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

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

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MEMORANDUM

DATE: December 10, 1981

SUBJECT: Proposed Tolerance for Bolero (Thiobencarb) on Rice (0.1 ppm), PP#0F2322; Acc. Nos. 070470, 070480, 070481, 070482, 070485, 070486, 070487, 070489, 070490, 070491, 070492, 070493, 070494; Tox. Chem. 207DA

FROM: Gary J. Burin, Toxicologist
Toxicology Branch/HED (TS-769)

TO: Dick Mountfort (23)
Registration Division (TS-767)

THRU: Dr. Orville E. Paynter, Chief
Toxicology Branch/HED (TS-769)

Registrant: Chevron Chemical Company
Ortho Agricultural Chemicals Division
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Richmond, California 94804

Action Requested

The registrant has proposed the establishment of a tolerance for thiobencarb (S[(4-chlorophenyl)methyl]diethylcarbamothioate) and its metabolite 4-chlorobenzyl methylsulfone in or on rice grain at 0.1 ppm.

RCB, however, has recommended that tolerances be set at 0.2 ppm in or on rice grain, eggs, the meat, fat and meat by-products of cattle, goats, hogs, horses, poultry and sheep; 1.0 ppm in or on rice straw and 0.05 ppm in milk (memo of 2/13/81 from M. Nelson).

Summary/Recommendations

Available Toxicology data submitted by the registrant to support the proposed tolerances can be summarized as follows:

(Recently submitted data)

Oncogenicity - A mouse study has been submitted and a rat oncogenicity/chronic feeding study is in progress. The mouse study has tentatively been classified as "Supplementary Data" due to the lack of identification of the number of animals examined for each tissue type. However, no oncogenic effect is apparent at the highest dose tested (1600 ppm).

Teratology - A range finding teratology study has been submitted and the findings (excluding skeletal examination) of a subsequent teratology study in rats have also been submitted. Although both studies are classified as "Supplementary Data", no teratogenic effect is apparent in either.

Subchronic/Chronic Toxicity - No study designed specifically to assess chronic or subchronic toxicity has been submitted. Limited information is available from interim reports (26 and 52 weeks) for a chronic rat study which is currently in progress. Although an apparent palatability problem at every dose level partially confounds the findings, a conservative NOEL of 20 ppm for systemic toxicity is indicated.

(Previously submitted data)

Mutagenicity - A dominant lethal and an Ames assay have both been reviewed and found acceptable. Neither study indicates a mutagenic response.

Neurotoxicity - Two studies designed to assess acute delayed neurotoxicity have been submitted. One of these studies was conducted at IBT, classified as "Supplementary Data" during validation and found to be inconclusive upon subsequent evaluation. The other study has been found to be "Core Minimum" and indicates a lack of delayed neurotoxic potential at the highest dose tested (1.6 g/kg).

Thus, although the toxicology data base for Bolero is quite limited and major data gaps exist, no oncogenic, mutagenic, teratogenic or neurotoxic effects have been associated with this compound. If tolerances are established at the levels recommended by RCB, the provisional ADI (based on a conservative NOEL of 20 ppm and a 1000 fold safety factor, see Discussion for explanation of the safety factor selection) will be 243% utilized.

If conditional registration is approved, the following conditions are recommended:

1. Submission of a Final Report for the recently submitted teratology study conducted at Science Applications, Inc., Study Number 581007. This should be required since no skeletal teratogenic evaluation is currently available. It should be submitted prior to application of Bolero in the next growing season. In addition, historical data for this strain of rat at this laboratory should be included in the Final Report, when submitted (see Review of Data, p. 7).

2. Submission of data allowing the determination of the number of animals examined for each tissue type in the recently submitted mouse oncogenicity study conducted at Life Science Research, Study No. 81/KCI040/527. See Review of Data, p. 15.

3. Submission of raw data from the recently submitted paired feeding study in rats. In addition, a satisfactory explanation should be requested from the laboratory that conducted the study with respect to the inconsistent results obtained with the paired male rats. In lieu of that explanation, a subchronic study in rats by gavage may be required due to the importance of the palatability issue in the interpretation of the chronic rat study.

