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

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MAR 24 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg.#524-EUP-LA; MON 097; PP#1G2454; Petition of temporary tolerances on Corn and Soybeans. CASWELL #3B; Accession#099807-11

FROM: William Dykstra, Toxicologist
Toxicology Branch, HED (TS-769)

WHD for LDC 3/25/81

TO: Robert Taylor (25)
Registration Division (TS-767)
and
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

WHD for WLB C.J. Chaisson

Recommendations:

1) The temporary tolerances are not toxicologically supported. A NOEL was not demonstrated in the 119 day dog feeding study at the low-dose of 25 mg/kg/day. This study needs to be repeated at lower dosages which can demonstrate a NOEL in order for a provisional ADI to be calculated.

2) The submitted toxicology studies are acceptable as Core-Minimum Data.

EUP Program:

Monsanto requests 24,300 pounds active ingredient of MON-097 formulated as an 8 lb a.i./gal EC for use in this two year experimental program. This amount of material will treat 12,150 acres in 41 States. This amount of material is required to complete the program. The following table summarizes the request.

Crop	No. States	Two-Year Request Pounds A.I.	Acres
corn	39	11,900	5,950
soybeans	30	12,400	6,200
		24,300	12,150

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Composition of Formulated Product to be marketed:

Ingredient	Percent
2-chloro-N-ethoxymethyl-N-(2-ethyl-6-methylphenyl)acetamide	86.4
[redacted]	
	100.000

Inerts cleared under 180.1001. INERT INGREDIENT INFORMATION IS NOT INCLUDED

Section F: Proposed Temporary Tolerances

Request is made to establish temporary tolerances for acetochlor in or on the raw agricultural commodities as follows:

corn (all) grain ---------- 0.1 ppm
soybean grain ---------- 0.4 ppm

Residue tolerances on corn are established for the following herbicide:

Atrazine 40 CFR 180.220

corn fodder and forage ---------- 15.0 ppm
(field corn, sweet corn, popcorn)

corn, fresh ---------- 0.25 ppm
(sweet corn, kernals plus cob)

corn grain ---------- 0.25 ppm

Residue tolerances on soybeans are established for the following herbicides:

Linuron 40 CFR 180.184

soybeans (dry or succulent) ---------- 1.0 ppm

soybean forage ---------- 1.0 ppm

soybean hay ---------- 1.0 ppm

Metribuzin 40 CFR 180.332

soybeans ---------- 0.1 ppm

soybean forage and hay ---------- 4.0 ppm

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Data from residue studies of MON 097 plus atrazine, linuron, or metribuzin show increase in residues of acetochlor or the other three compounds. Therefore, Monsanto requests that tank mixes of MON 097 plus atrazine. linuron or metribuzin be permitted under the EUP.

Review:

1. The following conditional studies as defined by 163.112-4 were judged not to be required for this specific petition.

   (a) Inhalation LC_{50}; 163.81-3. None of the three conditions listed in 163.81-3 will exist for either the technical grade product, CP-55097, or formulated product, MON 097, 8 lbs./gal E.C. The product does not produce a gas or respirable vapor nor is 20 percent or more of the aerodynamic equivalent of the product composed of particulates not larger than 10 microns in diameter.

   (b) Skin Sensitization Study. Pursuant to 163.81-6, this study is required to support the registration of those products whose use will involve "repeated human skin contact". This condition is not met for MON 097, 8 lbs./gal. In accordance with this petition, MON 097, 8 lbs./gal. will be applied to the soil by mechanical sprayer prior to crop and/or weed emergence. The label instructs the user to wear rubber gloves while handling. Not only is the potential for dermal exposure minimal for this use, the results of the acute skin irritation study demonstrate than MON 097, 8 lbs./gal. E.C., produced essentially no irritation.

   (c) Acute Delayed Neurotoxicity; 163.81-7. The active ingredient, CP-55097, 2-chloro-N-ethoxymethyl-6'-ethyl-ortho-acetotoluidide, does not belong to chemical classes known to cause acetyl cholinesterase depression or delayed neurotoxicity.

   (d) Photosensitization; CP-55097 is not structurally related to or is not a known photosensitizer.

2. Acute Oral Toxicity of MON 097 8 lbs./gal. E.C. to Rats (Environmental Health Laboratory Report No. 80-49; October 15, 1980)

   Groups of 5M + 5F Sprague-Dawley CD rats were given single oral doses by gavage of 1250, 1768, 2500, 3536, and 5000 mg/kg of test material. Observation for 15 days.

