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

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JAN 23 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Robert J. Taylor, PM #25
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Registration Division (TS-767C)

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THRU: Theodore M. Farber, Ph.D. *Theodore M. Farber*
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Hazard Evaluation Division (TS-769C) *1-23-85*

SUBJECT: Metribuzin Registration Standard

Attached is the Toxicology Chapter for the Metribuzin Registration Standard. Included are the following:

1. Summary of toxicology data for Metribuzin.
2. Updated TOX "One-liners".
3. Data Summary Table A, which indicates TOX data gaps.
4. Tolerance reassessment.
5. Bibliography
6. Evaluations of all studies reviewed during the course of this standard.

Stephen C. Dapson 1/22/85

Stephen C. Dapson, Ph.D.
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TOXICOLOGY DATA SUMMARYAcute Toxicity

An acute oral toxicity study (DuBois and Kinoshita, 1969) in the rat places this compound in Toxicity Category III with LD₅₀ of 2,200 mg/kg reported for the male and 2,345 mg/kg for the female. Data submitted for the mouse, rabbit, cat and chicken (Kimmerle et al, 1969) also indicate acute oral LD₅₀s greater than 500 mg/kg for these species whereas the LD₅₀ in the guinea pig was found to be 274.5 mg/kg. An acute inhalation toxicity study found an LC₅₀ of >20mg/l (Toxicity Category IV). Eye irritation testing in the rabbit found this compound not to be an irritant (Toxicity Category IV) and a dermal irritation study found this compound to have little potential for dermal irritation (PIS= 0.33/8.0). Metribuzin technical should thus be considered Toxicity Category III for oral toxicity and Toxicity Category IV for all other forms of toxicity.

Teratology

One teratology in the rat and three teratology studies in rabbits have been submitted for metribuzin. A teratology study in rats (Machemer, 1972) was conducted using 4 dosages of SENCOR, 5, 15, 50 and 100 mg/kg/day with treatment of pregnant females from day 6 to 15 of gestation. There was evidence of minimal maternal toxicity at the high dose level in the form of reduced maternal body weight gain. No evidence of fetal toxicity or teratogenicity was noted at the dose levels used in this study. This study is classified as Core-Supplementary Data.

Three rabbit teratology studies were conducted at IBT (Ladd 1971, Ladd and Smith 1972a) and were found to be Invalid by the Canadian government. An additional study in the rabbit (Unger and Shellenberger, 1981) was a replacement for the IBT Study No. J-9027. This study indicated that SENCOR in the dosages tested caused maternal toxicity without significant fetal toxicity at the high dose (135 mg/kg/day) with no maternal or fetal effects evident at the low dose (15 mg/kg/day). No evidence of teratogenicity was observed at the dose levels tested. The NOEL for maternal and fetal toxicity is 15 mg/kg/day with a LOEL of 45 mg/kg/day for maternal toxicity. This study is classified as Core-Guidelines.

Reproduction

A multigeneration (3 generation) reproduction study in rats (Loser and Siegmund, 1974) employed three dosages of BAY

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94 337 (35, 100 and 300 ppm, equivalent to 3.5, 10 and 30 mg/kg) mixed in the animal feed. There was no evidence of compound related reproductive or fertility effects in the three generations of rats examined. The high dose (300 ppm) did not induce any toxicity as is required by CORE, however the NOEL for reproductive effects can be set at 300 ppm (HDT). This study is classified as Core-Supplementary Data.

Chronic and Oncogenicity

Two mouse oncogenicity studies are available. The first study (Smith and Gordon, 1972 a and b) was conducted at IBT and was found to be Invalid in a review by the Canadian Government. The second study (Hayes et al, 1981), a replacement for IBT Study No. B-9069, was a two year feeding study in the mouse employing groups of 50 male and 50 female mice. They were given diets containing 0, 200, 800 or 3200 ppm Metribuzin (equivalent to 0, 28, 111 and 435 mg/kg/day for males and 0, 35, 139 and 567 mg/kg/day for females). Minimally toxic effects were observed at the high dose level in the form of increased liver weight and changes in the hematocrit and hemoglobin measurements. Although some increase in the number of tumor bearing animals was observed in low and mid dose females, significant increases in the incidence of specific tumor types were not observed at any dose level. It was concluded that under the conditions of the test, did not increase the incidence of tumors in mice. This study is classified as Core-Guidelines.

In a two year feeding study in rats (Loser and Mohr, 1974) 4 doses of BAY 94 337 were utilized (25, 35, 100 and 300 ppm, equivalent to 1.25, 1.75, 5, and 15 mg/kg/day) mixed in the animal feed. Analysis of the neoplastic histopathological observations indicated a statistically significant ($p < .05$) increase in the incidence of adenoma of the liver bile duct and pituitary gland in the 300 ppm females. Non-neoplastic histopathological observations showed a statistically significant increase in liver "changes in the nucleus" in the females of the 300 ppm test group. However, not enough animals were examined histopathologically in the other 3 dosage groups to allow a judgement to be made in regard to a dose response effect of the chemical for either neoplastic or nonneoplastic lesions. Further data must be supplied by the registrant in the form of histopathological examinations of the animals not previously examined in the other 3 dosage groups along with historical control data on the incidence of these tumors in this particular strain of rat. No systemic NOEL can be determined without the additional histological data. This study is classified as Core-Supplementary Data.

A 2 year feeding study (Loser and Mirea, 1974) was conducted in groups of 4 male and 4 female beagle dogs using three dosage levels (25, 100 and 1500 ppm, equivalent to 5, 15, 50 and 150 mg/kg/day) of BAY 94 337. Decreased body weight of the animals at the high dose, increased relative liver weight along with the related clinical tests and the histopathological findings also indicate that a dose level of 1500 ppm is associated with toxicity. Histopathological observations included evidence of liver parenchymal necrosis, interstitial infiltration and other changes not observed in the control, 25 and 100 ppm test groups. The 2 lower doses did not show any compound related effect. The NOEL for this study is 100 ppm with a LOEL of 1500 ppm (HDT). This study is classified as Core-Minimum Data.

Subchronic

Two subchronic (90 day) feeding studies were conducted in rats. The first (Loser et al, 1969) used doses of 50, 150, 500 and 1500 ppm (equivalent to 5, 15, 50 and 150 mg/kg/day). Based on the data provided in this study the systemic NOEL is below 50 ppm since the increase in liver weight was statistically significant at all 4 dose levels in the females. This study is classified as Core-Supplementary Data since no NOEL could be established for this study, no protocol was provided for the pathological examinations and only limited organs and small numbers of animals were used for histopathological studies.

The second subchronic study in rats (Loser et al, 1970) used doses of BAY 94 337 of 10, 25 and 60 ppm. An increase in liver weight was observed in the females, statistically significant at the 60 ppm and a trend of an increase was observed in the males. Histopathology that was provided was unremarkable between test groups. A systemic NOEL of 25 ppm can be set as determined by the increase in liver weight in the 60 ppm females. The 60 ppm dose is the LOEL for this study. This study is classified as Core-Supplementary Data based on the limited organs and the small number of animals examined for histopathology and the limited clinical chemistry.

An IBT subchronic dog study (Lindberg and Richter, 1970) was found to be valid in a review by the Canadian Government. In a subsequent IBT Evaluation Report prepared for the Agency, it concluded that this study had been compromised because of the incomplete gross and histopathological data and the absence of clinical observations of signs of toxicity and that a NOEL for subchronic toxicity could not be determined based on this study. It was noted also that a dose-related increase in liver weight and the liver to body weight ratio was found in treated animals.

Mutagenicity

The selection of assays for a mutagenicity battery should consider the nature of the test chemical, and a justification for test selection should be provided.

Minimum requirements are:

1. Microbial point mutation tests
2. Mammalian point mutation tests in vitro
3. In vivo cytogenetics tests in mammals with either heritable translocation or dominant lethal studies.
4. Tests for primary DNA damage such as sister chromatid exchange or unscheduled DNA synthesis assays.

The mutagenicity studies submitted by the registrant (Machemer and Lorke, 1974a, 1974b, 1975, 1976; Inukai and Iyatomi, 1977; Shirasu et al, 1978). The first requirement is partially satisfied by the Inukai and Iyatomi (1977) and Shirasu et al (1978) reports. These microbial point mutation assays did not indicate a mutagenic potential for metribuzin in the test systems utilized. The other 4 studies done by Machemer and Lorke (1974a, 1974b, 1975 and 1976), although limited to only one dose level, indicated that SENCOR does not induce dominant lethal mutations in mice or chromosomal aberrations in hamster spermatogonia at dose levels of 300 mg/kg and 100 mg/kg, respectively. These studies satisfy the third requirement mentioned above. Additional mutagenicity testing is required to satisfy the other requirements in this area.

Metabolism

A metabolism study was conducted in rats with oral dosing of radiolabeled SENCOR (Flint et al, 1973) evaluating excretion and tissue residue levels as well as the pattern of metabolites. The excretion studies found sex related differences with the males excreting the radiolabel primarily in the feces and the females excreting the label primarily in the urine. However, an inadequate number of animals was used in this study (one male and one female in one study and two males in another study). Tissue distribution studies also suggest slight sex related differences in distribution up to the 28 hour interval (after administration) with similar patterns of reduction in residue levels after that time point (however, the females tended to present with higher overall levels at all time points measured). The investigators found a metabolic scheme for SENCOR in rats that was similar to what was found in to an earlier study in soybeans. The metabolites that were identified were the deaminated, diketo and deaminated diketo parent compound. Due to an inadequate number of animals and other deficiencies, these studies were classified as Supplementary Data.

A metabolism study was conducted in 4 dogs using oral dosing of radiolabeled SENCOR (Khsawinah et al, 1972) evaluating absorption, distribution and metabolites. Analysis of blood samples showed a peak level at 4 hours. The excretion study data indicated that 52 to 60% of the administered dose was eliminated in the urine and 30% in the feces. The true patterns of metabolites could not be accurately determined. However, it appeared that the same metabolites found in an earlier study in soybeans and a concurrent study in rats were found in this study. Due to deficiencies including the small number of animals and the use of only a single dose level, this study is classified as Supplementary Data.

Toxicology Data Gaps

The available studies satisfy data requirements for the mouse oncogenicity, chronic nonrodent study and rabbit teratology studies and partially satisfy the requirements for mutagenicity. The rat teratology, reproduction and chronic rat studies are not completely adequate for regulatory purposes and thus should be considered data gaps. The upgrading of one or more of these studies may be possible upon the submission of additional data. Acceptable metabolism and acute inhalation studies must also be submitted.

Data Requirement	Composition ^{1/}	Use Patterns ^{2/}	Does EPA have Data to Satisfy This Requirements? (Yes, No or Partially)	Bibliographic Citation	MRID#	Must Addition Data Be Submitted Under FIFRA 3(c)(2)(ii)?
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SUBCHRONIC TESTING:

82-1 - 90-Day Feeding - Rat	TGAI	A, B	N/A	00106161 and 650181-06		No
82-2 - 21-Day Dermal Dog	TGAI	A, B	N/A	00106162		No
82-3 - 90-Day Dermal	---	---	N/A	---		No
82-4 - 90-Day Inhalation - Rat	---	---	N/A	---		No
82-5 - 90-Day Neurotoxicity - Human/Mammal	---	---	N/A	---		No

CHRONIC TESTING:

83-1 - Chronic Toxicity - Rat	TGAI	A, B	Partially*	00061261		Yes
Dog	TGAI	A, B	Yes	00061260		No

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83-2 - Oncogenicity Study -

Rat - See chronic rat
Mouse

TGAI

A, B

Yes

00061256
and
00079527

No

83-3 - Teratogenicity -
Rat
Rabbit
83-4 - Reproduction -
3 generation

TGAI
TGAI

A, B
A, B

Partially*
Yes

00061257
00087796

Yes
No

MUTAGENICITY TESTING:

84-2 - Gene Mutation

PAI

A, B

Partially*

00086770
00109254

Yes

84-2 - Chromosomal Aberration

PAI

A, B

Yes

00086766
00086765
00086767
00086768

Yes

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84-2 - Other Mechanisms of Mutagenicity

PAI

A, B

No

Yes

TABLE A

GENERIC DATA REQUIREMENTS FOR Metribuzin (BAY 94 337, SENCOR, LEXONE)

Data Requirement	Composition ^{1/}	Use Patterns ^{2/}	Does EPA Have Data To Satisfy This Requirements? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Sect 3(c)(2)(B)? ^{3/}
SPECIAL TESTING:					
85-1 General Metabolism	Rat PAIRA	A, B	Partially *	00045265	Yes
	Dog PAIRA	A, B	Partially *	00045264	Yes
85-2 - Domestic Animal Safety	—	—	N/A		No

Composition: Material to be tested is technical grade unless otherwise specified in footnotes. PAI= Pure Active Ingredient.

The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C = Aquatic, Food Crop; D = Aquatic, Non-Food; E = Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor; IP = Industrial Preservative.

*** This study was Core Classified as Supplementary Data.**

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Metribuzin Tolerance Reassessment

A previous acceptable daily intake (ADI) for Metribuzin was based on a NOEL of 300 ppm in a 2 year chronic rat feeding study (Loser and Mohr, 1974). On 1/25/79, using a subsequent 2 year chronic dog feeding study (Loser and Mirea, 1974) which presented with a lower NOEL of 100 ppm, the ADI was recalculated. The ADI (with a safety factor of 100) was determined to be 0.025 mg/kg/day with a maximum permissible intake (MPI) of 1.5 mg/day for a 60 kg adult human. The current theoretical maximum residue concentration (TMRC) for Metribuzin based on established tolerances is 0.3508 mg/day for a 1.5 kg diet and the percent of the ADI currently utilized is 23.39 (see attached computer printout).

The previously mentioned 2 year chronic rat feeding study was re-reviewed under CORE and classified as Core-Supplementary Data since no systemic NOEL could be determined due to a lack of sufficient data. An increased incidence of liver histopathology ("changes in the nucleus") was observed in the high dose group. There also appeared to be an increase in the incidence of adenoma of the liver bile duct and pituitary gland in the 300 ppm females. However, not enough animals were examined in the other 3 dosage groups to allow an adequate determination of potential cancer risk or to establish a NOEL for nonneoplastic liver lesions.

The 2 year chronic dog feeding study was re-reviewed in this standard and the NOEL was found to be 100 ppm. The Agency recommends that the ADI continue to be based on this chronic dog study. Upon the submission of an additional chronic rat study (or the upgrading of the existing one), the ADI can then be re-evaluated.

