHEM. NO.: 72A

TEST MATERIAL: NP-55 (Sethoxydim)
Lot No. KK-1240 (96.86% Pure)
Yellow viscous liquid

MRID NO.: 406290-01

SYNONYMS: Poast

STUDY NUMBER(S): 1. BASF 88/5026; IRDC 449-010
2. BASF 85/5028; Xenos XNS12D.2

SUBMITTED BY: BASF Corporation Chemicals Division

TESTING FACILITY: 1. International Research and Development Corporation (Michigan)
2. Xenos (New Jersey)

TITLE OF REPORT: 1. One Year Dietary Toxicity Study in Dogs
2. A Blinded Histopathologic Review of Spleen and Bone Marrow

AUTHOR(S): 1. Eric J.F. Spicer (IRDC)
2. Conrad D. King (Xenos)

REPORT ISSUED: 1. March 14, 1984, and attachment dated April 29, 1988 (IRDC)
2. April 26, 1988 (Xenos)

CONCLUSIONS: There was little toxicity observed at the doses tested (0, 300, 600, and 3600 ppm) other than mild anemia and hepatotoxicity, and no evidence of carcinogenicity. The defined doses were as follows:

NOEL = 300 ppm (8.86/9.41 mg/kg/day, M/F)
LEL = 600 ppm (17.5/19.9 mg/kg/day, M/F) - Equivocal anemia in males.

STUDY CLASSIFICATION: This study is classified CORE GUIDELINE. It received Quality Assurance Review.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: Groups of 6 male (5.5-9.1 kg) and 6 female (4.0-7.4 kg) beagle dogs (3-4 months old; from Ridglan Farms, WI) were orally dosed with NP-55 in their feed at concentrations of 0 (vehicle control), 300, 600, and 3600 ppm. Test diets were prepared weekly. ACS grade acetone was used to dissolve the test article during feed formulations, and was added to the vehicle control feed in the same concentration. Dose concentration analyses were performed at weeks 1, 2, 3, 4, 8, 13, 26, 39, and 52. Test article homogeneity analyses were performed for each of the three concentrations, and stability analyses were conducted for material stored at room temperature for 10 days.

The dogs were individually housed in metabolism cages, with food and water available ad libitum except prior to the collection of blood. They were observed twice daily for clinical signs, and weekly for body weights and food consumption. Water consumption was measured during weeks 12, 25, 39, and 51. Ophthalmologic examinations were conducted pretest, and at 6 and 12 months using a binocular indirect ophthalmoscope, and a direct or slit lamp as needed. Each dog received a physical examination pretest and at 3, 6, and 12 months by a staff veterinarian.

Jugular blood from fasted dogs was collected at study initiation, and at 1, 2, 3, 4, 5, 6, and 12 months. Urine was collected at each of these intervals during the last 16 hours of the 24 hour fasts. The following clinical pathology parameters were measured:

Hematology

- Erythrocytes
- Hemoglobin
- Hematocrit
- Reticulocytes
- Mean corpuscular volume
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Erythrocyte morphology
- Leukocytes, absolute
- Leukocytes, differential
- Platelets

Clinical Chemistry

- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Lactic dehydrogenase
- Bromsulfophthalein (BSP)
- Total protein
- Albumin
- Serum globulin
- Blood urea nitrogen
- Phenosulfonphthalein
- Bilirubin, total
- Glucose
- Cholesterol
- Creatinine
- Calcium
- Chloride
- Sodium
- Potassium
- Phosphorus

Urinalysis

- Appearance
- Color
- Volume
- pH
- Urobilinogen
- Specific gravity
- Glucose
- Protein
- Bilirubin
- Ketone bodies
- Occult blood
- Sediments
- Nitrites

The phenosulfonphthalein excretion test (PSP) was performed to clarify positive findings (without other supporting indicators of renal toxicity) in a previous IRDC 6-month dog study with NP-55.

At the end of the study all survivors were sacrificed with sodium pentobarbital and necropsied. The following tissues were preserved and evaluated histopathologically (those marked with an asterisk were also weighed at necropsy):

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* Adrenals
Pancreas
* Pituitary
Thymus
* Thyroid and parathyroids
Bone (sternum, vertebrae)
Bone marrow (sternum)
* Brain (fore, mid, hind)
Eyes
Spinal cord (cervical, lumbar)
Nerve (sciatic)
* Heart
* Spleen
Salivary gland
Esophagus
Stomach
Duodenum
Jejunum
Ileum
Colon
* Kidneys
* Liver
Lungs (w/ bronchi)
Trachea
Lymph nodes (mediastinal, mesenteric, regional)
Skin
Mammary gland
Skeletal muscle (thigh)
Urinary bladder
* Testes (w/ epididymides)
Prostate
* Ovaries (with fallopian tubes)
Uterus
Cervix
Gross lesions
Masses with regional tissue

RESULTS: Analyses of formulated feed prior to using acetone showed a lack of homogeneity. When acetone was added, the dose formulations were homogeneous. Stability analyses were performed during week 1. After 10 days, the high-dose formulation showed little evidence of degradation, but the low and mid-dose formulations had both degraded to approximately 30% of nominal. Another stability study during study week 4 showed little or no degradation over 10 days. The reason for the peculiar results in the first analyses is uncertain. Dose concentration analyses showed that test article formulations at each interval were generally within 11% of nominal for the low and mid-dose groups, and within 5% of nominal for the high-dose group. The low-dose group was 23% less than nominal at 26 months, however. Since this was the only anomalous value, there was probably no effect on the study's validity.