   Results: LD_{50} (both sexes) = 2953 (2136-4761) mg/kg
   LD_{50} (males) = 3712 (2794-5297) mg/kg
   LD_{50} (females) = 2018 mg/kg

   Toxic Signs: Convulsions, prostation, ataxia, lethargy, salivation, body temors, lacrimation, urine-stained fur, diarrhea, emaciation, ptosis, muscular weakness, and shallow breathing.

   Body Weight: Survivors gained weight.

   Necropsy: Necrotic spots on liver, test material in thoracic cavity, intestinal hemorrhaging.

Toxicity Category III: CAUTION

Classification: Core-Minimum Data

3. Acute Dermal Toxicity of MON 097 8 lbs./gal. E.C. to Rabbits (Environmental Health Laboratory Report No. 80-48; October 15, 1980)

Groups of 4 NZW rabbits (2M + 2F) received dermal applications of 2000, 2828 and 4000 mg/kg of test material on the intact skin (one half of the rabbits were further abraded) under an impervious cuff for 24 hours. Observation was for 14 days.

Results: LD_{50} (both sexes) = 3667 (3017-4458) mg/kg
LD_{50} (males) = 3999 (1796-8907) mg/kg
LD_{50} (females) = 5631 (3054-4156) mg/kg

Toxic Signs: Convulsions, tremors of the head, loss of balance, labored breathing, grinding of teeth, muscular weakness, ptosis, vocalization (while convulsing), lacrimation, body weight loss, defatting of the skin is treatment area, and hardening of the skin in the treatment area.

Body Weight: Most survivors gained weight.

Necropsy: Yellow areas of liver (not considered compound related).

Toxicity Category III: CAUTION

Classification: Core-Minimum Data

4. Primary Skin Irritation of MON 097 8 lbs./gal. E.C. to Rabbits (Environmental Health Laboratory Report No. 80-50; October 15, 1980)

0.5 ml of test material was applied to intact and abraded skin sites on 6 NZW rabbits under an impervious cuff for 24 hours. Observations and scoring according to Draize at 24, 48 and 168 hours after exposure.

Results: P.I. = 0.6/8.0

All skin irritation had subsided by the seventh day. No apparent signs of systemic toxicity were observed.

Toxicity Category IV: CAUTION

Classification: Core-Minimum Data

5. Primary Eye Irritation of MON 097 8 lbs./gal. E.C. to Rabbits (Environmental Health Laboratory Report No. 80-51; October 15, 1980)

0.1 ml of test material was instilled into the right eye of nine NZW rabbits with the untreated left eye serving as control. Three rabbits had their treated eyes rinsed with physiological saline. Observation and scoring according to Draize on days 1, 2, 3, 4, 7 and 10 after exposure.

Results: Unwashed Eyes

Average Draize score was 18.8; corneal opacity in 6/6 on day 1 and 0/6 at day 7; iritis in 5/6 on day 1 and 0/6 on day 3; conjunctivitis in 6/6 day 1, 1/6 on day 7 and 0/6 on day 10. All treated eyes had regained normal appearance by day 10.

Washed Eyes

Average Draize score was 1.2; corneal opacity in 1/3 day 1 and 0/3 on day 2; no iritis; conjunctivitis in 3/3 on day 1 and 0/3 on day 2.

Toxicity Category II: WARNING

6. CP-55097: 91-Day Feeding Study in the Rat (Pharmacopathics Report No. 7914; October 10, 1980)

Two hundred and ninety (145 males and 145 females) random bred, Sprague Dawley, CD weanling (21 days old) albino rats were used in the study. Of the 290 rats, twenty were used for baseline studies as per protocol and 240 were used for the 91-day phase of the study. The remaining 30 rats were sacrificed by day zero (July 30, 1979). During the quaramtine period the animals were randomized by weight into four groups, each consisting of 30 male and 30 female rats. During the quaramtine period the rats were individually ear punched. The rats were individually housed.

The control rats received the basic diet, Charles River 19RF rat/mouse/hamster meal. The low dose group received 800 ppm of CP-55097 in the diet, the mid-dose received 2000 ppm, and the high dose group received 6000 ppm daily in the diet.

All rats were inspected daily by the animal caretakers and weekly by the study coordinator. The following clinical chemistry determinations were performed on ten male and ten female rats prior to initiation of the study, on a different set of 10 males and 10 females after 45 days and on a third set of 10 males and 10 females after 91 days on test: total protein, albumin, globulin, SPGT, SAP, SGOT, LDH, BUN, fasting blood sugar, total bilirubin, direct bilirubin, cholesterol, K^+, Ca^{++}, Na^+, Cl^-, CO_2.