File last updated 6/25/82

ACCEPTABLE DAILY INTAKE DATA

Dose	NOEL	S.F.	ADI	MPI
mg/kg	ppm		mg/kg/day	mg/day (60kg)
2.500	100.00	100	0.0250	1.5000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day (1.5kg)
Potatoes (127)	0.600	5.43	0.04884
Soybeans (oil) (148)	0.100	0.92	0.00138
Sugar, cane/beet (154)	0.100	3.64	0.00546
& Dairy Products (93)	0.050	28.82	0.02146
Eggs (54)	0.010	2.77	0.00042
Asparagus (5)	0.050	0.14	0.00011
Corn, all types (38)	0.050	2.51	0.00188
Peas (117)	0.100	0.69	0.00104
Tomatoes (163)	0.100	2.87	0.00431
Lentils (83)	0.050	0.04	0.00003
Meat, inc poultry (89)	0.700	13.85	0.14540
Barley (8)	0.750	0.03	0.00034
Wheat (170)	0.750	10.36	0.11658

MPI 1.5000 mg/day (60kg) THRC 0.3472 mg/day (1.5kg) % ADI 23.15

Current Action 4E3112

CROP	Tolerance	Food Factor	mg/day (1.5kg)
Soybeans (oil) (148)	0.100	0.92	0.00138
Carrots (24)	0.300	0.48	0.00216

MPI 1.5000 mg/day (60kg) THRC 0.3508 mg/day (1.5kg) % ADI 23.39

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(was combined with IBT No. J 1851)

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↑ SAME ↓ (different MRID #'s Submission #'s)

15

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MRID # 00087796

The following have no bibliographic reference

Chemagro # ~~33045~~ 33045 Acute Oral LD₅₀ - Guinea Pig
3/20/72

Accession No. 112032

Chemagro # 32862 Primary eye irritation - Rabbit
3/21/72

Accession No. 112032

also Primary dermal irritation - Rabbit
under same numbers

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104 CHEM NO. 33 D. MICHAELSON (Vol. 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100)

Study/Lab/Study #/Date	Material	Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	TOX Category	CORE Grade/Doc. No.
Teratology - rabbit; IBT; J-233; 11/12/71; MRID #	Technical		Teratogenic NOEL > 30 mg/kg (HDT) CANADA INVALID combined with IBT # J-1851		001151
Teratology - rabbit; IBT; J-1851; 11/21/72; Mobay # 35159; MRID # 00061256	Technical	112892	Maternal toxicity NOEL > 30 mg/kg (HDT) Terata NOEL > 30 mg/kg (HDT) CANADA INVALID		001148 001151
Teratology - rabbit; IBT; #J-9027; 5/18/71; Mobay # 30172; MRID # 00061254;	Technical; Batch # 9059332	112892	Maternal toxicity NOEL > 15 mg/kg (HDT) Terata NOEL > 15 mg/kg (HDT) CANADA INVALID		001148 001151
Teratology - rabbit; Mobay; MRI # 7212-B; 10/30/81; Mobay # 80051; MRID # 00087796	Technical; Purity= 93.0% Ref. # 77-297-50	246397	Teratogenic NOEL > 135 mg/kg/day (HDT) Maternal Toxic NOEL = 15 mg/kg/day Maternal Toxic LOEL = 45 mg/kg/day Fetal Toxic NOEL = 15 mg/kg/day Fetal Toxic LOEL = 45 mg/kg/day		Guideline 001761
Teratology - rat; Bayer AG; #3678; 9/29/72; Mobay # 35073; MRID # 00061257	Technical; Consignment 1603/71, Batch 17, Rcd. 6/71 Purity= 99.5%	112892	Maternal toxicity NOEL > 100 mg/kg (HDT) Terata NOEL > 100 mg/kg (HDT)		001148 Supplementary
3 Generation reproduction - rat; Bayer AG; #4889; 9/24/74; Mobay # 41818; MRID # 00061262	Technical; Sdg. 1603/71 Purity= 99.5%	112891	Reproductive NOEL > 300 ppm (HDT) Maternal toxicity NOEL > 300 ppm (HDT)		001147 001148 Supplementary
90 Day feeding - rat; Bayer AG; #1719; 11/20/69; Mobay # 26488; MRID # 00106161	Technical	112032	Systemic NOEL = 150 ppm Systemic LEL = 500 ppm Re-review: Systemic NOEL below 50 ppm (LDT), see next study		001146 Supplementary

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Study/Lab/Study #/Date	Material	Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	TOX Category	CORE Grade/Doc. No.
90 Day feeding - rat; Bayer AG; #2150; 7/6/70; Mobay # 27908; MRID #	Technical	112032	Systemic > 60 ppm (HDT) Re-review: Systemic NOEL = 25 ppm Systemic LOEL = 60 ppm (HDT)		001146
90 Day feeding - dog; IBF, #C-7760; 1/9/70; Mobay # 26488; MRID # 00106162	Technical; Batch # 9050332		Systemic NOEL = 150 ppm Systemic LOEL = 500 ppm <u>CANADA VALID</u>		001146 001151 Supplementary
2 Year feeding - dog; Bayer AG; #4887; 9/24/74 ; Mobay # 41814; MRID # 00061260	Technical; Batch 1603/71 Purity= 99.5%	112892	Systemic NOEL = 100 ppm Systemic LOEL = 1,500 ppm (HDT); weight reduction, increased mortality, hematological changes, liver and kidney damage)		001147 001148 Supplementary
2 Year feeding - rat; Bayer AG; #4888; 9/25/74 ; Mobay # 41816; MRID # 00061261	Technical; Batch 1603/71 Purity= 99.5%	112891	Systemic NOEL > 300 ppm (HDT) Oncogenic NOEL > 300 ppm (HDT) Re-review: Systemic NOEL and oncogenic potential could not be determined		001147 001148 Supplementary
18 Month oncogenic-mice; IBT; #B-9069 ;8/15/72; Mobay # 34481; Pathology Addendum; 12/21/73; Mobay # 34481a; MRID # 00061256 and 00079527	Technical; Batch # 9050332 and 1050265	112892	Oncogenic NOEL > 2500 ppm <u>CANADA INVALID</u>		001147 001148 001151
Oncogenic - mice; Mobay ; # 218, #78CCM01; 10/30/81; Mobay # 80050; MRID # 00087795	Technical; Batch # 77-297-50 Purity= 92.9%	246397	Did not increase the incidence of tumors in test conditions. However apparent increases in tumor incidences noted must be evaluated with results from second species.		Guideline 001761 003911

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Study/Lab/Study #/Date	Material	Accession No.	Results: LD ₅₀ , LC50, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Metabolism - rat; Chemagro; #33366; 7/5/73 ; Mobay # 33366; MRID # 00045265	14C and 3H SENCOR and 14C SENCOR		Excretion was essentially through the urine and feces. No radioactive material was detected in expired gases		001146 Supplementary
Metabolism - dog; Chemagro; #33361; 5/1/72 ; Mobay # 33361; MRID # 00045264	14C Sencor		60% excreted in urine 30% excreted in feces		001146 Supplementary
Mutagenic- dominant lethal - mice; IBT; #E-8922; 6/14/71; Mobay #; MRID #	Technical	112032	Not a mutagen at 20 mg/kg <u>CANADA INVALID</u>		001146 001151
Mutagenic - dominant lethal - mice; Bayer AG; #5523; 7/10/75 ; Mobay # 45023; MRID # 00086767	Technical; Batch 6/71 Consignment 1603/71 Purity= 99.5%	246226	Negative for dominant lethal effects in male treated mice at 300 mg/kg		Acceptable 001762
Mutagenic - dominant lethal - mice; Bayer AG; #6110; 5/19/76 ; Mobay # 49068; MRID # 00086768	Technical; Batch 6/71 Consignment 1603/71 Purity= 99.5%	246226	Negative for dominant lethal effects in male treated mice at 300 mg/kg		Acceptable 001762
Mutagenic - dominant lethal - mice; Bayer AG; #4942; 10/5/74 ; Mobay # 43068; MRID # 00086766	Technical; Batch 6/71 Consignment 1603/71 Purity= 99.5%	246226	Negative for dominant lethal effects in female treated mice at 300 mg/kg/day		Acceptable 001762

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Study/Lab/Study #/Date	Material	Accession No.	Results: LD50, IC50, PIS, NOEL, LEL	TOX Category	CORE Grade/Doc. No.
Mutagenic - cytogenetic-chinese hamster; Bayer AG; #4961; 10/7/74; Mobe; # 43067; MHID # 00086765	Technical; Batch 17 Consignment 1603/71 Purity= 99.5%	246226	Negative for chromosomal aberrations at 100 mg/kg in treated mice		Acceptable 001762
Mutagenic - <u>S. typhimurium</u> and <u>B. subtilis</u> ; Nitokuno Agric Chem. Instit.; #67; 12/19/77; Mobay # 54127; MRID # 00086770	Technical; Purity= 93.7%	247885	The results should be considered with other rec assay and reversion assay data such as that provided in the 1978 study.		002778 Acceptable
Mutagenic - <u>S. typhimurium</u> , <u>E. coli</u> , and <u>B. subtilis</u> ; Inst. Environ. Tox.; 8/17/78; Mobay # 66748; MRID # 00109254	Technical; Purity= 93.3%	247885	These results should be considered with those described in the 1977 mutagenic report. No mutagenic activity was observed.		002778 Acceptable
Mutagenic - mice; micro-nucleus test; Bayer AG Inst. of Toxicology; #10718; 10/3/82	DIC-1468 (Sencor Active ingredients)	251219	Negative response when the test compound was administered twice orally with a stomach tube at an interval of 24 hours. (Tested at 2 x 200 and 2 x 400 mg/kg dose levels) The assay was not performed properly in accordance with the accepted procedures.		Unacceptable 003865

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Study/Lab/Study #/Date	Material	Accession No.	Results: LD ₅₀ , LC ₅₀ , PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenic - mitotic gene conversion in <i>Saccharomyces cerevisiae</i> D. Siebert and E. Lemperle; Mutation Res. 22 (1974), 111-120	Sencor	251219	The test compound at 1000 ppm did not induce a significant increase in the conversion frequenc (convertants/106 survivals) neither in the ade 2 nor the trp 5 locus of the diploid strain D 4 of of <i>saccharomyces cerevisiae</i> . (tested at a single dose of 1000 ppm without metabolic activation) The assay was not performed properly in accordance with the accented procedures.		Unacceptable 003865
Dermal irritation - human	Technical		No irritation (24 hrs) (M)	III	001146
Acute oral LD ₅₀ - rat; 6/3/69; Mobay # 25118	Technical; in 20% ethanol and 80% PPG; Batch # 9050332		LD ₅₀ = 1985.9 mg/kg (male) LD ₅₀ = 1937.0 mg/kg (female)		001146
Acute oral LD ₅₀ - guinea pig; 6/3/69; Mobay # 25118	Technical; in 20% ethanol and 80% PPG; Batch # 9050332		LD ₅₀ = 198.3 mg/kg (male)		001146
Acute oral LD ₅₀ - rat; Bayer AG; #1574; 9/12/69; Mobay # 25942; MRID # 00106158	Technical	112032	LD ₅₀ = 2200 mg/kg (male) LD ₅₀ = 2345 mg/kg (female)		001146
Acute oral LD ₅₀ - mice; Bayer AG; #1574; 9/12/69; Mobay # 25942; MRID # 00106158	Technical	112032	LD ₅₀ = 698 mg/kg (male) LD ₅₀ = 711 mg/kg (female)		001146

Study/Lab/Study #/Date	Material	Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	TOX Category	CORE Grade/Doc. No.
Acute oral LD50 - guinea pig; Bayer AG; 1574; 9/12/69; Mobay # 25942; MRID # 00106158	Technical	112032	LD50 > 250 mg/kg (approximately) (male)		001146
Acute oral LD50 - rabbit; Bayer AG; #1574; 9/12/69 ; Mobay # 25942; MRID # 00106158	Technical	112032	LD50 > 500 mg/kg		001146
Acute oral LD50 - cat; Bayer AG; #1574; 9/12/69 ; Mobay # 25942 MRID # 00106158	Technical	112032	LD50 > 500 mg/kg		001146
Acute oral LD50 - chicken; Bayer AG; #1574; 9/12/69 ; Mobay # 25942; MRID # 00106158	Technical	112032	LD50 > 1,000 mg/kg		001146
Acute oral LD50 - guinea pig; Chemagro; 3/20/72; Mobay # 33045	Technical	112032	LD50 = 274.5 mg/kg		001146
Acute dermal LD50 - rabbit; Chemagro; 4/10/72; Mobay # 33123	Technical	112032	LD50 > 20 gm/kg (male and female)		001146
Acute dermal LD50 - rat; Chemagro; 4/10/72; Mobay # 33123	Technical	112032	LD50 > 20 gm/kg (male and female)		001146

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Study/Lab/Study #/Date	Material	Accession No.	RESULTS: LD50, LC50, PIS, NOEL, LEL	LVA Category	WHILE WAIVER/ Doc. No.
Acute inhalation LC50 - rat; Chemagro; 1/19/72; Mobay # 31931	Technical	112032	LC50 > 20 mg/L/1 hour		001146
Acute intraperitoneal LD50 - rat; Bayer AG; #1574; 9/12/69 ; Mobay # 25942; MRID # 00166158	Technical	112032	LD50 = 363 mg/kg (male and female)		001146
Acute intraperitoneal LD50 - mice; Bayer AG; #1574; 9/12/69 ; Mobay # 25942; MRID # 00106158	Technical	112032	LD50 = 247 (male) LD50 = 275 (female)		001146
Primary dermal irritation - rabbit; Chemagro; 3/21/72; Mobay # 32862	Technical	112032	PIS = 0.33/8.0		001146
Primary eye irritation - rabbit; Chemagro; 3/21/72; 3/21/72	Technical	112032	Not an eye irritant		001146
Acute oral LD50 - rat; Chemagro; #29347; 2/9/71	DADK Metabolite Control No. 70-109-22	112032	LD50 = 1,100 mg/kg (female)		001146
Acute oral LD50 - rat; Chemagro; #31656; 12/21/71	DA Sencor 50% WP (metabolite)	112032	275 < LD50 < 300 mg/kg		001146
Acute oral LD50 - rat; Chemagro; #31656; 12/21/71	DK Sencor (metabolite)	112032	600 < LD50 < 900 mg/kg		001146

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Study/Lab/Study #/Date	Material	ACCESSION No.	RESULTS:	Category	Guideline Minimum 001145
Primary eye irritation - rabbit	4-Amino-6-(1,1-dimethyl-ethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one 75%	3125-325	No corneal opacity or iris irritation, discharge present in 4/6 animals, but all irritation had cleared by day 4.	III	Guideline
Acute oral LD ₅₀ - rat; Dupont Haskell Lab; HLR-315-78	Lexone DF (75% a.i.)		LD ₅₀ = 2795 mg/kg (male) dyspnea, weakness, weight loss	III	Minimum 001145
Acute dermal LD ₅₀ - rabbit; Dupont Haskell Lab; HLR-287-78; 6/2/78	Lexone 75 DF 84% technical		LD ₅₀ > 7500 mg/kg (male) mild to moderate skin irritation	III	Minimum 001145
Primary eye irritation - rabbit; Dupont Haskell Lab; HLR108-78; 3/17/78	Lexone 75 DF 84% technical		Keratitis and conjunctivitis persisting at 72 hours	I	Minimum 001145
Primary dermal irritation - guinea pig; Dupont Haskell Lab; HLR443-78; 8/4/78	Lexone 75 DF 84% technical		Mild irritation when tested as a 20% suspension		Guideline 001145
Dermal sensitization - Guinea pig; Dupont Haskell Lab; HLR-443-78	Lexone DF (75% a.i.)		Not a sensitizer		Guideline 001145
Primary dermal irritation - rabbit; Dupont Haskell Lab; HLR-98-78; 3/17/78	Lexone 75 DF 84% technical		Not a skin irritant	IV	Minimum 001145