4. Initiation of studies to replace those studies conducted at IBT that were determined to be "Invalid" and which are necessary for registration. These include a second teratology study, a reproduction study and a 6 month or longer study in a nonrodent species (dog). In addition, the completion and submission of the chronic feeding study in the rat which is currently in progress is required. This study must continue to support a NOEL for compound-related effects.

Discussion

Except for certain acute, mutagenicity, and neurotoxicity studies, all previously submitted Bolero toxicity studies were conducted at IBT and have been declared "Invalid". (See the attached computer printout for a summary of all toxicology studies conducted with Bolero). Recently submitted studies partially address the endpoints of teratogenicity, oncogenicity and subchronic toxicity and based on the limited information submitted with these studies, no teratogenic mutagenic, or oncogenic effect is apparent. Based on the interim report (1 year) of the chronic (2 year) rat feeding study, a conservative NOEL of 20 ppm is suggested due to an effect on BUN at the levels of 100 ppm and 500 ppm in both males and females. Although a safety factor of 2000 is normally applied to a subchronic rat study, it is recommended that 1000 be used in this case due to the following:

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1. It seems likely to this reviewer that, given the marginal effect on BUN at 26 and 52 weeks, lack of progression in severity during that interval and the lack of histopathologic lesions associated elevated BUN (e.g. renal disease), the NOEL for BUN may remain at 20 ppm through terminal sacrifice. The appropriate safety factor would then become 100 and this suggests that, with respect to BUN, the use of a 2000 fold safety factor may be excessive at this time.

2. The mouse life-time oncogenicity study, though not designed to assess chronic toxicity including clinical chemistry effects, suggests that a NOEL of 25 ppm for the mouse based on hepatic histopathology.

Using a NOEL of 20 ppm and a safety factor of 1000, a provisional ADI of .0005 mg/kg/day (.03 mg/person/day) can be established. The necessary tolerances, corresponding food factors and dietary contributions of Bolero residues are as follows;

Proposed Tolerance	Food Factors	Residue Contribution
.05 ppm (milk)	28.62%	.021465 mg/person/day
.2 ppm (rice)	.55%	.00165
.2 ppm (eggs)	2.77%	.00831
.2 ppm (meat)	13.85%	.04155
1.0 ppm (rice straw)	0	0
	TOTAL =	.072975 mg/person/day

The TMRC will therefore utilize approximately 243% of the provisional ADI. However, if the NOEL remains at 20 ppm through terminal sacrifice in the rat study, a safety factor of 100 will then be appropriate and the percentage of the ADI utilized will decrease to 24.3%.

See the attached computer printout for a summary of all toxicology studies conducted with Bolero.

Review of Data

1. Pilot Teratology Study in Rats, performed at Science Applications, Inc., La Jolla, California, November 16, 1981 and submitted by Chevron Chemical Company.

   Thirty Sprague-Dawley derived rats were mated for a 9 day period or until mating took place. The morning following initial cohabitation and each subsequent morning, the females were examined for vaginal plugs and/or sperm in the vaginal fluid. The date that an animal exhibited a positive response for mating was considered as day 0 of gestation.

Animals were dosed on day 6-19 of gestation. Six females per dose level were administered 0, 2, 10, 50 and 250 mg/kg of Bolero (93% pure) in deionized water via gavage (5 ml/kg of body weight).

Body weights were measured on day 0 and days 6-19 of gestation, and prior to cesarian section. Food consumption was measured on days 0, 3, 6; 10, 14, 17 and 20 of gestation. Observations were made twice daily.

On day 20 of gestation animals were killed by CO_2 asphyxiation. A laparohysterectomy was then performed on each dam. Reproductive organs were examined in situ. Number of corpora lutea and the distribution of live and dead fetuses in each uterine horn was recorded, as well as resorption sites. Each fetus was examined for external anomalies. Fetal body weights and sex were recorded. Dams and fetuses were discarded after examination.