The following hematological determinations were performed on the same rats used in clinical chemistry and at the same time intervals: RBC, hematocrit, hemoglobin, WBC, differential WBC, platelet estimate, reticulocyte count (if signs of anemia were seen), RBC morphology.

The following urinalysis parameters were performed on the same rats used for clinical chemistry and at the same time intervals:

color, appearance, specific gravity, pH, protein (qualitative), glucose (qualitative), ketones, urobilinogen, bilirubin, WBC, RBC

All rats received a complete gross necropsy under the direct supervision of a Board Certified Pathologist.

All animals that became moribund were sacrificed within 16 hours so as to prevent autolysis of tissues. Animals were fasted overnight prior to necropsy. All rats were euthanized with ether. Organ weighing and tissue blocking were performed after fixation in 10% buffered formalin for at least 72 hours. Blocking was done in double labeled plastic cassettes. The following organs were weighed from each animal:

brain, gonads (combined weight), heart, kidneys (combined weight), liver.

Organ-to-body weight ratios were calculated for each animal. Based on the individual ratios the corresponding means and standard deviations were calculated and a comparison for statistical intergroup differences was performed. Organ-to-brain weight ratios were calculated for each animal. Based on the individual ratios the corresponding means and standard deviations was calculated and a comparison for statistical intergroup differences were performed.

A spectrum microscopically from (a) randomly selected ten male and ten female rats prior to initiation of the study; (b) all rats in the control and high-dose groups at the end of the study; (c) all gross lesions observed in the course of the complete necropsy; (d) heart, lungs, liver and kidneys of all rats from the intermediate dose groups, and (e) if any significant findings occurred in any other organs and tissues in the high-dose group, said organs or tissues were examined from all rats in the low and mid-dose groups.

Animals which received complete histopathology had all the following tissues blocked: adrenals, urinary bladder, bone, bone marrow, brain, cecum, colon, duodenum, esophagus, eye and optic nerve, heart, ileum, jejunum, kidneys, liver, lungs and bronchi, lymph nodes, mammary glands (if palpable), skeletal muscle, peripheral nerve (sciatic), ovaries, pancreas, parathyroids, penis, pituitary, prostate, salivary glands (submaxillary), spinal cord, spleen, stomach, testes, thymus, thyroids, trachea, uterus and vagina.

Statistical analyses of the data were performed.

Results:

No abnormal clinical signs were observed in any of these rats, either test or control, during the entire period of the study. All rats survived the duration of the study. In the male rats the following statistically significant fluctuations were observed in the mean weekly feed consumption data between the various test groups and the corresponding control group: (a) the low-dose group showed a decrease at weeks 5 and 9; (b) the mid-dose showed a decrease at weeks 3, 5, 6, 9 and 10, and (c) the high-dose group also showed a decrease at weeks 1, 2, 5, 8, 9 and at weeks 11 through 13.

In the female rats the following statistical fluctuations were observed in the mean weekly feed consumption data between the various test groups and the female control group: (a) the low-dose group showed a decrease at weeks 4 and 6; (b) the mid-dose group showed a decrease at week 11, and (c) the high-dose group showed a decrease at week 6 and at weeks 10 through 13. The feed efficiency data for the different dose levels in both sexes were not remarkable, nor did they appear to be different from the control groups.

The following statistically significant fluctuations were observed in the mean weekly body weight data of the male rats using the Student's t-test: (a) the low-dose group showed a decrease (3-8%) at weeks 2 through 5 and at weeks 8 through 13; (b) the mid-dose group showed a decrease at weeks 1 through 13, and (c) the high-dose group also showed a decrease at weeks 1 through 13. The difference in the mean weekly body weight gains between the control and the low-dose group of male rats was more pronounced during weeks 4 to 10 than during the last three weeks.

The data for the control and low-dose groups in both sexes were further statistically analyzed using the Dunnet's t-test. For the males, Dunnet's t-test analysis showed that the mean body weights of the control and low dose group were statistically significantly different at weeks 5 and 8 through 13 as compared to weeks 2 through 5 and 8 through 13 using the Student's t-test.

The following statistically significant fluctuations were observed in the mean body weight data of the female rats using the Student's t-test: (a) the low-dose group showed a decrease (4-6%) at weeks 3, 4, 6 and weeks 9 through 13; (b) the mid-dose group showed a decrease at weeks 3, 5 and weeks 6 through 13, and (c) the high-dose group showed a decrease at weeks 1 through 13.