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Study/Lab/Study #/Date	Material	Accession No.	results: LD50, LC50, PIS, NOEL, LEL	Category	Doc. No.
Primary eye irritation - rabbit; Stanley Res; #68534; 2/22/80	Sencor 75%	125325	No corneal opacity or iris irritation Discharge present in 4/6 animals with clearing by day 4	III	Guideline 001149
Primary eye irritation - rabbit; Stanley Res; #68535; 2/22/80	Sencor 75%	3125325	No corneal opacity or iris irritation Erythema and discharge with clearing by day 4	III	Guideline 001149
Acute oral LD50 - rat; Mobay; #78-R-020; 9/25/78; Mobay #66552	Sencor 75 WG 75% AI		LD50 = 2379 mg/kg (male) LD50 = 2794 mg/kg (female) Tremor, convulsion, tremor, lacrimation	III	Guideline 001150
Acute dermal LD50 - rabbit; Mc Y; #78-R-020; 9/19/78; Mobay #66553	Sencor 75 WG 75% AI		LD50 > 5,000 mg/kg (male & female) Single dose tested	III	Guideline 001150
Primary eye irrit.- rabbit; Mobay; #78-R-020; 9/25/78; Mobay #66554	Sencor 75 WG 75% AI		Corneal opacity in 5/6 animals (unwashed eyes) with clearing by day 7 Irritation of the iris and conjunctivae persisted at 7 days	II	Minimum 001150
Primary dermal irritation - rabbit; Mobay; #78-R-020; 9/25/78; Mobay #66554	Sencor 75 WG 75% AI		PIS = 0.17/8.0 slight erythema	IV	Guideline 001150
Acute inhalation LC50 - rat; Mobay; # 68-22; 9/25/78; Mobay #66555	Sencor 75 WG 75% AI		LC50 > 20 mg/L/1 hour (male & female)	IV	Supplementary 001150
Acute oral LD50 - rat; Chemagro Lab	Lexone 4L		LD50 = 2890 mg/kg		001145
Acute dermal LD50 - rabbit; Chemagro Lab	Lexone 4L		LD50 > 7500 mg/kg		001145

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LD50, LC50, PIS, NOEL, LEL, LFL, Category, Doc. No.

Study/Lab/Study #/Date	Material	ACCESSION No.	LD50, LC50, PIS, NOEL, LEL, LFL, Category	Doc. No.
Primary dermal irritation - rabbit; Chemagro Lab	Lexone 4L		PIS = 3.2/8.0	001145
Primary eye irritation - rabbit; Chemagro Lab	Lexone 4L		Irritant to the eyes	001145
Acute oral LD50 - rat; Chemagro Lab	Sencor 4F		LD50 > 500 mg/kg	001145
Acute dermal LD50 - rabbit; Chemagro Lab	Sencor 4F		LD50 > 20 gm/kg	001145
Acute inhalation LC50 - rat; Chemagro Lab	Sencor 4F		LC50 > 1920 ug/L	001145
Primary dermal irritation - rabbit; Chemagro Lab	Sencor 4F		Not an irritant	001145
Primary eye irritation - rabbit; Chemagro Lab	Sencor 4F		Severe ulcerations of the conjunctivae	001145
Acute oral LD50 - rat; Chemagro Lab; Mobay #26014	70% WP		LD50 > 1,400 mg/kg (females)	001146
Acute oral LD50 - rat; Chemagro; #29987; 4/29/71	70% WP	112032	LD50 > 2,000 mg/kg (male)	001146
Acute dermal LD50 - rabbit; Chemagro #29987; 4/29/71	70% WP	112032	LD50 > 20 gm/kg	001146
Acute inhalation LC50 - rat; Chemagro; #29987; 4/29/71	70% WP	112032	LD50 > 160 mg/l/1 hour	001146

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Study/Lab/Study #/Date	Material	Accession No.	Results:		TOX Category	CORE Grade/ Doc. No.
			LD ₅₀ , LC ₅₀ , PIS, NOEL, LEL	LD ₅₀ , LC ₅₀ , PIS, NOEL, LEL		
Acute oral LD ₅₀ - rat; Chemagro; #31936; 1/2/72	50% WP	112032	LD ₅₀ = 4,000 mg/kg (male) LD ₅₀ = 4,753 mg/kg (female)			001146
Acute dermal LD ₅₀ - rabbit; Chemagro; 4/10/72; Mobay #33123	50% WP	112032	LD ₅₀ > 20 gm/kg (male and female)			001146
Acute dermal LD ₅₀ - rat; Chemagro; #33123; 4/10/72	50% WP	112032	LD ₅₀ > 20 gm/kg (male and female)			001146
Acute Inhalation LC ₅₀ - rat; Chemagro; # 31931; 1/19/72	50% WP	112032	LC 50 > 20 mg/L/1 hour			001146 001145
Primary dermal irritation - rabbit; Chemagro; #32862; 3/21/72	50% WP	112032	PIS = 0.33/8.0			001146
Primary eye irritation - rabbit; Chemagro; #32862; 3/21/72	50% WP	112032	Not an eye irritant			001146

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GENERIC DATA REQUIREMENTS FOR Mutribuzin (BAY 94 337, -SENCOR, LEXON)

Does EPA have Data
to Satisfy This
Requirements? (Yes,
No or Partially)

Use
Patterns^{2/}

Composition^{1/}

Bibliographic
Citation

MRID #

Must Additional
Data Be Submitted
Under FIRPA Section
3(c)(2)(B)?^{3/}

150.1135 Toxicology

ACUTE TESTING:

81-1 - Oral LD ₅₀ - Rat	TGAI	A, B	Yes	00106158	No
81-2 - Dermal LD ₅₀	TGAI	A, B	Yes	GS0181-01	No
81-3 - Inhalation LC ₅₀ - Rat	TGAI	A, B	Partially*	GS0181-02	Yes
81-4 - Primary Eye Irritation	TGAI	A, B	Yes	GS0181-03	No
81-5 - Primary Skin Irritation	TGAI	A, B	Yes	GS0181-04	No
81-6 - Dermal Sensitization	MUP	A, B	Yes	GS0181-05	No
81-7 - Acute Delayed Neurotoxicity - Ilen	—	—	No	—	No

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Data Review:

Study Identification:

Study Title: SENCOR (BAY 94 337) Studies for Possible Embryotoxic and Teratogenic Effects on Rats after Oral Administration (Bay Report No.: 3678)

EPA Identification Numbers: EPA Accession No. 112892

Sponsor: Mobay Chemical Corporation
Chemagro Agricultural Division
Kansas City, Missouri 64120

Testing Laboratory: BAYER AG
Institut Fur Toxikologie
Wuppertal-Elberfeld

Study Number: 3678

Report Number: 35073

Date of Study: September 29, 1972

Study Directors: Dr. L. Machemer

Test Compound: SENCOR, BAY 94 337 (4-amino-6 tert.-butyl-3 (methylthio)-1,2,4-triazin-5-one) (also called Metribuzin)
Purity: 99.5%
Consignment 1603/71, Batch 17, Received 6/71

Vehicle: Cremophor EL, 1.5% aqueous emulsion

Dosage Used: 5, 15, 50 and 100 mg/kg/day

Test Animal: Rats, FB 30 Strain
Males: 3 to 6 months old, 350 to 500 gm.
Females: 2 1/2 to 3 1/2 months old, 200 to 250 gm.
No source of animals given.

Materials and Methods: A copy of the methods and materials section from the investigators report is appended.

The investigators stated that there were 21 to 22 "fertilized rats" in each study group. There was no mention of how many rats were used for mating at study initiation. Although elsewhere in the report they state in a table that 22 to 24 inseminated females were used, with 21 to 22 females considered fertilized and 20 to 22 females presenting as pregnant. There was no mention of the number of male rats used in this study.

Animals were housed singly except during the mating period. For the mating period 1 male rat was housed with 2 female rats.

Altromin R pelleted food and tap water were made available ab lib. There was no mention of analysis of food or water for contaminants, also no mention of collection of food consumption data.

Confirmation of copulation was by vaginal smear with positive confirmation of sperm considered as day 0.

Although there was no mention in this report if the technical grade of SENCOR was used, the consignment number and batch was the same as in other studies where it was stated that the compound was of technical grade.

Animals were treated on day 6 through 15 with doses of either the vehicle or prepared Sencor at a volume of 5 ml per kg body weight daily.

Ether was used to narcotize animals for cesarean section.

Only average weight of fetuses were given (both per litter and per study group), no individual fetal weight determinations were provided.

One-third of the fetuses were examined for soft-tissue anomalies and the other 2/3 were examined for skeletal anomalies.

Fetuses for soft-tissue evaluation were inspected by a modified Wilson technique for visceral malformation. There was no mention of the "method of modification".

The fetuses for skeletal examination were first eviscerated, the organs examined and then processed for staining of the skeletal system.

References given after statement "the method was published in:", make no reference to what method or procedure the references relate to.

Results:

Clinical Observations:

There was no maternal mortality in any of the study groups.

The investigators stated that no effect was seen in the dams at dosage of 15 mg/kg/day and below. One dam in the 50 mg/kg/day dosage group and 2 dams in the 100 mg/kg/day dosage group presented with ruffled coats, dyspnea and reduced activity, however this is limited evidence of any maternal toxicity. The other animals from each of those two group appeared unaffected. No individual clinical observation data was presented.

Necropsy observations for the dams were apparently not recorded.

Maternal Weight:

Maternal weight data was only provided in terms of weight gain during the treatment period and for the entire gestation period. Weight gain data during the treatment period was presented as individual numbers with no animal identification whereas the weight gain data for the entire gestation period provided animal identification numbers and therefore the data for individual animals could not be reliably compared. See Table 1 below:

Table 1. Maternal Weight Changes (gms + S.D.) Sencor (mg/kg/day)

	<u>Control*</u>	<u>5</u>	<u>15*</u>	<u>50</u>	<u>100</u>
Number of Animals	20	22	21	22	21
Days 6 to 15	44.3+11.6	42.4+13.2	41.5+9.3	42.9+8.5	38.0+11.9
Days 0 to 20	118.1+19.2	121.1+21.1	117.5+22.7	119.7+18.6	109.8+17.1

*One dam from each group not included in calculation due to complete loss of embryos.

Data extracted from BAYER AG Report No. 3678 Results and Tables 1 through 5.

The dams of the high dose group on the average gained slightly less weight during the treatment period (days 6 to 15) and over the entire gestation period (days 0 to 20).

No other weight data was provided. There was no initial (start of study), weekly or terminal weights provided.

Cesarean Section Observations: (Table 2)

There was no difference in pregnancy rate between any of the 5 study groups (95.2 to 100%).

No significant differences were observed in the number of implantations per dam, fetuses per dam and mean fetal body weight. There appears to be an increase in the number of resorptions per dam at the high dose level, also when calculated as group mean post implantation loss, a similar increase is seen. There was also a dose-related decrease in mean placental weight (statistically significant from control at the high dose level).

No corpora lutea data was provided. This data would have allowed for determination of preimplantation loss.

There was no separation of resorption data into early and late observations.

Although not stated, one must assume from the data that all fetuses in the study were viable.

The sex of the fetuses was apparently not determined.

Table 2: Cesarean Section Data - Sencor (mg/kg/day)

	Control	5	15	50	100
Number of Animals	21	22	22	22	21
Pregnancy Rate	95.2%	100%	95.5%	100%	100%
Total Implantations	247	239	251	247	251
Implantations/Dam	11.8±2.3	10.9±3.2	11.4±2.7	11.2±1.9	12.0±1.9
Total Fetuses	217	214	231	221	215
Fetuses/Dam	10.3±2.9	9.7±3.4	10.5±3.3	10.1±2.4	10.2±1.7
Total Resorptions	30	25	20	26	36
Resorptions/Dam	1.4±2.4	1.1±1.4	0.9±1.2	1.2±1.9	1.7±1.8
Group Mean Post Implantation Loss	12.2%	10.5%	8.0%	10.5%	14.3%
Mean Fetal Weight (gms)	3.90±0.20†	4.15±0.30	3.98±0.25†	4.00±0.32	3.98±0.34
Mean Placental Weight (gms)	0.547±0.054	0.559±0.079	0.557±0.116	0.525±0.083	0.502±0.052*

Data presented as mean ± S.D. or as indicated

† - One dam left out of calculation due to complete loss of fetuses.

* - Statistically significantly different from control.

Data extracted from BAYER AG Report No. 3678 Tables 1 through 6.

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Fetal Morphological Observations:

There were no observable differences between numbers of stunted fetuses in any of the study groups. See Table 3. However, fetal crown-rump data (this data was suggested as useful by CORE) would have been helpful in evaluation of these fetuses.

Only 2 incidences of malformations were observed, 1 fetus in the control group with micrognathia (mandible) and 1 fetus in the low dose group with hypoplasia of the mandible. No other malformations were observed. See Table 3 A.

There were no observable differences in incidence of "slight bone alterations" (this term must be defined by the registrant, other than the reference stated) between any of the study groups. See Table 3 B. However, no data was provided on individual fetal or litter expression of the separate bone alteration observations, the only data provided was for total number of fetuses showing bone alterations (of any kind) by litter and average by study group.

Table 3: Fetal Morphological Observations - Sencor (mg/kg/day)

	<u>Control</u>	<u>5</u>	<u>15</u>	<u>50</u>	<u>100</u>
Litters:	20	22	21	22	21
Fetuses:	217	214	231	221	215
division for examination:					
Soft Tissue (Wilson)	67	63	70	65	64
Skeletal	150	151	161	156	151

Stunted Fetuses (<3 g)	3(3)†	2(1)	3(2)	4(3)	0(0)

<u>A. Malformations:</u>					
Micrognathia	1(1)	0(0)	0(0)	0(0)	0(0)
Hypoplasia of the mandible	0(0)	1(1)	0(0)	0(0)	0(0)

continued

Table 3: continued

B. "Slight Bone Alterations":

Total incidence:	75(18)†	64(18)	68(18)	75(20)	76(19)
as % of fetuses††:	50.0%	42.4%	42.2%	48.1%	50.3%
# of fetuses showing the following "slight bone alterations"					
Sternum	6	1	5	6	5
Hyoid	14	3	14	11	11
Vertebrae	47	37	39	47	50
Ribs	21	32	30	24	14
Skull	13	4	7	1	11
Extremities	0	0	1	0	0

† - Data presented as fetuses (litters).
 †† - examined for skeletal abnormalities

Data extracted from BAYER AG Report No. 3678 Tables 1 through 5 and 7.

No historical control data of any kind was provided with this study.

Conclusions:

The dosage of Sencor used (5, 15, 50 and 100 mg/kg/day), based on the data presented, produced slight evidence of maternal toxicity at the 100 mg/kg/day dose level, in the form of reduced maternal weight gain. There was slight corroborative clinical observation data.