Results:

One dam from the 250 mg/kg dose group was killed in extremis during the study. Necropsy of this dam found severe hydronephrosis and severe erosions in the stomach. Clinical signs of toxicity were observed only in the 250 mg/kg dose group and consisted of hypoactivity, mucus discharge from the mouth and mild to moderate dyspnea. The 250 mg/kg group also evidenced a decreased mean weight gain. Mean daily food consumption was consistently lower than controls for the 10, 50 and 250 mg/kg dose groups from day 0-20 gestation.

No compound-related effects were observed for the percentage of pregnant dams, mean number of corpora lutea and mean number of implantations per dam. A reduction in the mean number of live fetuses per litter was observed at 10 mg/kg due to one dam having only 2 live fetuses and six early resorptions. At 250 mg/kg, the mean number of live fetuses decreased (to 10.6/litter from 12.8/litter in controls), the mean live fetal weight decreased (to 2.5 grams from 3.7 grams in the controls), the number of resorbed fetuses increased (to 2.6/litter from 0.5/litter in the controls). Two fetuses were considered to be runts in the high dose group - no other fetuses were reported as grossly abnormal in any dose group.

Core Classification:

Supplementary data. This study serves only range finding purposes. The data suggests that frank maternal and fetal toxicity is observed only at 250 mg/kg. No terata were observed at levels as high as 250 mg/kg after an external examination of the fetuses. No deficiencies in study design or execution are apparent.

2. Data from Teratology Study in Rats with Bolero, performed at Science Applications, Inc., La Jolla, California, Final Report in progress, submitted by Chevron Chemical Company. (Actual study procedures have not been reported at the time of this review. The procedures noted below are derived from the study protocol of February 26, 1981 and subsequent amendments.)

One hundred Sprague-Dawley derived female rats were mated with male rats for a 14 day period or until pregnancy occurred as detected by a vaginal plug and/or sperm in the vaginal fluid. The day that an animal exhibited a positive response for mating was considered as day 0 of gestation.

Animals were dosed on days 6-19 of gestation. Twenty five females per dose level were administered 0, 5, 25 or 150 mg/kg via oral intubation. Tween 80 (carboxymethyl cellulose sodium salt) and dionized water was used as a vehicle. Control animals received only the vehicle.

Body weights were taken on days 0, 6-19 and prior to cesarian section. Food consumption was measured on days 3, 6, 10, 14, 17 and 20. Mortality and observations were recorded twice daily.

On day 20 of gestation, animals were killed by CO_2 asphyxiation. Animals were examined for gross morphological abnormalities. Abnormal tissues were preserved for possible histological examination. The uterus and ovaries were removed, weighed and examined for number of corpora lutea, number of live and dead fetuses, number of late and early resorptions and the condition of the uterus and placentae were examined.

Fetuses were removed, weighed, sexed and examined externally for abnormalities. Approximately one-half of the fetuses were decapitated and the heads were fixed in Bouin's solution for at least one week. The heads were then sectioned and examined for soft tissue abnormalities. Each fetus was also examined viscerally with care taken not to disturb skeletal structure. Following visceral examination, all fetuses were stained with Alizaria Red S and examined for skeletal abnormalities.

Results:

A Final Report of study results was not available at the time of this review.

Maternal toxicity was evident only at 150 mg/kg and was indicated by decreased mean weight gain (78.5 grams compared to 98.1 grams in the control). No clinical observations of toxicity were evident in any group.

No apparent effect on resorptions/litter, implantations/litter or number of live pups/litter was observed. The mean weight of live fetuses was decreased in the high dose group (3.3 g compared to 3.8 g in controls). Fetotoxicity was suggested only in 150 mg/kg dose group based on visceral and external examination of fetuses and this dose level also evidenced maternal toxicity. An increased number of runts were observed in that group (10 runts /20 litters compared to 1/17, 1/23 and 3/23 in the 0, 5 and 25 mg/kg groups, respectively) and an increased incidence of hydroureter was also observed in the 150 mg/kg dose group (5 occurrences/20 litters compared to 1/23, 2/23 and 3/17 in the 0, 5 and 25 mg/kg groups. However it is noted that only 3 litters were affected at the high dose (hydroureter and/or hydronephrosis).