Using the Dunnet's t-test to analyze the statistical differences between the body weights of the low-dose and control female groups changes the interpretation of these results. In this case, Dunnet's test analysis shows that the mean body weights of the control and the low-dose groups in the females are statistically different only at test weeks 6 and 12 as compared to weeks 3, 4, 6, 9 and 10 through 13 using the Student's t-test.

In the male rats, the mean total protein values showed a statistically significant decrease as compared to the controls in the mid-dose and high-dose levels at 91 days. This decrease was not considered to be biologically meaningful because it was within the laboratory's normal range. The mean total protein values in the female rats were normal except for the low-dose level at 45 days and for the high-dose level at 91 days, both of which showed a statistically significant decrease as compared to the controls. This decrease was not considered biologically meaningful because it was within the laboratory's normal range.

In the male rats the mean Albumin values showed a significant decrease as compared to controls in the low-dose level at 45 days and in the mid-dose and high-dose levels at 91 days. This decrease was not considered biologically meaningful because it was within the laboratory's normal range. The mean Albumin value for the female rats were all normal except for the low-dose level at 45 days that showed a statistically but not biological significant decrease at 45 days since it was within the laboratory's normal range and was not dose-related. No statistical or biological significance was observed in the mean globulin values in the males at 45 and 91 days. The mean values for the female rats were normal except for the high-dose level at 91 days that showed a significant decrease as compared to the control group. This decrease was not considered biologically meaningful because it was within the laboratory's normal range.

The mean SGPT values in the male rats were normal except for the mid-dose level at 91 days that showed a statistically but not biologically significant decrease since it was within the laboratory's normal range. and was not dose-related. In the female rats the mean SGPT values showed a significant decrease as compared to the control group in the high-dose level at 45 and 91 days and in the low-dose level at 91 days. These decreases were not considered to be biologically meaningful since they were within the laboratory's normal range.

In the female rats the mean SGPT values showed a significant decrease as compared to the control group in the high-dose level at 45 and 91 days and in the low-dose level at 91 days. These decreases were not considered to be biologically meaningful since they were within the laboratory's normal range.

In the male rats the SAP values showed a significant decrease in the high-dose level at 45 days and in the mid-dose as well as in the high-dose levels at 91 days. These decreases were not considered to be biologically meaningful since they were within the laboratory's normal range.

In the female rats the mean SAP values at all levels showed a statistically but not biologically significant decrease at 45 days as compared to the control group, since they were within the laboratory's normal range.

All mean SGOT values in the male rats were statistically and biologically normal. The mean SGOT values in the female rats showed a significant decrease in the high-dose level at 45 days and in the low-dose level at 91 days. This decrease was not considered to be biologically meaningful since it was within the laboratory's normal range.

In the male rats the mean LDH values were normal except for the high-dose level at 91 days that showed a significant increase as compared to the controls; this increase was not considered to be biologically meaningful since it was within the laboratory's normal range. The mean LDH values in the female rats were both statistically and biologically normal for all groups throughout the study.

In the male and female rats all mean BUN values were both statistically and biologically normal at all times throughotu the study.

The mean free-blood sugar values in the male rats were normal except in the mid-dose level at 91 days that showed a significant increase as compared to the controls. This increase was not considered to be biologically meaningful since it was within the laboratory's normal range and was not dose-related. The mean free-blood sugar values in the female rats were normal except for the mid-dose level at 91 days that showed a significant increase as compared to the controls. This increase was not considered to be biologically meaningful since it was within the laboratory's normal range.

In the male rats all mean total bilirubin values were normal except for the high-dose group at 91 days which revealed a statistically but not biologically significant increase since this value was within the laboratory's normal range. The mean total bilirubin values for the female rats were normal except for the high-dose level at 45 days and the low-dose level at 91 days, both of which showed a statistical decrease as compared to the controls. This decrease was not considered to be biologically meaningful since it was within the laboratory's normal range.

In the male and female rats the mean direct bilirubin values at 45 days were normal. It was later decided after the 45 day assay not to run the direct bilirubin assay at 91 days if the total bilirubin result was within the laboratory's normal range.

The mean cholesterol values in the male rats showed a statistically but not biologically significant increase as compared to the controls in: (a) the mid and high-dose levels at 45 days, and (b) the high-dose level at 91 days, since these values were within the laboratory's normal range. In the female rats the mean cholesterol values were both statistically and biologically normal for all groups at all times examined.