There was no evidence of fetal toxicity or teratogenicity at the dose levels used in this study.

This study lacked the following data:

1. Whether the test compound was of the technical grade.
2. Justification of the dose levels used in the study since there was only slight evidence of maternal toxicity.
3. Individual and study group maternal weight data, at initiation of study, weekly and at sacrifice.
4. Maternal necropsy observations.
5. Individual fetal and litter observation data for all parameters
6. The definition of the term "slight bone alterations".
7. Corpora lutea determinations.
8. Separation of resorptions into early and late.
9. Viability of fetuses.
10. Sex of the fetuses.
11. Individual fetal weight data.

Core Classification: Core-Supplementary Data based on inadequacy of data as stated above. This study may be updated if the deficiencies can be corrected.

METRI BAZIN

Page _____ is not included in this copy.

Pages 36 through 39 are not included.

The material not included contains the following type of information:

- Identity of product inert ingredients.
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 - Sales or other commercial/financial information.
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 - FIFRA registration data.
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Data Review:Study Identification:

Study Title: BAY 94 337, Multigeneration Study on Rats.

EPA Identification Numbers: EPA Accession No.: 112891

Sponsor: Mobay Chemical Corporation
Chemagro Agricultural Division
Kansas City, Missouri 64120

Testing Laboratory: BAYER AG
Institut fur Toxikologie

Report Numbers: 4889
41818

Date of Study: September 24, 1974

Study Directors: Dr. rer. nat. Eckhard Loser
Dr. med. vet. Fred Siegmund

Test Compound: BAY 94 337, Technical Grade Compound (also called
Metribuzin; SENCOR)
Purity: 99.5%
Sdg 1603/71

Dosage: 35, 100 and 300 ppm mixed in pulverized Altromin R
laboratory feed.

Test Animal: Rats, FB 30 strain
Elberfeld breed
33 days old at beginning of study
Average body weight 45 to 55 gms.

Materials and Methods: A copy of the materials and methods
section from the investigators report is appended.

Comment: The confidential stamp used by MOBAY should not be
placed over critical material in the text and tables, it obscures
data and important words. This reviewer requested an unmarked copy
from the registrant, however the copy obtained had numerous
illegible entries in the individual animal data addendum.

There was no rationale given for the selection of the dosage levels used in the study (the results revealed that the high dose level did not produce any sort of maternal toxicity).

The test material was mixed with pulverized Altromin R feed, first as a stock and then extended to proper dietary concentrations. The food mixtures were prepared twice a week.

A more frequent weighing of pups (than just at birth, 5 days after birth, one week after birth and then weekly) would be advantageous for growth rate determination, especially in the earlier days. Also the growth rates should be reported by sex (as required by CORE).

Culling of the pups 5 days after birth to standardize litter size can lead to bias by removing the smallest pups. There was no indication in the Materials and Methods section that the pups were randomly culled.

In the selection of pups for the F_{1b} and F_{2b} generation mating, there was no indication if the selection was such that pups of the same litter (siblings) were not mated.

There was no indication as to whether the animals were checked once daily for mortality, adverse effects on lactation, nursing instinct, and adverse effects on the newborn.

Apparently a full examination of the litters was not performed. According to CORE, the necessary determinations are number of offspring per litter, number of live and dead offspring by litter, fecundity, length of the gestation period and general condition of the offspring (especially gross anomalies) and mother through weaning. There was no indication of the parameters considered for gross examination of the pups.

Representative numbers of weanlings in each treatment group should have been necropsied and the second litter of the third generation should have been subjected to a complete necropsy rather than just one male and one female from each of 5 dams per study group (Materials and Methods section of the final report stated 4 dams, results indicated 5 dams).

Results:

I. Parental Data

A. Physical Signs

The investigators stated that for the F₀ generation, "during the study periods, the rats of the 35 to 300 ppm groups did not differ in appearance and behavior from its controls". However, no clinical observation data was presented to support this statement.

There was no mention of appearance or behavioral changes in the F_{1b} or F_{2b} rats.

B. Mortality

F₀ generation: One female in the 100 ppm dose group died after the 2nd mating. This animal was pregnant and no cause of death was determined. One female in the 300 ppm dose group was found to have severe inflammation of the middle ear and was sacrificed.

F_{1b} generation: One female control animal died during the 1st mating. This animal was not pregnant and no cause of death was determined. One female in the 300 ppm dose group died after the 1st mating. This animal was not pregnant and no cause of death was determined.

F_{2b} generation: One male in the control group died after 2nd mating due to massive pneumonia. One male in the 35 ppm dose group died before the 1st mating also of massive pneumonia. One female in the 35 ppm dose group died before the first mating. The cause of death could not be determined because of "decay". Two females in the 300 ppm dose group died before the first mating. One animal died of pneumonia and the cause of death in the other animal could not be determined.

C. Weight Changes

F₀ generation: From the plotted averages (graphs) provided there appears to be no dose-dependent differences in weight between treated and control animals up to the first mating in the females. After the 1st and after the 2nd mating there were slight fluctuations in the females but apparently the differences were not significant. In the males there were slight, non-significant fluctuation throughout the treatment period.

The individual data provided by the registrant is illegible and therefore could not be compared to the graphs provided, however in the future a table of mean weekly animal body weights would be helpful for evaluation.

F1b generation: Again from the graphs, apparently there were no differences in the weights of the females throughout the treatment period. For the males, there were no differences up to the second mating. After the second mating the treated groups were slightly lower in weight than the controls.

F2b generation: From the graphs, there were no differences in the weights of the females throughout the treatment period. For the males, between day 10 and 15, the treated animals gained less weight than the controls (the graphs indicated 20 to 30 grams less).

D. Length of Gestation

Not reported.

E. Fertility (Table 1)

First mating of the F₀ generation: There were essentially no differences in gestation rate between any of the 4 study groups.

Second mating of the F₀ generation: There was a slight reduction in gestation rate in all study groups as compared to first mating with a slightly greater reduction in the high dose group.

First mating of the F_{1b} generation: There were no significant differences in fertility noted between the study groups.

Second mating of the F_{1b} generation: The gestation rate was slightly lower than the first mating but no significant differences between study groups was noted.

First mating of the F_{2b} generation: There were lower gestation rates especially in the control group as compared to previous matings (see Table 1).

Second mating of the F_{2b} generation: Much lower gestation rates were seen in all study groups as compared to the 1st mating. The gestation rate in the control group was very low (20%), no explanation was provided by the registrant, except for the statement that the difference was "by chance", (see Table 1).

These lower fertility rates of the control groups of the F_{2a} and F_{2b} do not provide a valid control for comparison of the other groups.

Table 1: Fertility (Gestation Rate) BAY 94 337 Technical (ppm)
Number pregnant/number mated

	<u>Control</u>	<u>35</u>	<u>100</u>	<u>300</u>
<u>1st Mating F0</u>	20/20 100%	20/20 100%	19/20 95%	20/20 100%
<u>2nd Mating F0</u>	18/20 90%	18/20 90%	18/19 94.7%	15/19 78.9%
<u>1st Mating F1b</u>	17/19 89.5%	20/20 100%	20/20 100%	19/20 95%
<u>2nd Mating F1b</u>	16/19 84.2%	20/20 100%	18/20 90%	18/19 94.7%
<u>1st Mating F2b</u>	8/20 40%	15/19 78.9%	18/20 90%	16/18 88.9%
<u>2nd Mating F2b</u>	4/20 20%	11/19 57.9%	16/20 80%	11/18 61.1%

Data extracted from Report No. 4889 Tables 1, 5, 9a, 9b, 13a and 15.

II. Litter Data

A. Litter size (Table 2)

F1a litter: No significant differences between study groups.

F1b litter: No significant differences between study groups.

F2a litter: Slight larger litter size compared to previous and subsequent matings, but no treatment related effects could be discerned.

F2b litter: No significant differences between study groups.

F3a litter: No significant differences between study groups.

F3b litter: Slightly smaller litter size overall, but no significant differences between study groups.

Table 2: Number of Fetuses per litter at birth -
BAY 94 337 Technical (ppm)

	<u>Control</u>	<u>35</u>	<u>100</u>	<u>300</u>
F1a	11.4	10.8	11.9	11.9
F1b	9.2	9.6	11.7	10.1
F2a	11.5	12.0	12.5	12.1
F2b	11.9	11.9	11.1	10.6
F3a	11.4	9.6	10.5	9.9
F3b	9.8	8.4	9.7	8.5

Data extracted from Report No. 4889 Tables 2, 6, 10a, 10b, 14a and 14b.

B. Survival of pups (Table 3)

There were no significant differences in percent survival of pups to day 5 between any of the study groups. The F3b generation had a slightly lower overall survival as compared to the other generations.

Table 3: Percent Survival of Pups to Day 5 - BAY 94 337 Technical (ppm)

	Number of pups alive on day 5/number of pups at birth			
	Control	35	100	300
F1a	9.1/11.4 (79.8)*	9.4/10.8 (87.0)	9.2/11.9 (77.3)	9.8/11.9 (82.4)
F1b	7.4/9.2 (80.4)	7.9/9.6 (82.3)	10.8/11.7 (92.3)	9.7/10.1 (96.0)
F2a	10.8/11.5 (93.9)	10.8/12.0 (90.0)	12.0/12.5 (96.0)	9.2/12.1 (76.0)
F2b	10.3/11.9 (86.6)	9.4/11.9 (79.0)	10.7/11.1 (96.4)	8.2/10.6 (77.4)
F3a	8.9/11.4 (78.1)	8.0/9.6 (83.3)	8.2/10.5 (78.1)	9.1/9.9 (91.9)
F3b	7.8/9.8 (79.6)	6.4/8.4 (76.2)	6.9/9.7 (71.1)	7.3/8.5 (85.9)

*Numbers in parentheses are percentages.

Data extracted from Report No. 4889 Tables 2, 6, 10a, 10b, 14a and 14b.

After culling of the animals there were still no significant differences in litter size between any of the study groups in the various generations.

C. Survival to Weaning (Lactation Rate) (Table 4)

F_{1a} generation: There was a slight (not statistically significant) dose related decrease in lactation rate.

F_{1b} generation: There were no differences in survival between any of the 4 study groups.

F_{2a} generation: The lactation rates were comparable.

F_{2b} generation: The survival to weaning was comparable between all study groups. The low dose survival was slightly less than the other 3 groups.

F_{3a} generation: The total number of pups in all study groups was reduced overall, especially in the control group, but there were no differences observed in lactation rates.

F_{3b} generation: There was a further reduction in total numbers of pups, especially in the control group. The lactation rates were less than the previous F_{3a} generation and a slight, but not significant, dose related decrease was observed.

**Table 4: Survival to Weaning (Lactation Rate) -
BAY 94 337 Technical (ppm)**

# pups after reduction of litter size/# pups alive after 4 weeks	BAY 94 337 Technical (ppm)			
	Control	35	100	300
F1a	165/146 (88.5)*	170/149 (87.6)	160/138 (86.3)	171/142 (83.0)
F1b	121/112 (92.6)	135/122 (90.4)	164/155 (94.5)	127/114 (89.8)
F2a	164/155 (94.5)	183/170 (92.9)	192/187 (97.4)	148/131 (88.4)
F2b	144/129 (89.6)	166/139 (83.7)	159/155 (97.5)	131/115 (87.8)
F3a	64/61 (95.3)	117/107 (91.5)	133/119 (89.5)	133/130 (97.7)
F3b (3 weeks)	31/31 (100)	68/59 (86.8)	101/88 (87.1)	77/63 (81.8)

*Numbers in parentheses are percentages.

Data extracted from Report No. 4889 Tables 3, 7, 11a, 11b, 15a and 15b.

D. Pup Body Weights (Table 5)

F1a generation: There were slight differences in mean birth body weights between control and high dose groups but the differences were not statistically significant. From graphs of pup body weights over the 4 week period, there appeared to be no significant differences between any of the 4 study groups. The data on the graphs combined both males and females.

F1b generation: There were no real differences between birth weights of any of the 4 study groups over the 4 week period (from graph).

F2a generation: There were slightly reduced mean body weights at birth compared to control in all 3 treatment groups. However, over the 4 week weaning period no differences between study groups was apparent (from graph).

F2b generation: The body weights at birth of the low dose group was slightly lower (not statistically significant) than control. Over the 4 week period, a slight, but not statistically significant, difference continued to be observed (from graph).

F3a generation: The mean body weights at birth of the 3 treatment groups were slightly lower (dose related) than control. The 4 week weaning period showed slight variations, but not significant (from graph).

F3b generation: The 3 treatment groups had lower mean body weights at birth than that of control, especially the mid dose group. The differences were not significant, possibly due to reduced numbers of animals in the control group. Over the 3 week period there were slight, not significant, variations (from graph).

Table 5: Mean Body Weights (gm) of Young at Birth
BAY 94 337 Technical (ppm)

	<u>Control</u>	<u>35</u>	<u>100</u>	<u>300</u>
F1a	6.38	6.32	6.38	6.28
F1b	6.34	6.21	6.42	6.88
F2a	6.54	6.08	6.22	6.01
F2b	6.69	5.90	7.03	6.36
F2a	6.75	6.55	6.24	6.18
F3b	7.08	6.46	5.99	6.40

Data extracted from Report No. 4889 Tables 4, 8, 12a, 12b, 16a and 16b.

E. Malformations

The investigators stated that there was no evidence of gross malformations in the F1a, F1b, F2a, F2b, F3a or F3b generations. However, no data was presented to substantiate this statement.

III. Necropsy Data

A. Parents

No necropsy data was reported.

B. Pups

1. Autopsies of the F3b generation.

Three weeks after birth, one male and 1 female of each of 5 dams in every dose group were narcotized with ether, sacrificed by exsanguination and then examined grossly. According to the investigators no gross alterations attributable to BAY 94 337 was seen, however, no data was presented to substantiate this claim.