TABLE I

Results of Fetal Visceral and External Examination Findings*

	0 mg/kg	5 mg/kg	25 mg/kg	150 mg/kg
Hydronephrosis	1/17 (1)	0/23 (0)	0/23 (0)	2/20** (2)
Hydroureter	1/17 (1)	2/23 (2)	3/23 (3)	5/20 (3)
Runt	1/17 (1)	1/23 (1)	3/23 (2)	10/20 (7)

*Number of pups with observation/number of litters examined. Number in parenthesis is number of litters affected.
**Both pups with hydronephrosis also had hydroureter and are included in both categories in this table.

Core Classification

Supplementary Data. A Final Report has yet to be submitted and the results of fetal skeletal examination have not yet been reported. The tentative NOEL for maternal and fetotoxicity is 25 mg/kg. Further examination of the effect of Bolero on renal development should be examined in a reproduction study and adequate historical control data for this laboratory should be submitted demonstrating that the findings with respect to renal development are within the normal range.

3. Bolero: Palatability Study By Paired Feeding in the Rat, performed at Life Science Research, Stock, Essex, England, February 11, 1980, submitted by Chevron Chemical Company.

Ten male and ten female Fischer F344 rats were fed diet containing either 60 or 300 ppm of technical Bolero for a period of 6 weeks. A second group of rats was fed a quantity of stock diet equal to the amount of diet/test compound mixture consumed by individual rats of the same sex and similar initial body weight at the 60 and 300 ppm levels. Thus individual untreated rats were "paired" with treated rats for the purpose of achieving similar food consumption. A third group of ten male and ten female rats was allowed to feed ad libitum. Fresh diets were prepared weekly for all groups.

All animals were 4 to 5 weeks old and weighed between 72-92 grams (males) or 70-93 grams (females) at the start of the study. Animals were individually housed and allowed to drink water ad libitum.

Food consumption was measured daily and body weights were recorded twice weekly. After 6 weeks on test, all animals were killed by carbon dioxide asphyxiation. A necropsy was performed on all animals and the adrenals, brain, heart, kidneys, liver, spleen adn thyroids were weighed. The weighed organs were preserved for possible histological examination.

Results:

There were no clinical observations indicative of a compound-related effect. All animals on test including controls showed symptoms of an acute viral injection involving the salivary glands for varying periods of time starting at week 2. These symptoms included "dark, red-rimmed eyes, rales and in some animals a swollen neck." The disease symptoms are similar to that described by Benirschke et al* and considered to be due to a cytomegalovirus infection. Outbreaks of this disease are common in rodent colonies.

There were no mortalities during the course of the study and no gross lesions suggestive of compound toxicity were observed.

Food consumption and body weight gains of paired females were similar to that of the Bolero-treated females with which they were matched. Both groups of females showed consistently lower weight gain and less food consumption than females allowed to feed ad libitum.

The food consumption and body weight gains of paired males were somewhat less than the Bolero-treated males with which they were paired. The animals fed a quantity of diet equal to that consumed by the Bolero treated animals consumed an amount 6-8% less than the treated animals. Both groups of males showed consistently lower weight gain and food consumption than males allowed to feed ad libitum.

The findings in the paired females suggest that palatability may indeed be a problem as no concurrent toxicity was observed and animals consuming similar amounts of test compound were comparable in body weight gain.

The Final Report of this study states "No satisfactory explanation was found to account for the observed differences in food intake between the treated rats and their pair-fed control counterparts" regarding the males. An explanation is also not apparent to this reviewer.

Core Classification

Supplementary data. The study results suggest that unpalatability of Bolero may be a reason for the decreased consumption of diet containing Bolero by female rats. Further explantation should be required regarding the paradoxical effects observed in males.

*Benirschke, K., Garner, F.M. and Jones, T.C. "Pathology of Laboratory Animals", Springer-Verlag, New York, 1978, pp. 188-189

4. Combined Oncogenicity and Chronic Feeding Study in the Rat: Summary Report After Premature Termination After 25 Weeks of Treatment, performed at Life Science Research, Stock, Essex, England, July 30, 1980, and submitted by Chevron Chemical Company.