The mean K^+ values for the male rats were normal except for the high-dose level at 45 days that showed a statistically significant decrease as compared to the controls. This decrease was not considered to be biologically meaningful since it was within the laboratory's normal range. The mean K^+ values in the female rats showed a significant increase as compared to the control group in the mid-dose group and the high-dose group at 91 days; this increase was not considered to be biologically meaningful since it was within the laboratory's normal range.

The mean Ca^{++} values in the male and female rats were normal throughout the study.

The mean Na^+ values in both the male and female rats were normal throughout the study.

The CO_2 values in the male rats were normal except for the low-dose level at 45 days that showed a statistically but not biologically significant decrease, and the high-dose level which showed a statistically but not biologically significant increase at 91 days, since both of these values were within the laboratory's normal range.

In the female rats the mean CO_2 values for the low-dose and mid-dose levels at 45 days showed a statistically significant decrease as compared to the controls. The high-dose level should a significant decrease as compared to the control group at 91 days. These decreases were not considered to be biologically meaningful since they were within the laboratory's normal range.

The hematological values of male and female rats were normal throughout the study with the exception of the mean WBC count in female rats at the low-dose level at 45 days which showed a statistically and biologically significant increase as compared to the controls since it was outside the range normally established at the laboratory and was not dose-related. All rats both male and female, displayed normal urinalysis at all times examined.

Mean organ weights of treated animals were occassionally significantly different from the controls. However, there were no corroborative histopathological findings in any of the organs. The mean brain weight for the mid-dose and high-dose male rats showed a significant decrease as compared to the corresponding controls. The mean heart weight in the high-dose male and female rats showed a significant decrease as compared to the controls. The mean liver weight of the various test groups did not show any significance at any dose level in either sex. The mean kidney weight of the various test groups did not show any significance at any dose level in either sex. The mean testicular weight of the male test groups did not show any statistical significance, whereas the mean ovarian weight of the low and mid-dose female rats was significantly higher than the corresponding controls.

The brain-to-body weight ratio showed a statistically significant increase as compared to the control group at the low-dose level in the female rats and at the high-dose level in both sexes. The heart-to-body weight ratio did not show any significance at any dose level in either sex. The liver-to-body weight ratio showed a significant increase as compared to the control group at the high-dose level in both sexes. The kidney-to-body weight ratio showed a statistically significant increase as compared to the control group at the low-dose level in the female and at the high-dose level in both sexes. The gonads-to-body weight ratio showed a significant increase as compared to the control group at the high-dose level in the males and at all dose levels in the females.

A significant decrease in the heart-to-brain ratio at the high-dose level in the female as compared to the control group was observed. No statistical significance was observed in the liver-to-brain weight ratios at any dose level in either sex. No statistical significance was observed in the kidney-to-brain weight ratio at any dose level in either sex. A statistically significant increase as compared to the control groups was observed in the gonads-to-brain weight ratios at the high-dose level in the males and at both the low-dose and mid-dose levels in the females.

No gross pathology findings were observed in any of the rats at terminal sacrifice except for two mid-dose female rats that showed dilation of the renal pelvis of both the left and right kidney. Some of the rats in both sexes showed various histopathological findings. They were not, however, considered to be compound-related since most of them are randomly seen in normal young random-bred CD derived Sprague-Dawley albino rats.

Conclusions:

From the cumulative data, it is concluded that CP-55097, when fed to the rat under the conditions of the study, caused a statistically and biologically meaningful effect in the feed consumption and body weight of the mid and high-dose levels in both sexes. On the other hand differences in these parameters between the control and low-dose levels were, although statistically significant (3-8% decreases), not considered to be as biologically meaningful in either sex at the low dose. The NOEL is considered to be 800 ppm (40 mg/kg/day) in the diet for 13 weeks. Additionally, the LEL of 25 mg/kg/day in the dog demonstrates the dog is the more sensitive species and would be used to calculate a PADI.

7. CP-55097; 119-Day Study in the Dog (Pharmacopathics Report No. 7920; October 10, 1980)

The dogs used in this study were purebred beagles received from Hazelton Laboratories Inc., Vienna, Virginia, on July 27, 1979. Forty-eight dogs (24 male and 24 female) were received at the laboratory and were examined immediately for any abnormalities. The animals were temporarily housed in the quarantine room in order to be acclimatized to the environment of the laboratory and each dog was given 2 ml of IMFERON intramuscularly.

Because one dog was found to have a few hook-worm eggs, all dogs were treated for hook-worm infection with NEMEX (Purantel pamoate, PFizer) at a single dose of 5 ml of NEMEX per five pounds of body weight.