-10-

2. Histopathological Examinations.

Histopathological examinations were carried out on the thyroid, heart, thymus, lung, liver, spleen, kidneys, adrenals and gonads. The following are summary of the findings:

a. Lungs:

Minimal to medium grade focal interstitial pneumonia with peribronchial, peribronchiolar and perivascular lymphocytic infiltrates (includes infiltrate only findings) in the following incidences:

Control:	6/10
35 ppm :	8/10
100 ppm:	9/10
300 ppm:	10/10

Low grade hemorrhage in the alveolar space in the following incidence:

Control:	0/10
35 ppm :	1/10
100 ppm:	0/10
300 ppm:	1/10

Congestion in the following incidence:

Control:	0/10
35 ppm :	0/10
100 ppm:	3/10
300 ppm:	0/10

b. Liver:

Low grade interstitial lymphocytic and/or lympho-histiocytic infiltrates, particularly within the region of the Glisson trignals in the following incidence:

Control:	5/10
35 ppm :	10/10
100 ppm:	5/10
300 ppm:	10/10

c. Heart:

Minimal to low-grade mesenchymal activation in the form of minute lympho-histiocytic infiltrates in the following incidence:

Control:	3/10
35 ppm :	1/10
100 ppm:	2/10
300 ppm:	0/10

d. Kidney:

Focal interstitial lympho-histiocytic infiltrates in the cortical area and a focal dilation of the tubui contori in the following incidence:

Control:	1/10
35 ppm :	1/10
100 ppm:	0/10
300 ppm:	0/10

Dilation of the Bowman's capsule spaces in the following incidence:

Control:	0/10
35 ppm :	1/10
100 ppm:	1/10
300 ppm:	0/10

e. Adrenal:

Minute focal leucocyte infiltrates in the following incidence:

Control:	2/10
35 ppm :	0/10
100 ppm:	1/10
300 ppm:	2/10

f. Thymus:

Hemorrhage within the cortical substance (1 lobule) in the following incidence:

Control:	0/10
35 ppm :	1/10
100 ppm:	0/10
300 ppm:	0/10

g. Thyroid:

Epithelial desquamation within one follicle in the following incidence:

Control:	0/10
35 ppm :	0/10
100 ppm:	0/10
300 ppm:	1/10

There were no observed changes in the spleen or gonads. The above findings do not indicate any dose related effect of BAY 94 337. The incidences of inflammatory changes in the lung were attributed by the investigators to "rat-specific pneumonia" (historical data may have been helpful), there were no dose-dependent changes between any 4 of the study groups.

Conclusions:

The dosages of BAY 94 337 tested (35, 100 and 300 ppm) induced no compound related reproductive or fertility related effects in the 3 generations of rats tested. The No Observed Effect Level (NOEL) for reproductive effects appeared to be 300 ppm (HDT).

Deficiencies of this study include:

1. The rationale for selection of dosage levels was not provided since the high dose level used did not induce any toxicity in parental animals as required by CORE.
2. Representative numbers of weanlings from each treatment group were not necropsied.
3. The entire F_{3b} litter was not subjected to a complete histological examination.
4. There was no indication if selection of pups for the F_{1b} and F_{2b} generation mating provided that pups from same litter (siblings) were not mated.
5. The litters were not examined fully as recommended by CORE for general condition especially for gross anomalies.
6. There was a lack of maternal clinical observation data.
7. The individual weight data provided by the registrant was illegible.
8. There was not a valid control group for either the F_{2a} and F_{2b} (in terms of the fertility index), there may have been a problem with the animal husbandry.

Core Classification: Core-Supplementary Data based on the above mentioned deficiencies.

Metribuzin

Page _____ is not included in this copy.

Pages 52 through 57 are not included.

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 quality control procedures.
 - Identity of the source of product ingredients.
 - Sales or other commercial/financial information.
 - 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.
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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.

008190

008190

Data Review:

Study Identification:

Study Title: BAY 94 337 Chronic Toxicity Studies on Rats (2-year feeding experiment)

EPA Identification Numbers: EPA Accession No. 112891

Sponsor: Mobay Chemical Corporation
Chemagro Agricultural Division
Kansas City, Missouri 64120

Testing Laboratory: BAYER AG
Institut für Toxikologie
Wuppertal-Elberfeld

Report Numbers: 4888 & 41816

Date of Study: September 25, 1974

Study Director: Dr. rer. nat. Eckhard Loser

Histopathological Examination: Prof. Dr. med. U. Mohr

Test Compound: BAY 94 337 (Metribuzin) Technical (also called SENCOR)
Purity: 99.5%
Batch No.: 1603/71

Dosage: 25, 35, 100 and 300 ppm mixed with pulverized Altromin R feed (from Altrogge, Lage/Lippe).

Test Animal: SPF Rats (Wistar Strain) bred by Winkelmann, Kirchborchen, Kreis Paderborn. At start of experiment rats were about 28 to 32 days old with males having a mean body weight of 51.4 gm. and females with a 52.1 gm mean body weight.

Materials and Methods: A copy of the materials and methods section from the investigators report is appended.

Hematology examinations were performed on 5 rats per sex at 3, 6 and 12 month intervals (although Core recommends 4 month intervals). At 24 months the test were conducted on 10 rats per sex.

The hematology examination protocol was adequate and included reticulocyte counts.

The blood chemistry determination did not include Ca, P₀₄, fasting glucose, urea nitrogen but did include blood sugar (not fasting) and cholesterol determinations.

Urinalysis tests were conducted on urine collected for 16 hours at 3, 6, and 12 months on 5 rats per sex and at 24 months on 10 rats per sex.

Thyroid function tests utilized 20 rats per sex for temperature studies at 6, 12 and 24 months and 5 rats per sex at 6 and 12 months and 10 rats per sex at 24 months for protein bound iodine determinations.

The investigators examined all tissues that are required by CORE, however histopathology was performed on all animals only in control and the high dose group. In the other three dose groups only selected tissues in selected animals (10 per group) were examined (see page 7, this review).

Results:

I. Clinical Observations:

The investigators observed no differences in "physical appearance and behavior from the control rats" in any of the test groups. No data was provided for these observations.

II. Clinical Data:

A. Food Consumption:

Although not stated in the table provided, the data presented for "average food consumption" is for 24 months. The "average quantity of active ingredient ingested" is stated as being "related to the animal body weight after 12 months of feeding". There was no statistical difference between groups in the amount of total food consumed, however as would be expected the males consumed more total food than the females (mean food consumption by males was 19.03 ± 0.59 g/animal/day and mean food consumption by females was 15.12 ± 0.50 g/animal/day, based on all groups combined).

When "average quantity of active ingredient ingested" is calculated, it was found that the female received more active ingredient than the male. See Table I below:

Table I: Active Ingredient (mg/kg body weight/day)

<u>Dose (ppm)</u>	<u>Male</u>	<u>Female</u>
Control	0	0
25	1.30	1.68
35	1.87	2.28
100	5.27	6.53
300	14.36	20.38

Data Extracted from BAYER AG Report No. 4888 Table 1.

B. Body Weight:

The investigators found no significant difference between control and the 25 to 100 ppm test groups through the 24 month test period. The males of the 300 ppm test group (from body weight curves) showed significant differences at weeks 70 to 80 and 90 to 100 while the females showed significant differences (according to the investigators: $p < 0.05$) from weeks 20 to 100, but at the end of the test period there was only a slight difference from control (for the females).

The registrants provided graphed mean data (curves) and individual weekly weight data for the animals. Numerous entries on the individual animal weekly weight data that were provided was illegible (including the "new" copy provided by the registrant).

C. Mortality:

At 12 months there was no significant mortality noted by the investigators. Survival to study termination was excellent, see Table II below. There was no apparent difference in mortality between any of the treatment groups and control.

Table II: Mortality Rates (in percent)

<u>DOSE (ppm)</u>	<u>After 1 year</u>	<u>At study termination</u>
<u>Males</u>		
Control	2.5	17.5
25	0	22.5
35	2.5	20.0
100	0	25.0
300	0	27.5
<u>Females</u>		
Control	0	10.0
25	2.5	12.5
35	0	22.5
100	0	17.5
300	2.5	12.5

Data extracted from BAYER AG Report No. 4888 Table 2.

D. Hematology:

At 3 months there were no significant differences in hematological parameters.

At 6 months there appears to be a slight dose related decrease in reticulocyte count in both males and females and a slight decrease in leucocytes in the male rats.

However, at the 12 and 24 month intervals there were no apparent differences in reticulocyte or leucocyte counts or other hematological parameters.

E. Liver Function Tests:

There were no significant differences between test groups at 3, 6, 12 or 24 months for male and female plasma enzyme alkaline phosphatase or the transaminases (GOT and GPT) or total protein levels.

F. Urinalysis and Kidney Function Tests:

At 3 months there was a slight increase in protein in the urine in both male and female animals of the test groups as compared to control. This was not apparent at the 6 month interval in the males, but slight increases were still seen in the females (dose related). At the 12 month interval there were no apparent differences noted and at 24 months the controls had higher levels of protein in the urine than the test groups.

G. Blood Sugar and Cholesterol Determinations:

There were no significant differences between control and test groups at the 3, 6, 12 and 24 month intervals.

1. Body temperature: There were no meaningful differences seen between control and test groups at 6, 12 and 24 months.

2. Protein-bound iodine: There were no significant differences seen between control and test groups at 6, 12 and 24 months.

III. Necropsy Data:

The investigators stated that examination of all rats that died during the study and were autopsied showed "No pathological changes attributable to administration of the test compound". However, for many of the animals which died during the course of the study, the comment in the table under the causes of death was stated as "not determinable due to decay of animal", see Table III below. Many of the animals showed evidence of "massive pneumonia" as the cause of death.

The investigators further state, that the animals grossly examined at final sacrifice "showed no signs of any specific damage".

Table III: Number of Animals Lost to "Decay"

DOSE (ppm)	Males	Females
Control	5/14 (36%)	4/8 (50%)
25	1/9 (11%)	2/5 (40%)
35	2/8 (25%)	4/9 (44%)
100	2/10 (20%)	0/7 (0%)
300	2/11 (18%)	1/5 (20%)

Demoninators refer to animals dying prior to end of experiment.

Data extracted from BAYER AG Report No. 4888 Tables 15a and 15b.

A. Organ Weights:

The absolute weights of female rat heart (significant at 100 and 300 ppm) and lung (significant at 300 ppm) showed a dose related decrease. The absolute kidney weight in males showed a dose-related decrease with the 300 ppm level being statistically significant. See Table IV below:

Table IV: Absolute Organ Weight (in mg)

Male Rats							
Dose(ppm)	Thyroid	Heart	Lung	Liver	Spleen	Kidney	
0	24.7	1012	1902	1019T	842	2602	
25	26.2	1058*	1809	11547**	921*	2510	
35	26.9*	1009	1863	10880*	804	2497	
100	28.6**	1029	1913	10521	915	2491	
300	27.4	979	1867	9711	781	2362**	
Female Rats							
Dose(ppm)	Thyroid	Heart	Lung	Liver	Spleen	Kidney	
0	21.9	772	1319	8610	669	1761	
25	21.5	754	1332	8411	649	1676	
35	24.5	766	1483	8156	725	1767	
100	20.2	715**	1231	7605**	663	1656**	
300	20.9	721**	1199**	7762	613*	1705	

*p < 0.05
**p < 0.01

Data extracted from BAYER AG Report No. 4888 Table 16a.

The average relative organ weights show a similar pattern except that liver weight is reduced over control in the 35, 100 and 300 ppm dosage levels. See Table V below:

Table V: Relative Organ Weights (in mg/100 gm body weight)

Male Rats						
Dose(ppm)	Thyroid	Heart	Lung	Liver	Spleen	Kidney
0	6.2	255	408	2553	211	654
25	6.0	246	424**	2683*	215	584**
35	6.8*	250	466	2702	198	620
100	6.8*	247	458	2511	217	595**
300	6.8	243	466	2416	193	588**
Female Rats						
Dose(ppm)	Thyroid	Heart	Lung	Liver	Spleen	Kidney
0	8.7	301	519	3336	260	685
25	8.2	290	514	3236	250	646
35	9.1	285	548	3031**	270	660
100	7.9	283*	483	2999**	264	656
300	8.3	283*	471*	3028**	238*	668

*p < 0.05

**p < 0.01

Data extracted from BAYER AG Report No. 4888 Table 16a.

B. Histopathology:

The investigators evaluated the following organs from 66 males and 72 females in the control group and 29 males and 35 females in the high dose group: brain; pituitary gland; eyes; cervical lymph nodes; aorta; trachea; sternum including bone marrow; mammary gland; esophagus; stomach; 4 intestinal segments; pancreas; epididymus; prostate; seminal vesicle; urinary bladder; uterus; thyroid; heart; lung; liver; spleen; kidneys; adrenal glands; testicles or ovaries; skeletal muscle with femur and sciatic nerve; salivary glands.

For the other treatment groups, the following organs of 10 animals per sex were examined: thyroid; heart; liver; spleen, kidney; adrenal gland; testicles or ovaries.

The "main" organs of animals which died during the study were also examined.

The pathologist stated that the "histological findings of the present compound investigation in Wistar rats cannot be proven to be treatment or dose dependent and it must be assumed that the found tumors lie within the range of the normal spontaneous tumor rate for this species".

The investigators supplied a summary table of "histological findings of suspected tumor material" without any reference (in the majority of the observations presented) to the organ in which the tumor was found. This reviewer utilized the provided individual histopathological findings and produced a summary table with organ by organ incidence of "suspected tumor" findings (see Table VI). As can be seen on Table VI, the females of the 300 ppm test group showed a statistically significant increase ($p < 0.01$ done by independent chi square method) over the control group for liver bile duct adenoma. A statistically significant increase ($p < 0.05$ done by independent chi square method) was also observed for pituitary adenoma and a slight, but not statistically significant, increase in ovarian adenoma (23% as compared to 13% in control) was observed. Further data is required on the animals from the other 3 dosage groups along with historical control data on the incidence of these tumors in this breed of rat before evaluation of this study can be completed.

No tumors were found by the investigators in the (both sexes) aorta, bone marrow (sternum), brain, cervical lymph glands, epididymus, esophagus, eyes, heart, kidneys, lungs, skeletal muscle with femur, nerve, prostate gland, salivary gland, seminal vesicle, spleen (male), stomach (female), trachea and urinary bladder of the animals examined at final sacrifice.

Table VI: Histopathological Findings of Suspected Tumor Material
(rat sacrificed at the end of the study)

Dose (ppm):		<u>Control</u>	<u>25</u>	<u>35</u>	<u>100</u>	<u>300</u>
Adrenal gland-adenoma	M	8/66	1/10	1/10	0/10	1/29
	F	0/72	0/10	0/10	0/10	0/35
"Tumor"†	M	0/66	0/10	0/10	0/10	0/29
	F	0/72	0/10	2/10	0/10	0/35
Intestine-"Tumor"†	M	1/66	-††	-††	-††	0/29
	F	0/72	-	-	-	0/35
Liver-bile duct adenoma	M	19/66	10/10	8/10	5/10	9/29
	F	13/71	4/10	5/10	1/10	19/35**
Pancreas-adenoma	M	1/65	-	-	-	0/29
	F	1/71	-	-	-	1/35
Pituitary-adenoma	M	10/62	-	-	-	6/29
	F	27/71	-	-	-	21/35*
carcinoma	M	2/62	-	-	-	1/29
	F	11/71	-	-	-	5/35
Spleen-lymphoma	M	0/66	0/10	0/10	0/10	0/29
	F	0/72	0/10	(1/5)†††	0/10	(1/4)†††
Stomach-carcinoma	M	1/66	-	-	-	0/29
	F	0/72	-	-	-	0/35
Thyroid gland-adenoma	M	0/65	2/10	1/10	0/10	1/29
	F	2/72	0/10	0/10	2/10	0/35
papilloma	M	0/65	0/10	0/10	0/10	0/29
	F	3/72	0/10	1/10	1/10	0/35
Testes- interstitial cell tumor		3/66	1/10	0/10	0/10	0/29
"Tumor"†		0/66	0/10	1/10	0/10	0/29
Mammary gland-adenoma		5/72	-	-	-	0/35
Ovaries- adenoma		9/72	1/10	1/10	1/10(1/3)	8/35(2/4)
Uterus- adenoma		1/72	-	-	-	0/35
	"Tumor"†	0/72	-	-	-	1/35
polyps		5/72	-	-	-	3/35

continued

Table VI continued:

* p < 0.05
** p < 0.01

† - unspecified tumor (must be explained further by the registrant).
†† - tissue not examined.
††† - number in parenthesis, animals died prior to end of experiment.