   Ninety male and 90 female F344 rats received diet containing 0, 3, 15 or 75 mg/kg/day of Bolero in the diet. After 25 weeks, all animals were killed. Food consumption and body weights were recorded weekly during the in-life phase and a gross necropsy was conducted on 15 males and 15 females from each group after sacrifice.

   Results

   Significantly ($p < 0.01$) decreased weight gain was recorded for all treatment groups receiving Bolero. The percentage of decrease ranged from 10 to 25% and appeared to be dose related. Food consumption was also decreased. Two mid-dose males died at week 10; no other mortalities occurred. No clinical observations suggestive of toxicity were noted. No gross pathological observations suggestive of toxicity were noted but the exam (as noted above) was limited to only 15/sex/dose level.

   Due to a reduction in weight gain in each treated group, a decision was made by the sponsor to terminate the study prematurely.

   Core Classification

   A core classification is not applicable to a prematurely terminated study. A palatability problem was suggested for dose levels of 3 mg/kg and greater. No signs of toxicity were observed at any dose level.

5. Combined Oncogenicity and Toxicity Study in Dietary Administration to the Rat, Interim Reports: 0-26 and 0-52 Weeks, performed at Life Science Research, Stock, Essex, England, September 28, 1981 and submitted by Chevron Chemical Company.

   One hundred males and 100 females F344 rats are being administered 0, 20, 100 or 500 ppm of technical Bolero in the diet. The rats are individually housed in cages and test groups are randomly distributed throughout the laboratory space. Feeding is ad libitum and fresh diets are prepared weekly.

   Rats are being observed at least once daily and all rats are palpated at least once weekly. Body weights are recorded weekly for the first 24 weeks and biweekly for the remainder of the study.

Blood samples for clinical pathology were taken from 20 male and 20 female rats prior to study day 0. After 25 and 51 weeks of treatment, blood samples were taken from 10 males and 10 females per dose. Urine samples were collected from the same animals used in blood sampling. After blood sampling at 26 weeks, the sampled animals were killed and subjected to a necropsy and after 52 weeks, the sampled animals were killed, subjected to a necropsy and the following tissues were examined microscopically:

- Adrenal gland
- Bone (sternebrae with marrow)
- Brain (three levels)
- Colon
- Head - nasal cavity
  - nasopharynx
  - oral cavity
  - sinuses
- Heart
- Ileum
- Jejunum
- Kidneys
- Liver
- Lungs and mainstem bronchi
- Lymph nodes - cervical
  - mesenteric
- Mammary glands - posterior
  - anterior
- Oesophagus
- Ovaries
- Pancreas
- Pituitary gland
- Prostate gland
- Duodenum
- Eyes and optic nerve (one only sectioned initially)
- Harderian glands
- Head - middle ears
- Skeletal muscle
- Skin
- Spinal cord (in situ) (two levels)
- Spleen
- Stomach
- Testes
- Thymus
- Thyroid and parathyroid glands
- Tissue masses and suspected tumors and regional lymph nodes
- Trachea
- Urinary bladder
- Uterus (including cervix).

Animals dying during the 52 week period were also examined microscopically. The following organs were weighed from all animals killed after 26 or 52 weeks (or sacrificed in extremis);

- Adrenal glands
- Brain
- Heart
- Kidneys
- Liver
- Lungs
- Ovaries
- Pituitary
- Spleen
- Testes
- Thyroid glands with parathyroids (after formalin fixation for 24 hours).

Results

No treatment-related histological effects are suggested. (However, the number of tissues examined is not reported i.e. it can not be ascertained how many pituitaries, harderian glands, etc. were examined. For the histopathology report to be submitted with the Final Report, it is recommended that the number of tissues examined be reported for each individual tissue and animal.)

No treatment-related gross pathology is suggested.

No treatment-related clinical observations were noted. One male and 4 females died during weeks 0-52. The cause of death of three of these animals was described as "traumatic or accidental" and the remaining two deaths were associated with cerebral lesions. No deaths appear to be treatment-related.