The animals were randomized by weight and heredity into four groups, each consisting of six males and six females. The dogs were housed in individually suspended cages in two rooms and were fed 350 grams of Wayne Dog (meal form) once a day. The dosages of CP-5507 were as follows: (a) control group of animals received a sham capsule for the duration of the study; (b) the low-dose group received 25 mg/kg/day in capsules for the duration of the study; (c) the mid-dose group received 25 mg/kg/day during the first week, 50 mg/kg/day during the second week, and 75 mg/kg/day during the third through 17th weeks in capsules; and (d) the high-dose group received 50 mg/kg/day during the first week, 100 mg/kg/day during the second weeks, 150 mg/kg/day during the third week, and 200 mg/kg/day during the 4th through 17th weeks in capsules. Capsules were given once daily, approximately one hour after the feed was withdrawn.

All dogs were weighed once a week on a Toledo Floor Balance. Three hundred and fifty grams of the basic diet were weighed on a Toledo Bench Scale, poured into a stainless steel bowl, then entered into the daily log book as the "full" weight. After approximately one hour the bowl was withdrawn and the remaining feed poured into the scale and the weight recorded and entered as the "empty" weight. The difference between the two weights represented the daily feed intake of that particular dog.

Clincial Chemistry determinations included the following: total protein, albumin, globulin, SGPT, SAP, SGOT, LDH, BUN, total bilirubin, direct bilirubin, cholesterol, K^+, Ca^{++}, Na^+, Cl^-, CO_2. These clinical chemistry determinations were performed prior to initiation of dosing, monthly thereafter and at termination prior to sacrifice.

The hematological determinations performed on all dogs included the following: RBC, hemoglobin, hematocrit, WBC, differential WBC, platelet estimate, reticulocyte count (only in the case of anemia), RBC morphology. The hematological determinations were performed prior to initiation of dosing, monthly, thereafter, and at termination prior to sacrifice.

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The following urinalysis parameters were performed: color, appearance, pH, specific gravity, protein (qualitative), glucose (qualitative), ketones, urobilinogen, bilirubin, microscopic examination of sediment for WBC and RBC. The urinalysis examinations were performed prior to initiation of dosing, monthly thereafter and at termination prior to sacrifice.

All animals underwent a complete necropsy under the direct supervision of a Board Certified Pathologist. All animals that became moribund were sacrificed within 16 hours so as to prevent autolysis of tissues. The following organs were weighed from each animal: brain, pituitary, spleen, gonads, thyroids/parathyroids, heart, liver, adrenals, kidneys (combined weight). The large organs were weighed fresh while the small organs (thyroids/parathyroids, adrenals, gonads and pituitary) were weighed after fixation in 10% buffered formalin. Organ-to-body weight ratios were calculated for each animal. Based on the individual ratios the corresponding means and standard deviations were calculated and a comparison for statistical intergroup differences were performed. Organ-to-body weight ratios were calculated for each animal. Based on the individual ratios the corresponding means and standard deviations were calculated and a comparison for statistical intergroup differences were performed. A spectrum of tissues were examined microscopically from: (a) all dogs at the end of the study; (b) all gross lesions observed in the course of a complete necropsy. Animals which received complete histopathology had all the following tissues blocked: adrenals, urinary bladder, bone, bone marrow, brain, cecum, colon, duodenum, esophagus, eye and optic nerve, gall bladder, heart, ileum, jejunum, kidneys, liver, lungs and bronchi, mammary glands (if palpable), skeletal muscle, peripheral (sciatic) nerve, ovaries, pancreas, parathyroids, penis, pituitary, prostate, salivary glands (submaxillary), spinal cord, spleen, stomach, testes, thymus, thyroids, uterus and vagina.

Results:

As the study progressed the high-dose group of animals was visibly affected; the signs in both sexes consisted of bloody diarrhea and vomiting of both the feed and the compound. The high-dose females were more severly affected than the high-dose males; the females were thinner, weaker and generally in worse physical condition than the males. Appetites varied in this high-dose group from poor to almost outright refusal of food. Retention of eaten food was variable.

Several male dogs, control as well as test, exhibited intermittent episodes of diarrhea and occasional vomiting. Several female dogs, control as well as test, exhibited intermittent episodes of diarrhea and vomiting throughout the duration of the study. The following dogs died or were sacrificed in a moribund condition during the course of the study:

One high-dose male dog#1295 and one high-dose female dog #1286 during the 5th week; one high-dose male dog #1287 during the 6th week; two high-dose male dogs, #1289 and #1291 and three high-dose females, #1288, #1290 and #1296 during the 7th week; one high-dose male dog #1293 during the 8th week; one mid-dose male dog #1281 and one high-dose female dog #1294 during the 11th week, and one high-dose female dog #1292 during the 12th week.