Data extracted from addendum to BAYER AG Report No. 4888.

The investigators also did not supply a summary table of non-neoplastic histopathological findings. This review again utilized the provided individual animal histopathological findings to produce a summary table (see Table VII). As can be seen in Table VII there were numerous observations of inflammatory cellular infiltration (ICI) in the heart, kidneys and trachea as well as the presence of lymphocytes in the kidneys, liver and trachea. The liver showed the most significant observation of "changes in the nucleus" with a slight increase in the males and a statistically significant increase (p < 0.01 done by independent chi square method) in the females of the 300 ppm test group. This observation of "changes in the nucleus" in the liver must be further defined by the registrant as must the observation listed as "tumor" (unspecified) in the table. There also was a statistically significant increase (p < 0.05 done by independent chi square method) in parasitic (stated as "possible" by the registrant) cellular granuloma observed in the 300 ppm males. The 300 ppm females presented with a slight, but not statistically significant, increase in incidence of cysts and of uterine hypertrophy/hyperplasia. The lungs showed evidence of emphysema, pneumonia, bronchitis, blockages, peribronchial lymphocyte infiltration and occasional hyperplasia of the bronchial mucous membrane.

Table VII: Non-neoplastic Histopathological Findings
(rats sacrificed at the end of the study)

Dose (ppm):		Control	25	35	100	300
Heart- ICI†	M	15/66(2/9)††	5/10	4/10(1/6)	4/10(1/8)	11/29
	F	22/72	1/10	1/10	4/10(1/7)	4/35(1/4)
Kidneys- ICI	M	3/66(3/6)	0/10	0/10	1/10(1/8)	0/29
	F	1/72	2/10	(1/5)	1/10	2/35
Lymphocytes	M	39/66	3/10(2/8)	4/10(2/6)	6/10	9/29
	F	15/72	2/10	3/10	0/10	2/35
Glomerular Damage	M	0/66	0/10	0/10	0/10	0/29
	F	1/72	2/10	3/10	0/10	4/35
Liver-"Changes in the nucleus"	M	6/66	3/10	3/10	3/10	4/29
	F	10/71	0/10	1/10	6/10	18/35**
Lymphocytes	M	18/66	2/10	2/10	2/10	9/29
	F	11/71	3/10	3/10(1/5)	1/10	4/35
Parasitic cellular granuloma (pcg)	M	7/66	0/10	0/10	5/10	8/29*
	F	0/72	1/10	0/10	0/10	0/35
Spleen- Megakaryocytes	M	0/66	0/10	0/10	0/10	1/29
	F	1/72	0/10	0/10	0/10	2/35
Trachea- ICI	M	2/66	-†††	-	-	2/29
	F	2/71	-	-	-	1/35
Lymphocytes	M	4/66	-	-	-	0/29
	F	1/71	-	-	-	2/35
Mammary glands- Cysts		9/72	-	-	-	9/35
Uterus- Hypertrophy/Hyperplasia		7/72	-	-	-	7/35

Lungs - see text for description of findings

* p < 0.05

** p < 0.01

† - ICI = Inflammatory cellular infiltration.

†† - number in parenthesis, animals died prior to end of experiment.

††† - tissue not examined.

Data extracted from addendum to BAYER AG Study No. 4888.

Conclusions:

There was no evidence of a compound related effect on hematological, clinical-chemical, urinalysis, kidney function, liver function and thyroid function test parameters. There also was no compound related effect on mortality or food consumption. However there was a statistically significant reduction of weight gain seen in the high dose (a table of weekly body weight gain data must be supplied by the registrant). Relative organ weights showed a significant decrease in heart (200 and 300 ppm females), lungs (300 ppm females), liver (35 to 300 ppm females), spleen (300 ppm females) and kidney (25, 100 and 300 ppm males), however there is a lack of dose response in these findings and there are no histopathological observations that correspond with these findings. The neoplastic histopathological observations consisted of a statistically significant increase in the incidence of adenoma of the liver bile duct and the pituitary gland in the 300 ppm females. However, not enough animals were examined histopathologically in the other 3 dosage groups to allow a judgement to be made with respect to a dose response effect of the chemical. Further data must be supplied in the form of histopathological examinations of the animals not previously examined in the other 3 dosage groups along with historical control data on the incidence of these tumors in this particular rat strain. The registrant must also explain the observation of "tumor" in certain tissues. Non-neoplastic observations showed a statistically significant increase in liver "changes in the nucleus" in the females of the 300 ppm test group. The registrant will also have to provide the non-neoplastic observations in the animals of the other 3 dosage groups that were not previously examined. No systemic No Observed Effect Level (NOEL) can be determined without this data.

The registrant is directed to provide summary tables of the neoplastic and non-neoplastic findings as produced in this review (see Tables VI and VII).

Certain biochemical parameters were not determined (Ca, PO₄, fasting glucose and urea nitrogen) and data for clinical observations was lacking.

Core Classification: Core-Supplementary Data since the oncogenic potential of the test compound cannot be fully ascertained without the above mentioned neoplastic histopathologic observations on animals of the 25, 35 and 100 ppm dosage groups. The non-neoplastic histopathologic observations are also lacking for the same group of animals. Historical control data of the incidence of neoplastic and non-neoplastic histopathological findings of the rat strain used in this study must be supplied by the registrant. The registrant must also explain the terms "changes in nucleus" and the observation of "tumor" (unspecified) seen in certain tissues on the individual animal pathology findings sheets. A table of mean weekly body weight data divided by sex for each study group must also be supplied. This study may be upgraded if the requested data is submitted and eliminates the deficiencies.

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Data Review:

Study Information:

Study Title: BAY 94 337 Chronic Toxicity Studies on Dogs (Two-Year feeding experiment)

EPA Identification Numbers: EPA Accession No. 112892

Sponsor: Mobay Chemical Corporation
Chemagro Agricultural Division
Kansas City, Missouri 64120

Testing Laboratory: BAYER AG
Institut fur Toxikologie
Wuppertal-Elberfeld

Study Numbers: 4887 & 41914

Date: September 24, 1974

Study Authors: Dr. rer. nat. Eckhard Loser
Dr. med. vet. Dumitru Mirea

Test Compound: BAY 94 337 (Metribuzin), Technical (also called SENCOR)
Purity: 99.5%
Batch 1603/71

Dosage: 25, 100 and 1500 ppm mixed in pulverized Altromin H
(Altrogge, Lage/Lippe)

Test Animal: Beagle Dogs, Male and Female
Vendor: Appleton Kennels
England
Age at start of experiment: 6 to 8 months old.
Treated for parasites as necessary and vaccinated against distemper.

Materials and Methods: A copy of the materials and methods section from the investigators report is appended.

Study groups consisted of 4 male and 4 female dogs.

The animals were weighed weekly during the first year and every 2 weeks during the second year.

Clinical-chemical tests were performed prior to the beginning of the study and at 2, 4, 6, 12 and 24 months (with an additional hematological test at 23 months). The specific tests are presented in the materials and methods section (from the investigators report) appended.

Most of the tissues recommended by CORE were examined in all animals at the end of the experiment except for spinal cord, trachea, skin and sections of the sternbrae, vertebrae or tibio-femoral joint. However, the investigators included in the examinations the following tissues not recommended by CORE: tonsils, aorta and diaphragm.

Results:

I. Clinical Observations:

The investigators stated that the dogs of the 25 and 100 ppm test groups did not differ in appearance from those of the control group relative to such parameters as "activity, condition of coat, appetite or thirst", however no clinical observation data was presented.

It was noted after 2 weeks of feeding that the 1500 ppm test group animals "appeared weakened, their coats were dull and bristly and feed was frequently refused".

Three dogs were found to have severe Candida infection after 12 months, one male in the 100 ppm test group and one male and one female of the 1500 ppm test group.

The investigators stated that the eye examinations found "no dullness on the cornea or lenses" and "no changes in the fundus oculi" in any of the animals of the study.

Mortality was high in the 1500 ppm test group, while only one other death occurred (in the 25 ppm test group), see Section II C.

II. Clinical Data

A. Food Consumption:

The animals in the control, 25 and 100 ppm groups consumed nearly equal mean amounts of food. The 1500 ppm test group, however, showed slightly reduced food intake. See Table 1 below.

Table I: Mean Food Consumption (g/animal/day)

<u>Dose (ppm)</u>	<u>Male</u>	<u>Female</u>
Control	298.10	297.91
25	298.10	298.10
100	298.10	296.39
1500	279.01	283.86

Data extracted from BAYER AG Report No. 4887 Table 1.

There were no sex related differences in the mean quantity of test compound ingested. See Table II below:

Table II: Mean Quantity of Test Compound Ingested
(mg/kg body weight/day)

<u>Dose (ppm)</u>	<u>Male</u>	<u>Female</u>
Control	0	0
25	0.82	0.84
100	3.44	3.56
1500	55.65	55.30

Data extracted from BAYER AG Report No. 4887 Table 1.

B. Body Weight:

No differences were observed in weight gain between control and the 25 and 100 ppm dose groups. However, animals of the 1500 ppm test group gained significantly less weight than the control animals, but after approximately 65 weeks only 1 male and 1 female survived in the 1500 ppm test group and the female showed normal weight gain. The investigators only provided data in the form of graphs (curves) and individual animal data, no mean weekly animal body weight by group was provided. Some of the animals in the mid dose group may have reduced weight gain but the small numbers of animals used in the study groups preclude any statistical significance. In addition it is noted that there may not have been enough food provided to the animals to allow normal growth especially during the winter months.

C. Mortality:

There was one death noted after 1 year in the 25 ppm test group (a female) and 4 deaths in the 1500 ppm test group (2 males and 2 females) with 2 more deaths in this group after 2 years (1 male and 1 female).

D. Hematology:

Hematological tests were conducted prior to the start of the experiment and no unusual findings were observed.

At 2 months the 1500 ppm test group showed significant differences in test results seen as an increase in sedimentation rate and reticulocyte count, a decrease in thrombocyte and erythrocyte counts, medium cell volume (males) hemoglobin (as percent), hematocrit, medium cell hemoglobin, prothrombin time with only small changes in the differential blood counts such as a decrease in eosinophils, large lymphocytes, mature polymorphonuclear neutrophils (females) and an increase in monomorphonuclear neutrophils as well as evidence of immature polymorphonuclear neutrophils. The hematological changes were greatest in males.

At 4 months the 1500 ppm test group showed significant effects on nearly all the measured parameters. A similar pattern was seen at 6, 12, 23 and 24 months in the 1500 ppm test group with the females showing greater changes than were seen at 4 months. An increase in leucocyte counts were seen and differential blood counts at 23 and 24 months showed variability but no specific pattern.

E. Liver Function Tests:

Liver function tests were also conducted prior to the initiation of the study.

At 2 months there were slight decreases in plasma alkaline phosphatase (ALP) levels in the male and ornithine-carbonyl transferase (OCT) levels in both males and females of the 1500 ppm test group.

At 4 months the 1500 ppm test group showed increased ALP levels in the males and decreased OCT levels in both sexes.

At 6 months there were increased plasma glutamate-pyruvate transaminase (GPT) levels in all 3 test group males and a slight increase in 1500 ppm females. An increase in total bilirubin of the 1500 ppm males was observed. The investigators state that after 6 months, GPT and bilirubin levels "reached pathological values" in the males of the 1500 ppm test group.

At 12 months there were increased GOT levels in the 1500 ppm males and females, decreased ALP levels in all 3 test group females, increased GPT levels in all 3 treatment group male and female (dose related), a large increase in OCT levels in the 1500 ppm males and females, increased BSP retention in 1500 ppm males and decreased BSP retention in 1500 ppm females, increased total bilirubin in the 1500 ppm males and increased total protein in both males and females of the 1500 ppm test group. The investigators state that at 12 months there was increased GOT, GPT, OCT and BSP retention in the 1500 ppm male dogs and that the GOT in the 1500 ppm females was on the "borderline of normality". However, the GPT, OCT and total protein levels were increased over the other test groups in the 1500 ppm females.

At the 24 month period, only one male and one female survived in the 1500 ppm test group. The male showed slight increases in ALP, OCT and BSP retention and the female showed a slight increase in GOT. There were no apparent effects on these parameters at the lower dose levels.

F. Urinalysis and Kidney Function Tests:

The investigators stated that no differences were seen in sugar, albumin, blood and bile pigment measurements in the urine "between treated groups and the controls", both "before the start of the feeding experiment and after 2, 4, 6, 12 and 24 months of feeding". However no values were provided for the examinations (certain tests were done on "clinical sticks"). They further stated that the urine sediments "exhibited the usual constituents". However, no data was presented for any of these parameters.

Kidney function tests conducted prior to the study initiation showed no real differences in urea, creatinine or total protein measurements in the urine between any of the study groups, except for a very slightly elevated protein in the urine in the 25 ppm test group male. The investigators state that this is within "the physiological range".

No differences were seen at the 2 month interval in any of the parameters and at 4 months only a doubling of measured protein in the urine (compared to control) of the 1500 ppm test group females was seen.

At the 6 month interval a slight decrease in creatinine was seen in males and females of the 1500 ppm test group. This was also seen at the 12 month interval. At the 12 month period a doubling of the measured urea (compared to control) was seen in the males of the 1500 ppm test group along with a doubling in measured total protein (compared to control) in the urine of the females in the same test group.

At 24 months no real differences could be seen between control and the low and mid dose groups. However, too few animals remained in the 1500 ppm test group for purposes of comparison to the control group.

G. Blood Sugar and Cholesterol Determinations:

No real differences were seen between study groups on tests conducted prior to initiation of the study.

At 2 months there were no differences except for an elevation of the cholesterol of the 1500 ppm test group males which persisted to the 4 month interval at which time the females of the same group exhibited slightly elevated cholesterol levels (persisting to 6 months).

At the 6 month time point there was a slight dose-response elevation in blood sugar in the males of the treated groups, however the females did not show any differences.

At 12 months both males and females of the 1500 ppm test group showed an increase in blood sugar and a slight elevation in cholesterol.

At 24 months there was a dose-related increase in blood sugar in the males of all the treated groups with females only showing a slight increase in all 3 treatment groups. The cholesterol levels showed no real differences.

The investigators stated that the elevation of blood sugar was at the "upper end of the normal range" and the the cholesterol was only "temporarily increased".

The transient increase in cholesterol levels could be due to a toxic effect of the test compound on the liver.

4. Thyroid Function Tests:

Body temperature and protein-bound iodine studies showed no change throughout the duration of the experiment.