No dogs died during this study, but several received veterinary care due to injuries or ailments not related to the test article. Most of the low, mid, and high-dose males and some of the high-dose females had relaxed nictitating membranes. There were no other compound-related clinical signs. The high-dose males had a slight increase in body weight gain compared to the controls, while the high-dose females had a significant (12%) decrease during the final quarter. Food consumption over the course of the study was increased 10% in the high-dose males, and 8% in the high-dose females, with a corresponding decrease in food efficiency. There were no changes in water consumption. Physical examinations did not reveal any toxic effects, and no compound-related eye lesions were found. The calculated doses based on food consumption were as follows:

| Dose (ppm) | Mean Dose (mg/kg/day) | |
|---|---|---|
| | Male | Female |
| 0 | -- | -- |
| 300 | 8.86 | 9.41 |
| 600 | 17.5 | 19.9 |
| 3600 | 110 | 129 |

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Although most of the RBC, HCT, and Hb values were within normal IRDC limits (ref. Xenos report), statistically significant anemia was observed in the males at the mid-dose (10-16% depression in erythroid parameters compared to controls) and high-dose (10-19% depression in erythroid parameters compared to controls) throughout the study (months 1-12). Reticulocytes were not released in response to anemia, and MCV, MCH, and MCHC values were only slightly increased in the high-dose males. The high-dose is interpreted as having mild anemia, and the mid-dose as equivocal for anemia. A slight thrombocytosis (approximately 50% increase in males, 35% increase in females) was seen during much of the study, but was not biologically significant. Mild neutrophilia was occasionally found in the high-dose males and females, but its significance is doubtful since it was not always dose-related.

Dose-related clinical chemistry anomalies found in the high-dose males included increases in alkaline phosphatase (0.7-4.0 fold compared to controls) during months 2-12, and ALT (2-fold compared to controls) at month 4. Albumin levels were slightly decreased (10-13% compared to controls) throughout the study, and total cholesterol levels were decreased (26-40% compared to controls) during months 1-5.

Dose-related clinical chemistry anomalies found in the high-dose females included increases in alkaline phosphatase (0.6-4.0 fold compared to controls) and ALT (62-71% compared to controls) during months 4-12. Albumin levels were slightly decreased (9-13% compared to controls) during months 2-12, and total cholesterol levels were decreased (20-32% compared to controls) during months 1-5.

The clinical chemistry data demonstrate a mild hepatotoxicity with slight impairment of albumin and cholesterol production in males and females. The phenosulfonphthalein (PSP) data for both sexes were too variable for meaningful evaluation, but there did not appear to be any dose-related effects. The urinalysis data were within normal limits, although sporadic urine pH decreases were seen in the high-dose males and females at half of the sampling intervals.

The only dose-related gross lesions were mild prominent medullary rays in the kidneys of 3 of 6 high-dose females, and mild clear pituitary cysts in 2 of 6 high-dose females. Neither of these gross lesions could be histopathologically substantiated as compound-related.

Dose-related histopathologic lesions were found in the liver, spleen, and bone marrow. A mild hepatocellular cytoplasmic alteration (ground glass appearance of cytoplasm with some swelling) was found in the low (1/6), mid (3/6), and high (6/6) dose males; and in the mid (1/6) and high-dose females (6/6). This was probably a normal detoxification response, and does not indicate liver damage. There was a slight increase in splenic hemosiderosis (seen in iron-stained sections only) in the high-dose males and females, but in the absence of marked anemia, the significance and the cause of this finding is uncertain. The IRDC pathologist did not find any bone marrow anomalies, but the Xenos evaluation revealed a slight decrease in myeloid erythropoiesis in the sternal bone marrow of the high-dose males.

No compound-related neoplastic lesions were found in either sex. One female in the high-dose group (#3216) had a mass on the skin of the ear which was found to be a histiocytoma (a benign tumor containing macrophages).

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The following table summarizes the organ weight anomalies (presented as percent of control values; values in parentheses are for reference only):

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | 300 ppm | 600 ppm | 3600 ppm | 300 ppm | 600 ppm | 3600 ppm |
| Liver | (+17%) | (+18%) | +39% | (0%) | (-7%) | +34% |
| Liver/BW | (+2%) | (+17%) | +36% | (+16%) | (+9%) | +49% |
| Thyroid/parath. | (+7%) | (+3%) | +36% | | | |
| Thyroid/parath./BW | (+1%) | (+1%) | +33% | | | |
| Pituitary | | | | (+3%) | (0%) | +16% |
| Pituitary/BW | | | | (+17%) | (+13%) | +36% |
| Kidney | | | | (-1%) | (+2%) | +22% |
| Kidney/BW | | | | (+15%) | (+16%) | +32% |

Of these anomalies, only the liver weights were substantiated with supporting data (elevated liver enzyme levels in the high-dose males and females).

These data suggest that there was a mild toxic effect on the liver of high-dose males and females. Alkaline phosphatase, and ALT levels were mildly increased, cholesterol and albumin levels were slightly decreased, and absolute and relative liver weights were increased. BSP clearance showed no effect on liver excretion. The urinalysis data were within normal limits. The PSP data for both sexes were too variable for reliable interpretation, but there did not seem to be a compound-related effect. Considering the lack of other indicators of renal toxicity, it appears that there were no toxic effects on the kidneys. The liver and bone marrow, rather than the kidneys, were the target organs. The defined doses are as follows:

NOEL = 300 ppm (8.86/9.41 mg/kg/day, M/F)
LEL = 600 ppm (17.5/19.9 mg/kg/day, M/F) - Equivocal anemia in males.

Toxicity observed at 3600 ppm (110/129 mg/kg/day, M/F) included decreased female body weights (12%), anemia, increased alkaline phosphatase and ALT levels, slightly decreased cholesterol and albumin levels, increased liver weights, and decreased myeloid erythropoiesis in the sternal bone marrow.

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Sethoxydim toxicology review

Page _____ is not included in this copy.

Pages 16 through 38 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.