Thus by the end of week 12 the following mortality was observed: one mid-dose male; five high-dose males and six high-dose females. All other animals survived the duration of the study.

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The mean feed consumption of the low-dose and mid-dose groups of males was reduced slightly compared to the controls from week 6 through the end of the study. These changes in feed consumption appear to be dose-related. The high-dose male group showed a statistically significant decrease in feed consumption from weeks 4 through 8; because only one dog was alive at week 8 no statistics were performed.

The low-dose female dogs had a meam feed consumption that was equal to or greater than controls throughout the study. The mid-dose female group showed a statistically significant decrease in feed consumption during weeks 8, 10, 11 and 14. The high-dose female group showed a statistically significant decrease in feed consumption for weeks 4 through 10. Thereafter, only one dog remained and no statistics were performed.

The feed efficiency data (change im body weight in grams per grams of feed per week) showed a remarkable decrease in the males at the high-dose level while they were alive (weeks 1 through 7). In the females there was a remarkable decrease at the high-dose level (weeks 1 through 10) and a noticeable decrease at the mid-dose level. The marked reduction in feed consumption and feed efficiency in both male and female animals is considered compound-related. With respect to body weight, the low-dose and mid-dose levels in the males did not show any statistical significance. A statistically significant decrease was observed in the high-dose males for weeks 4 through 6. The individual body weight data for this group show the dogs were losing weight progressively throughout the study. The mean body weight data for the low-dose and mid-dose female groups did not show any statistically significant differences as compared to the control; the middose dogs, nevertheless, did not gain as much weight as either the control or the low-dose groups. The high-dose female group showed a statistically significant decrease as compared to the control group at weeks 3 through 10. Individual body weight data showed a progressive decrease in body weight after the first week that continued throughout the study.

The decrease in body weight in both males and females, especially at the high-dose level and primarily manifested by wasting of subcutaneous fat, is considered compound-related.

The mean total protein values in both sexes were within the laboratory's normal range. The mean albumin and globulin values were within the laboratory's normal range. The mean SGPT values showed a statistically significant difference in the low-dose male group at month 4 and in the mid-dose male and female groups at months 3 and 4. These differences were also biologically significant (abnormally high). The mean SGPT values in the female dogs showed a low-dose group at months 1 and 2, reverted to normal at month 3, while at month 4 the mean values were slightly higher than the laboratory's normal range, although not statistically significant.

The mean SAP values of both sexes were within the laboratory's normal range.

Both a statistically and biologically significant increase was observed in the mean SGOT value of the mid-dose males at month 3, but returned to normal by month 4. Other SGOT mean values of both sexes were within the laboratory's normal range. The mean LDH values of both sexes were within the laboratory's normal range. The mean BUN values of both sexes were within the laboratory's normal range. The mean free-blood sugar values for both sexes were within the laboratory's normal range. The mean total bilirubin of both sexes were within the laboratory's normal range. The mean direct bilirubin, cholesterol, K^+, Ca^{++}, Cl^-, CO_2 were within the laboratory's normal range for both sexes.

The hematological findings were within the laboratory's normal range for both sexes.

High-dose male and female dogs exhibited abnormal urinalysis findings, particularly proteinuria and hematuria. These abnormal findings reflect the underlying renal histopathology and is considered compound related. Proteinuria and hematuria were observed only transiently in the low-dose and mid-dose animals, but there was no pertinent renal histopathology in these animals.

There were no statistically significant differences in the mean weight of brain, pituitary, heart, liver, kidneys, spleen or gonads. With respect to the thyroids/parathyroids and adrenals, there was a statistically significant increase in the low-dose female group only. There was no associated histopathology with these increased organ weights.

The organ-to-body weight ratios were not significantly affected for the brain, pituitary, heart, and kidney; the thyroid/parathyroid-to-body weight ratio showed a significant increase as compared to the control group at the low-dose level in the females. The liver-to-body weight ratio showed a significant increase as compared to the control group in the males at the mid-dose level and in the females at the low and mid-dose levels. In the high-dose level in the males the only surviving animal at the end of the study showed a remarkably high liver-to-body weight ratio as compared to the controls. No high-dose female dogs were alive at the end of the study. The adrenal-to-body weight ratios showed a significant increase as compared to the control group in the female dogs at the low and mid-dose levels. No high-dose female dogs were alive at the end of the study. The spleen-to-body weight ratio showed a significant decrease as compared to the control group in the female dogs at the mid-dose level. The gonads-to-body weight ratio showed a significant increase as compared to the low-dose level. None of the organ-to-brain weight ratios showed any statistical significance except for the low-dose level in the females that showed a significant increase as compared to the control group in the thyroid/parathyroid and in the adrenal-to-brain weight ratios.