III. Necropsy Data:

The autopsies conducted on the animals which died during the study revealed that one female of the 25 ppm dose group died of severe pneumonia (present for 220 days) and at least 3 out of the 6 animals that died in the 1500 ppm dose group also died of severe pneumonia. One male and 2 females of the 1500 ppm test group were sacrificed due to "severe malnutrition".

The investigators stated, relating to the autopsies of all the animals sacrificed at the end of the experiment, that "no specific changes were seen which could be considered with certainty to be due to administration of the test compound", however no data was presented to substantiate this statement (assuming the investigators are referring to gross necropsy observations which were not provided).

A. Organ Weights:

It is best to consider mean relative organ weights when considering the difference in dog body weights at terminal sacrifice. Also consideration must be made for the fact that only one male and one female survived to sacrifice in the high dose group and the small number of animals on test at each dose level.

An apparent increase in relative thyroid weight was noted in both of the animals of the 1500 ppm dose group, also a very slight increase in the relative heart weight of the male dog. Seen also in the 1500 ppm male was an increase in liver and pancreas relative organ weight.

An increase in the relative spleen weight occurred in all males of the 3 test groups over control and the females showed an increase in the relative weight of the pancreas while there was a very slight dose related decrease in relative kidney weight. See Table III below.

Table III: Mean Relative Organ Weights (g/kg body weight
except thyroid where mg/kg body weight)

Dose(ppm)	Thyroid	Heart	Liver	Spleen	Pancreas	Kidneys
Males						
0	85.11	9.09	34.84	1.96	2.70	5.28
25	74.39	8.14	29.59	2.90	2.51	4.35
100	67.98	8.70	33.38	2.59	2.55	4.68
1500	138.36	9.45	46.44	4.52	4.11	5.62
Females						
0	89.14	9.10	32.54	3.67	2.70	5.03
25	70.78	7.68	32.26	2.55	3.15	4.87
100	87.17	8.52	34.21	3.23	3.48	4.53
1500	111.54	9.13	32.79	3.46	2.88	4.13

Data extracted from BAYER AG Report No. 4887 Table 24b.

B. Histopathology:

Those animals which died early in the study and the cause of death diagnosed as severe pneumonia exhibited the expected histological signs (small foci of lympho-histocytic infiltrates, perivascular and focal lympho-histocytic infiltrates).

Relating histological findings to hematological observations, the changes observed in hematological tests may be related to changes in blood forming organs as evidenced by the increase in megakaryocytes observed in the bone marrow and spleen of the high dose group.

The results of the clinical tests along with the increase in liver weights of the 1500 ppm test group may indicate liver damage. Further evidence is the observation of parenchymal necrosis, interstitial infiltration and other changes not observed in the control or the 25 and 100 ppm test groups. The investigators believe that these changes are caused by "the increased destruction of erythrocytes caused by hypoxaemia" and based on this they further state that "BAY 94 337 does not have a primary hepatotoxic action". However, this must be considered as speculative since there is no evidence of activity that would reduce oxygen to the tissue and any subsequent destruction of red blood cells.

The other histological findings were either singular in nature or occurred in equal incidence in all treatment groups and consisted mostly of lymphocytic infiltration due to inflammation ("non-specific") involving the heart, lungs, liver, lymph nodes, kidneys, testes, prostate, adrenals and thyroid gland.

Conclusions:

The choice of dosage levels utilized in this study was questionable since 75% of the high dose animals died during the study (3 out of 4 animals of each sex). The clinical tests and histopathological examinations revealed an effect of the test compound at this dose. Decreased body weight of the animals at the high dose level, increased relative liver weight along with the related clinical tests and the liver and kidney damage that was noted by histopathology indicate that a dose level of 1500 ppm is associated with toxicity. The 2 lower doses did not show any compound related effect. A more conservative approach to choice of dosage would have produced a better study, possibly with less mortality at the high dose.

The systemic No Observed Effect Level (NOEL) for this study is 100 ppm.

Certain biochemical parameter recommended by CORE were not examined: calcium, phosphorus, fasting glucose and urea nitrogen.

Core Classification: Core-Minimum Data.

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Data Review:

Study Information:

Study Title: BAY 94 337 Subchronic Toxicological Studies on Rats
(Three-month feeding experiment)
Includes: Pathology Report of BAY 94 337 Three-Months
Feeding Study in Rats

EPA Identification Numbers: EPA Accession No. 112032

Sponsor: Mobay Chemical Corporation
Chemagro Agricultural Division
Kansas City, Missouri 64120

Testing Laboratory: Farbenfabriken BAYER AG
Institut für Toxikologie
Wuppertal-Elberfeld

Study Numbers: 1719 & 26469

Date: November 20, 1969
Pathology Report: December 31, 1969

Study Authors: Dr. rer. nat. Eckhard Loser
Pathology Report: Dr. Lionel E. Mawdesley-Thomas
(Study Director: Dr. med. Dietrich
Lorke)

Test Compound: BAY 94 337, Technical (also called Metribuzin, SENCOR)
Purity: not specified
Mixed in Altromin R powder feed

Dosage: 50, 150, 500 and 1500 ppm.

Test Animal: SPF Rats (Wistar Strain)
Bred by Winkelmann of Kirchbörchen
At beginning of study rats 28 to 32 days old, mean
body weight approximately 57 gms.

Materials and Methods: A copy of the materials and methods section
from the investigators report is appended.

The purity of the test compound was not provided.

There was no mention of criteria for daily clinical observations, although the results section mentions some observations ("appearance, behavior, activity and mobility").

Blood examinations, liver function tests, urinalysis, kidney function tests, blood sugar and cholesterol determinations were carried out on 5 animals per sex of each study group whereas Core recommends 8 animals per sex. Urinalysis and the other tests were carried out at 4 weeks and 3 months, the Core recommendation is every 30 days.

Complete hematological evaluations (including reticulocyte counts) were performed at 4 weeks and 3 months, another evaluation at 2 months should have been done, as per CORE recommendations of every 30 days.

The blood chemistry determinations of calcium, phosphorus, fasting glucose (although non-fasting blood sugar was measured) and urea nitrogen were not done. However, blood sugar, cholesterol and other blood tests for specific organ function were performed during the course of the study. These tests should also have been carried out prior to initiation of the study.

At post mortem all the organs recommended by Core were weighed except for the brain and pituitary. The investigators included the thymus in the examination.

A pathological examination report was provided as an addendum, however no protocol was provided. They presented observations in the liver, lungs, thyroid gland, pituitary gland, uterus and spleen in 5 animals per sex per group. Core recommends that all animals in the control and high dosage groups be examined with limited organ evaluation in the intermediate and low dosage groups.

Results:

I. Clinical Examinations:

The investigators stated that none of the treated animals differed from control in terms of "appearance, behavior, activity and mobility" or "with respect to consumption of feed or water", however no data was provided for these parameters.

II. Clinical Data:

A. Food Consumption:

Those animals receiving test compound in the diet consumed slightly less (not statistically significant) than that of the control group. See Table I below.

Table I: Mean Food Consumption

<u>MALES</u>	<u>Dose (ppm)</u>	<u>kg/animal</u>	<u>g/animal/day</u>
	Control	1.93	21.19
	50	1.66	18.27
	150	1.82	20.02
	500	1.77	19.49
	1500	1.71	18.76
<u>FEMALES</u>			
	Control	1.64	17.97
	50	1.38	15.12
	150	1.41	15.51
	500	1.33	14.66
	1500	1.34	14.73

Data extracted from Farbenfabriken BAYER AG Report No. 1719 Table 1.

In terms of ingestion of active ingredient, the females consistently received less (mg/kg b.w./day). See Table II below.

Table II: Mean Quantity of Active Ingredient Ingested (mg/kg body weight/day)

Dose (ppm)	Male	Female
Control	0	0
50	0.91	0.76
150	3.00	2.33
500	9.75	7.33
1500	28.13	22.09

Data extracted from Farbenfabriken BAYER AG Report No. 1719 Table 1.

B. Body Weight:

Based on data presented, the animals of the 50, 150 and 500 ppm test groups gained approximately the same amount of weight as the controls over the 90 day period, however both sexes of the 1500 ppm test group gained significantly less weight during the entire experimental period (females $p < 0.01$, males $p < 0.05$). See Table III below.

Table III: Mean Animal Body Weights (grams) at 3 Months

Dose (ppm)	Control	50	150	500	1500
Males	348.0	337.5	340.1	345.5	326.0*
Females	218.9	213.0	212.9	214.1	197.6**

* $p < 0.05$

** $p < 0.01$

Data extracted from Farbenfabriken BAYER AG Report No. 1719 Table 9a.

C. Mortality:

One male rat died in the control group (no cause of death provided) and one female rat was accidentally killed during a blood sampling.

D. Hematology:

At 4 weeks slightly decreased levels of hemoglobin were seen in 500 and 1500 ppm males and 150, 500 and 1500 females, also slight decreases in erythrocytes were seen in 500 and 1500 ppm animals of both sexes, reticulocytes were increased in a dose-related manner in 500 to 1500 ppm males and increased in all treated females, thrombocytes were decreased in 1500 ppm males. See Table IV.

At 4 weeks differential blood studies found that mature polymorphonuclear neutrophils appeared to be increased in 1500 ppm males and 50 to 1500 ppm females, also large lymphocytes were increased in all treated males and females. See Table IV.

Table IV: Hematological Parameters at 4 Weeks

<u>Dose (ppm)</u>	<u>HB†</u>	<u>ERY††</u>	<u>RETI†††</u>	<u>THROM††††</u>	<u>MPN†††††</u>
<u>MALES</u>					
Control	16.6	8.41	8.8	610	7.8
50	15.8	8.51	6.8	684	7.0
150	16.3	8.12	8.6	579	5.4
500	15.5	7.39	14.6	580	6.2
1500	14.6	7.29	21.4	447	9.2
<u>FEMALES</u>					
Control	16.0	8.07	8.8	541	4.6
50	16.0	8.88	12.0	529	6.8
150	14.9	8.30	11.2	646	4.2
500	15.1	7.22	16.2	498	5.4
1500	14.7	7.69	13.2	596	6.2

† - HB = hemoglobin as g%

†† - ERY = erythrocytes x 10⁶

††† - RETI = reticulocytes in 0/00

†††† - THROM = thrombocytes x 10³

††††† - MPN = mature polymorphonuclear neutrophils in %

Data extracted from Farbenfabriken BAYER AG Report No. 1719 Tables 2a and 2b.

The investigators state that these values are "within the normal range for the dosed rats", but no data were submitted to support this contention. There is no indication of any pathological condition.

At 3 months an increase in reticulocytes was seen in the 50 to 1500 ppm males and 500 and 1500 females, also an increase in leucocytes was seen in 500 and 1500 ppm males with a dose-response decrease in 50 to 1500 ppm females, thrombocytes were seen to have a dose related increase in 500 and 1500 ppm males and also an increase in 500 and 1500 ppm females. See Table V.

The differential blood count saw an increase in mature polymorphonuclear neutrophils in 500 and 1500 ppm males and 50 to 1500 ppm females with a decrease in large lymphocytes in 50 to 1500 ppm males and 150 to 1500 ppm females. See Table V.

Table V: Hematological Parameters at 3 Months

<u>Dose (ppm)</u>	<u>RETI†</u>	<u>LEUC††</u>	<u>THROM†††</u>	<u>MPN††††</u>	<u>L.L.†††††</u>
<u>MALES</u>					
Control	15.0	6.1	606	4.2	6.2
50	19.8	6.5	520	4.0	4.6
150	17.2	6.1	503	3.4	4.4
500	19.0	8.3	637	9.0	2.2
1500	19.0	7.6	672	4.8	3.4

continued

Table V: continued

FEMALES					
Control	19.6	6.7	534	3.8	3.4
50	20.2	6.4	535	8.8	3.0
150	15.2	5.4	557	4.8	1.4
500	24.4	4.7	630	8.4	2.8
1500	22.4	4.1	620	8.2	2.8

† - RETI = reticulocytes in 0/00
 †† - LEUC = leucocytes x 10³
 ††† - THROM = thrombocytes x 10³
 †††† - MPN = mature polymorphonuclear neutrophils in %
 ††††† - L.L. = large lymphocytes in %

Data extracted from Farbenfabriken BAYER AG Report No. 1719 Tables 3a and 3b.

The investigators stated that "the treated rats of all dose groups did not significantly differ from the control animals with respect to any of the examined parameters".

E. Liver Function Tests:

Studies at 4 weeks revealed slightly elevated alkaline phosphatase (ALP) levels in 150 and 1500 ppm males and 1500 ppm females, also an increase in glutamate-oxalacetate transaminase (GOT) levels in 150 to 1500 ppm males and 50 to 1500 ppm females, an increase in glutamate-pyruvate transaminase (GPT) levels in 150 to 1500 ppm females, there was an increase in total bilirubin levels in 1500 ppm animals of both sexes and an increase in total protein levels in 50 to 1500 ppm males and a dose-related increase seen in 50 to 1500 ppm females. See Table VI.

Table VI: Liver Function Tests at 1 Month

Dose (ppm)	ALP†	GOT††	GPT†††	BILI††††	PROT†††††
<u>MALES</u>					
Control	177.3	36.9	19.2	0.08	5.7
50	161.0	36.1	16.0	0.08	6.2
150	191.5	43.9	19.1	0.08	6.5
500	175.2	45.0	16.4	0.07	6.6
1500	204.3	53.2	20.3	0.15	7.7
<u>FEMALES</u>					
Control	147.6	52.2	14.8	0.07	5.0
50	134.7	64.9	14.8	0.06	6.0
150	127.6	70.6	17.7	0.07	6.3
500	148.1	55.4	16.1	0.06	6.4
1500	171.5	62.8	17.3	0.12	7.5

† - ALP = alkaline phosphatase in mU/ml
 †† - GOT = glutamate-oxalacetate transaminase in mU/ml
 ††† - GPT = glutamate-pyruvate transaminase in mU/ml
 †††† - BILI = total bilirubin in mg/100 ml
 ††††† - PROT = total protein in g/100 ml

Data extracted from Farbenfabriken BAYER AG Report No. 1719 Table 4.

At 3 months an elevation in ALP levels was seen in 1500 ppm males, increased GOT levels in 50 to 1500 ppm rats of both sexes, elevated GPT levels in 150 to 1500 ppm females and increased sorbital dehydrogenase (SDH) levels in 50 to 1500 ppm females and dose related in 50 to 1500 ppm males. See Table VII.

Table VII: Liver Function Tests at 3 Months

<u>Dose (ppm)</u>	<u>ALP†</u>	<u>GOT†</u>	<u>GPT†</u>	<u>SDH°</u>
<u>MALES</u>				
Control	86.2	25.0	17.4	2.3
50	85.0	28.5	17.2	2.6
150	82.7	28.7	19.4	3.0
500	83.8	30.4	17.5	3.6
1500	94.2	32.8	16.0	4.1
<u>FEMALES</u>				
Control	71.5	30.6	16.8	2.2
50	66.9	29.7	15.9	2.8
150	82.7	28.7	19.4	3.0
500	70.0	39.4	21.9	4.0
1500	73.2	33.7	20.0	3.3

† for definitions see Table VI

° - SDH = sorbital dehydrogenase in mU/ml

Data extracted from Farbenfabriken BAYER AG Report No. 1719 Table 5.