A number of differences between treated and control animals were observed which are likely to be due to poor palatability of diet containing Bolero. A dose related decrease in food consumption was reported for all treated groups compared to controls. The mean total amount of food consumed per animal over the 52 week period was 6038, 5861, 5562 and 5256 for the 0, 20, 100 and 500 ppm male groups, respectively. For females, the picture was similar: 4355, 4200, 4003 and 3843 grams consumed by the 0, 20, 100 and 500 ppm groups respectively. For mid and high dose males and females, food utilization was also somewhat less efficient.

Body weight gains were also decreased in treated groups in a dose related manner. Mean body weight gains for females were reported as 163, 149, 133 and 121 grams per animal for weeks 0-52 for the 0, 20, 100 and 500 ppm groups, respectively. Mean body weight gains for males were reported as 333, 323, 293 and 265 grams per animal for week 0-52 for the 0, 20, 100 and 500 ppm groups, respectively.

Absolute organ weights were decreased after 52 weeks for kidneys, liver, testes, lungs, and heart in treated male animals. Absolute organ weights were decreased in females for ovaries, adrenals, liver, lungs and heart. Absolute brain weights are similar in all groups of male and females, suggesting that decreases in absolute organ weights are related to smaller body weights, which, in turn, are related to decreased food consumption. Absolute thyroid weight in high dose females was significantly ($p < 0.01$) greater than controls.

A number of clinical chemistry and hematology parameters were sporadically different than mean control values: however, only blood urea nitrogen was consistently effected in both males and females after both 25 and 51 weeks. For females, BUN was significantly increased compared to controls in both mid and high dose groups at each sampling interval; for males, BUN was significantly increased compared to control in both the mid dose group and high dose group after 25 weeks and in the high dose group only after 51 week. Although no effect is observed histologically in the kidneys of the limited number of animals available for examination, the possibility that the elevated levels of BUN are associated with an early stage of renal disease can not be ruled out. Other possible explanations for the elevated levels of BUN include decreased fluid intake, decreased renal blood flow and excessive protein catabolism. No consistent effect on plasma or red blood cell cholinesterase was observed, although high dose females were significantly ($p < 0.05$) less than controls after 51 weeks.

No treatment-related effect on urinalysis was observed.

Core Classification

Supplementary Data. As an interim report from a chronic study, only limited information is available regarding subchronic toxicity due primarily to the small number of animals examined grossly and microscopically (10 animals/sex/dose).

Based on the available data, it is recommended that a conservative No Observed Effect Level be provisionally set at 20 ppm based on an effect on BUN at 100 and 500 ppm in both males and females.

6. Oncogenicity Study in the Mouse, performed at Life Science Research, Stock, Essex, England, October 23, 1981 and submitted by Chevron Chemical Company.

Seventy-two B6C3F1 hybrid strain mice per sex per dose level received either 0, 25, 100, 400 or 1600 ppm of Technical Bolero for 104 weeks (males) or 121 weeks (females). Animals were housed 4 animals of the same sex to a cage and were identified by ear-marking. Test diets were prepared weekly. Diet analyses were conducted at the start of the study and at three month intervals.

Animals were observed twice daily for the first two weeks of treatment and once daily for the remainder of the study. All animals were palpated weekly. Body weights were recorded initially, weekly for the first 14 weeks of the study and biweekly for the remainder of the study. Food consumption per cage will be recorded weekly for the first 13 weeks of the study and biweekly thereafter.

After 52 weeks and at terminal sacrifice, blood samples were taken from the retro-orbital sinus of 11 animals per group. Samples were analyzed for hematocrit, hemoglobin concentration, erythrocyte count, total and differential leukocyte count, platelet count and reticulocyte count. Animals sampled at 52 weeks were killed and necropsied. All moribund sacrifices were also necropsied.

After terminal sacrifice, all animals were euthanized by carbon dioxide asphyxiation and necropsied. Brain, heart, kidney, liver, ovaries and testes were weighed at the time of necropsy after both the interim and terminal sacrifices.