From the point of view of gross pathology, the most frequent findings observed consisted of congestion of lungs, stomach and renal medulla. These findings are often associated with agonal death, the result of agitation during attempts to euthanize the dogs. The most frequent histopathological diagnoses, observed mostly in the mid-dose and high-dose dogs, were fatty infiltration of the tongue (although this was also observed in the controls), atrophy and fatty infiltration of liver, fatty infiltration of the muscle, fatty infiltration of the renal tubules, atrophy of the thymus and hypocellularity of bone marrow. The atrophy and fatty infiltration of the liver, fatty infiltration of the muscle, fatty infiltration of the renal tubules, atrophy of the thymus and hypocellularity of the bone marrow, observed in the mid-dose and high-dose animals, is considered to be compound-related.

Conclusion:

It is concluded that CP-55097, under the conditions of the experiment, causes severe toxic effects at the high-dose level, moderate toxic effects at the mid-dose level and mild toxic effects (abnormally elevated and dose-related SGPT, increased liver-to-body weight ratio) at the low-dose without any accompanying histopathology in the low-dose group. A NOEL was not established in this study. The LEL is 25 mg/kg/day, the low dose group.

8. CP-55097 technical: Teratology Study in Rats IR-79-009 (IRDC Report No. 401-066; October 15, 1980)

Groups of 25 pregnant Charles River COBS CD rats were used to determine the teratogenic potential of CP-55097 technical. Dosage levels of 0, 50, 200 and 400 mg/kg/day were administered orally by gavage as a single daily dose on days 6 through 19 of gestation at a constant volume of 10 ml/kg. The control group received the vehicle only, Mazola corn oil, on a comparable regimen. Dams were observed for mortality, clinical signs of toxicity and body weight. Cesarean sections were performed on all dams on gestation day 20. Statistical analyses of the data were performed.

Results:

There were no statistically significant or biologically meaningful differences in mean maternal body weight gain, the mean numbers of corpora lutea, total implantations, post-implantation loss, viable fetuses, or the fetal sex distribution, in rats in the 50 or 200 mg/kg/day dosage groups when compared to the control group.

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Mating and/or staining of the anogenital region was noted for 13 of the 25 rats in the 400 mg/kg/day dosage group and excessive salivation was observed in three rats as a post-dose response on one occasion. A moderate decrease in mean maternal body weight gain during the treatment period and in the adjusted mean body weight gain on gestation day 20 was noted in this dosage group when compared to the control group. A slight but not dose-related increase in matting and/or staining of the anogenital region was noted in the 50 and 200 mg/kg/day dosage groups.

There were no statistically significant or biologically meaningful differences in the mean numbers of corpora lutea, total implantations, post-implantation loss, viable fetuses or the fetal sex distribution in the 400 mg/kg/day dosage group when compared to the control group.

A slight to moderate decrease in mean fetal body weight, although not statistically significant, was noted in the 400 mg/kg/day dosage group. Mean fetal body weight values in the 50 and 200 mg/kg/day dosage groups were comparable to the control group.

There were no malformations in the 50 mg/kg/day dosage group. Three fetuses in 2 litters at the mid-dose had dwarfism and skeletal malformations. The malformations noted in the 400 mg/kg/day dosage group were dwarfism and skeletal malformations noted in five fetuses in one litter. These 200 and 400 mg/kg/day findings were considered of genetic origin and not compound-related as dwarfism and similar malformations have occurred in several fetuses in litters in the historical control data provided.

Conclusion:

Treatment with CP-55097 technical did not produce a teratogenic response when administered orally to pregnant Charles River COBS CD rats at a dosage level of 400 mg/kg/day or less. The NOEL for fetotoxicity is 200 mg/kg/day.

Classification: Core-Minimum Data

9. Salmonella Mutagenicity Assay of CP-55097 (Monsanto Report No. MRC-DA-838; December 5, 1978)

CP-55097 was tested for mutagenic activity accordinng to Ames et. al. in the spot test and plate test using S. typhimurium strains TA-98, TA-100, TA-1535 and TA-1537 in the presence and absence of mouse and rat microsomal activation preparations. Positive cortrols were tested.

Results:

CP-55097 was not mutagenic towards any of the Salmonella strains assayed under these test conditions.

Classification: Core-Minimum Data