The following tissues were examined microscopically for all animals;

Adrenal glands
Bone (stifle joint)
Brain (3 levels)
Cervix
Colon
Duodenum
Eyes and optic nerve
Gall bladder
Harderian glands
Heart: atria
: ventricles
Ileum
Jejunum
Kidneys
Liver
Lungs and main-stem bronchi
Lymph nodes: cervical
: mesenteric
Mammary gland: posterior
: anterior
Middle ear
Nasal cavities and sinuses
Oesophagus
Ovaries
Pancreas
Pituitary gland
Prostate gland
Salivary gland
Sciatic nerve
Skeletal muscle
Skin
Spinal cord (in situ): (2 levels)
Spleen
Stomach: cardia
: fundus
: pylorus
Testes
Thymus or tissue from area
Thyroid and parathyroid gland
Tissue masses and suspected tumours and regional lymph nodes
Trachea
Urinary bladder
Uterus (including cervix)

In addition, samples of any other tissues showing macroscopic abnormality together with any normal contiguous tissue were examined.

A bone marrow smear and a blood smear was taken from each mouse and examined.

Results

No clear clinical signs of compound toxicity was observed in any test group. However, a somewhat lower incidence of abdominal swelling was observed in high dose females (63, 64, 66, 59 and 39 animals with abdominal swelling were observed in the 0, 25, 100, 400 and 1600 ppm groups, respectively) and a somewhat higher incidence of emaciation was observed (18, 14, 17, 15 and 26 animals in the 0, 25, 100, 400 and 1600 ppm groups, respectively). A hunched posture was also observed somewhat more frequently in the high dose females (13, 9, 16, 13 and 29 in the 0, 25, 100, 400 and 1600 ppm groups, respectively). Although decreased abdominal distension, increased emaciation and hunched posture might be associated with administration of 1600 ppm in females, the high background incidence of this findings is noted and the possibility that apparent effects are due to chance can not be eliminated.

High dose females, but not any other dose group had significantly reduced body weight gain. The Organ/Body weight ratios of the brain, heart, liver and kidneys of high dose females were significantly elevated ($p < .001$) at 52 weeks and brain and kidney ratios were also elevated at 121 weeks. Absolute kidney weights were decreased in each male dose group, not in females, after terminal sacrifice. Organ/Body weight ratios of the heart and liver were significantly elevated in high dose males; for kidneys, the corresponding ratio was decreased in the 100, 400 and 1600 ppm males. For high dose females, the kidney body weight ratio is increased ($p < .001$).

Terminal sacrifice hematology was unremarkable in either sex.

Gross pathological findings included an increased incidence of pale foci of the lung and pale livers in high dose males after terminal sacrifice. High dose females had an increased incidence of pale foci of the lung after terminal sacrifice.

Non-neoplastic histopathologic changes related to treatment were found only in the liver and lung. An increased incidence of hepatocytic (glycogen) pallor was observed in females treated at dose levels of 100, 400 and 1600 ppm and males treated at 100 ppm after terminal sacrifice. High dose males and females also showed an increase incidence of fatty vacuolization (moderate or marked mid-zonar). Moderate or marked fine fatty periacinar, vacuolization, was observed in high dose males. High dose males and females both showed an increased incidence of focal epithelialization of the alveolar walls with associated macrophages.

No neoplastic changes appeared to be related to treatment. Adenomas and carcinomas of the Harderian gland appeared to be increased in females (1, 2, 6, 5 and 7 for the 0, 25, 100, 400 and 1600 ppm groups, respectively). However, the control incidence of the tumor is lower than expected for females of this strain and the possibility that the incidence is due to chance can therefore not be eliminated.

Core Classification

Supplementary data. The number of animals examined for each particular tissue type has not been reported and it is not possible to determine precisely which tissues were examined for each animal on test. If this information is made available in tables on a per animal basis an upgrading of the study should be possible.

No neoplastic effect was found that could be associated with exposure to test compound at levels as high as 1600 ppm in the B6C3F1 mouse. Although not a chronic toxicology study, it is noted that a NOEL for systemic effects of 25 ppm is suggested, based on histopathologic changes observed in the liver of females.

TS-769:th:TOX/HED:GJBurin:12-8-81:card 2:Retype 12-10-81