The investigators stated that all the levels seen "in male and female rats of all dose groups were within the physiological range for young rats".

F. Urinalysis and Kidney Function Tests:

The investigators stated that the urinalysis at 4 weeks and 3 months revealed no significant difference between control and treated animals. They utilized the "clinical stick" method for analysis. They further stated that those samples which were "slightly positive when tested for procein were about just as frequent among the treated rats as among the untreated ones". No data was provided for these parameters.

The urea determinations made at 4 weeks showed a dose related increase in male rats with an increase in females. The creatinine at 4 weeks showed an increase in 1500 ppm males. See Table VIII.

At 3 months essentially no differences were seen in urea or creatine levels. See Table VIII.

Table VIII: Urea and Creatinine Levels at 4 Weeks and 3 Months
in mg/100 ml.

Dose (ppm)	in mg/100 ml.		in mg/100 ml.	
	Urea at 4 weeks	Creatinine at 4 weeks	Urea at 3 months	Creatinine at 3 months
MALES				
Control	25.3	0.83	27.1	1.05
50	29.4	0.87	29.5	1.12
150	31.0	0.85	32.9	1.18
500	30.8	0.86	32.0	1.17
1500	34.0	1.07	28.4	1.20
FEMALES				
Control	30.8	0.88	27.8	0.96
50	35.4	0.96	31.6	0.99
150	34.3	0.93	30.5	0.89
500	31.0	0.97	30.6	1.00
1500	33.2	0.99	30.1	0.99

Data extracted from Farbenfabriken BAYER AG Report No. 1719 Table 6.

Protein determinations were unremarkable at the end of the study. Levels in males were variable while females were less variable. No set pattern was seen. See Table IX.

Table IX: Total Protein in the Urine (mg/100 ml.)

Dose (ppm)	MALES	FEMALES
	Control	71.3
50	57.6	35.8
150	79.0	17.7
500	32.0	25.9
1500	57.8	28.8

Data extracted from Farbenfabriken BAYER AG Report No. 1719 Table 7.

The investigators stated that all "levels were within the physiological range for rats".

G. Blood Sugar and Cholesterol Determinations:

Blood sugar determinations at 4 weeks showed a reduction in males (dose related at 150 to 1500 ppm) with females showing a dose related increase at 50 to 1500 ppm while at 3 months no real differences in blood sugar were seen. See Table X.

Cholesterol levels at 4 weeks showed an increase in 1500 ppm males and 500 to 1500 ppm females and at 3 months there were increases in cholesterol of males and females of the 500 and 1500 ppm groups. See Table X.

Table X: Blood Sugar and Cholesterol Levels at 1 and 3 Months

Dose (ppm)	in mg/100 ml.			
	1 Month		3 Months	
	Blood Sugar	Cholesterol	Blood Sugar	Cholesterol
MALES				
Control	81	83.7	85	104.3
50	72	75.8	86	106.6
150	77	84.4	81	107.9
500	68	87.6	80	119.0
1500	63	100.3	93	121.4
FEMALES				
Control	69	94.1	98	111.2
50	66	91.5	88	111.8
150	76	95.6	88	104.3
500	74	100.2	93	128.3
1500	75	131.4	98	134.8

Data extracted from Farbenfabriken BAYER AG Report No. 1719 Table 8.

The investigators state that the results of the tests are not "within the pathological range".

III. Necropsy Data:

The investigators stated that "none of the autopsied rats showed any macroscopic changes of the inner organs attributable to the inclusion of the active ingredient in the diet". No data was provided to substantiate this.

A. Organ Weight:

An increase was observed in thyroid weight significant in 1500 ppm males and 500 to 1500 ppm females. The heart showed a significant decrease in weight in the 1500 ppm rats of both sexes. The lungs showed an increase in weight significant in females at 1500 ppm. The liver showed the greatest effects with an increase in weight, seen especially in females, dose related, significant at all 4 dose levels in females and at 1500 ppm in males. Spleen weight was significantly increased in females at 1500 ppm with males showing a trend towards an increase. The kidney weight showed a dose related trend of increase in females, significant at 1500 ppm, males were increased over control. Ovaries in the females were significantly increased at 1500 ppm. The thymus and adrenals showed no remarkable differences. See Table XI.

Table XI: Mean Absolute and Relative Organ Weights (mg)

Dose (ppm)	Absolute Organ Weights						
	Thyroids	Heart	Lung	Liver	Spleen	Kidneys(2)	Gonads
MALES							
Control	21.2	1050.6	1204.2	12578.4	563.8	2367.5	3248.9
50	22.1	978.5	1094.8	11452.8	555.9	2170.4	3123.7
150	21.3	1004.4	1122.3	11617.6	547.4	2231.9	3123.7
500	20.5	981.7	1112.5	11944.3	536.9	2396.3	3128.0
1500	27.8**	913.7**	1106.7	13371.1	597.6	2264.3	3113.7
FEMALES							
Control	17.0	718.5	860.0	7285.1	422.4	1448.2	121.8
50	19.4	707.1	917.8	7791.5	396.9	1444.9	119.1
150	18.6	717.6	890.4	8058.9*	408.6	1494.9	128.4
500	19.8*	704.8	896.6	8221.5*	435.8	1470.3	132.3
1500	27.5**	658.7**	875.2	8199.2*	411.9	1452.6	128.7

Relative Organ Weights (per 100 gm body weight)

MALES							
Control	6.1	302.0	346.2	3618.9	161.8	631.4	935.9
50	6.5	291.2	325.7	3399.4	164.5	645.8	932.9
150	6.2	295.5	330.5	3406.9	161.4	657.0	919.8
500	5.9	284.2	323.1	3450.4	155.3	697.6	909.1
1500	8.5**	279.6*	339.7	4083.6**	183.1	693.8	956.4
FEMALES							
Control	7.8	328.8	393.2	3332.1	192.9	661.0	55.7
50	9.2	333.0	431.3	3662.4*	186.2	679.1	56.1
150	8.9	337.9	420.2	3796.9*	192.8	705.5	60.9
500	9.2	329.0	418.8	3839.9**	203.3	686.7	61.7
1500	13.9**	334.6	444.2**	4156.8**	208.7*	735.7**	65.3**

*p < 0.05

**p < 0.01

Data extracted from Farbenfabriken BAYER AG Report No. 1719 Table 9a and 9b.

B. Pathological Examination:

This was included as an addendum to the report.

The pathologist found evidence of chronic interstitial pneumonitis (not graded, described as "evidence of some" or "minimal degree"). The liver had small changes in "hepatocyte size" (not specified) along with occasional lymphocytic infiltration. The thyroid gland showed evidence of hyperactivity (eg. changes in follicular size). The investigators stated that this occurred in the 1500 ppm animals with some minimal changes seen in the 500 ppm group, however, there is evidence in all dose groups (4/10 in control, 8/10 in 50 ppm, 10/10 in 150, 9/10 in 500 and 8/10 in 1500 ppm). Occasional pituitary cysts and hydrometria of the uterus were noted in both control and treated groups. The data provided did not include grading of lesions.

Conclusions: The investigators found no effects on "appearance, behavior, activity and mobility" or "with respect to consumption of feed or water". However there was a slight non-significant reduction in food intake in the treated groups. Body weight was found to be significantly reduced in the 1500 ppm group animals of both sexes.

Increases in weight in the 1500 ppm group thyroid, lung, liver, spleen, kidneys and gonads along with a reduction in heart weight were observed. The increase in liver weight was significant in all 4 dose groups in the females and at 1500 ppm in the males.

Pathological examinations revealed changes in lung and liver in relatively equal incidence in all groups.

Based on data presented the systemic No Observed Effect Level (NOEL) is below 50 ppm, since the increase in liver weight was statistically significant at all 4 dose levels in the females.

Core-Classification: Core-Supplementary Data since no NOEL could be established for this study, no protocol was provided for the pathological examinations and only limited organs and small numbers of animals were used for the histopathological studies. Another study was conducted subsequent to this one (BAYER AG Report Number 2150).

NETRIBUZIN

Page _____ is not included in this copy.

Pages 96 through 99 are not included.

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Data Review:Study Information:

Study Title: BAY 94 337 Subchronic Toxicological Studies on Rats
(Three-Month feeding experiment)
Includes: Pathology Report of BAY 94 337 Three-Months
Rat Study (Addendum to Report No. 2150)

EPA Identification Numbers: EPA Accession No. 112032

Sponsor: Mobay Chemical Corporation
Chemagro Agricultural Division
Kansas City, Missouri 64120

Testing Laboratory: Farbenfabriken BAYER AG
Institut für Toxikologie
Wuppertal-Elberfeld

Report Numbers: 2150 & 27908
Pathology Addendum: 3777/70/599 & 27908a

Date: July 6, 1970
Pathology Report: October 30, 1970

Authors: Dr. rer. nat. Eckhard Loser
Pathology Report: Eric J.F. Spicer
Study Director: Dr. med. Dietrich Lorke

Test Compound: BAY 94 337, Technical (also called Metribuzin, SENCOR)
Purity: not specified
mixed in Altromin R powder feed

Dosage: 10, 25 and 60 ppm.

Test Animal: SPF Rats (Wistar Strain)
Bred by Winkelmann of Kirchborchen
At the beginning of study rats were 28 to 32 days
old, average body weight: 52.7 gms for males; 53.9
gms for females.

Materials and Methods: A copy of the materials and methods section
from the investigators report is appended.

The purity of the test compound is not stated.

Clinical laboratory examinations were made on 5 rats per sex
at 4 weeks and 3 months, whereas Core recommends 8 animals per
sex every 30 days and should have been done on day 0 of study.

Hematology examinations (including reticulocyte counts) and
urinalysis were done only at 4 weeks and 3 months whereas Core
recommends every 30 days. The urinalysis studies utilized
"clinical sticks" for sugar, protein and blood. Bile pigment
content and microscopic examination of sediment were also analyzed.

Kidney function tests involved measurement of urea and creatinine in the serum along with blood sugar (not fasting) and cholesterol levels, however calcium, phosphorus, fasting glucose and urea nitrogen determinations were not performed.

Liver function tests involved alkaline phosphatase, glutamateoxalacetate transaminase, glutamate-pyruvate transaminase, sorbitol dehydrogenase, bilirubin content and total protein content in heparin plasma.

Post-mortems were conducted on all animals surviving to the end of the study. Thyroids, thymus, heart, lung, liver, spleen, kidneys, adrenals and gonads were weighed and macroscopically examined.

This study report included a pathology report (with protocol) as an addendum. The tissues that were examined are as follows: heart; kidney; lung; pituitary; testes; ovaries; uterus; cervix; liver; spleen; thymus; stomach; duodenum; adrenal; thyroid; cerebral cortex; thalamic nuclei; midbrain; cerebellum. Tissues that were not examined but recommended for examination by Core are as follows: spinal cord; eye; salivary gland; trachea; esophagus; large intestine; pancreas; urinary bladder; aorta; prostate; lymph nodes; bone with marrow; skeletal muscle; skin; sciatic nerve; mammary gland; skeletal joint.

The histological examinations were conducted for only 5 rats per sex in each group whereas Core recommends all animals in control and high dosage groups with limited organ evaluation in intermediate and low dosage groups.

Results:

I. Clinical Examinations:

The investigators stated that the test groups, "did not differ from the control animals in appearance, behavior, activity and mobility" also no differences were found "with respect to consumption of feed or water", however no data was provided for these observations.

II. Clinical Data:

A. Food Consumption:

There were no differences seen in food consumption. In reference to the average quantity of active ingredient ingested, the males received slightly more at the high dose (1.31 mg/animal/day) than the females (1.06 mg/animal/day).

B. Body Weight:

There was no significant difference in body weight gain in either males or females between the 3 study groups and control.

C. Mortality:

One male and one female of the control group were sacrificed due to poor condition, another male of the control group injured itself and another female control was killed by accident during blood sampling. One male of the 10 ppm group and one female from the 25 ppm group died, the cause of death diagnosed as pneumonia.

No compound related deaths were noted.

D. Hematology:

Although, at 4 weeks decreases in the reticulocytes and medium cell volume of 60 ppm females, increases in leucocytes in the 10 to 60 ppm males, increases in thrombocytes, in 25 to 60 ppm males and decreases in 10 to 60 ppm females were observed, along with differential blood counts at 4 weeks showing an increase in mature polymorphonuclear neutrophils in 10 to 60 ppm males and 25 to 60 ppm females, the effects on these parameters were not compound related. The changes were not seen in the earlier study (BAYER AG Study # 1719) at the higher dosage levels used. The investigators stated that the values "were within the normal range for the dosed rats of all groups", including the differential counts. See Table I.

Table I: Hematological Parameters at 4 Weeks

Dose (ppm)	RETI†	MCV††	LEUC†††	THROM††††	MPN†††††
<u>MALES</u>					
Control	19.2	63	5.6	698	5.0
10	22.4	67	6.3	627	7.2
25	16.6	65	6.0	710	8.2
60	24.2	62	6.6	782	5.6
<u>FEMALES</u>					
Control	21.0	66	6.5	774	5.6
10	20.4	65	5.5	725	2.6
25	19.8	63	6.5	713	9.2
60	13.4	56	5.7	642	8.0

† - RETI = reticulocytes in 0/00

†† - MCV = medium cell volume in μm^3

††† - LEUC = leucocytes $\times 10^3$

†††† - THROM = thrombocytes $\times 10^3$

††††† - MPN = mature polymorphonuclear neutrophils in %

Data extracted from Farbenfabriken BAYER AG Report No. 2150 Tables 3a and 3b.

At 3 months increased erythrocytes in 10 to 60 ppm males, increased reticulocytes in 10 to 60 ppm animals of both sexes and decreased thrombocytes of 60 ppm females were observed. See Table II.

The differential blood counts at 3 months showed variable counts mature polymorphonuclear neutrophils and large lymphocytes in both sexes. See Table II.

Table II: Hematological Parameters at 3 Months

<u>Dose (ppm)</u>	<u>ERY†</u>	<u>RETI††</u>	<u>THROM†††</u>	<u>MPN††††</u>	<u>L.L.†††††</u>
<u>MALES</u>					
Control	6.77	9.8	406	6.8	2.4
10	7.42	11.8	543	9.4	1.2
25	7.94	15.4	458	9.4	1.6
60	7.31	15.2	418	3.6	1.8
<u>FEMALES</u>					
Control	6.68	13.0	605	12.8	0.8
10	6.75	16.8	688	10.0	0.6
25	6.31	28.0	602	12.0	2.2
60	6.28	25.6	572	9.0	0.4

† - ERY = erythrocytes x 10⁶

†† - RETI = reticulocytes in 0/00

††† - THROM = thrombocytes x 10³

†††† - MPN = mature polymorphonuclear neutrophils in %

††††† - L.L. = large lymphocytes in %

Data extracted from Farbenfabriken BAYER AG Report No. 2150 Tables 4a and 4b.

There was no biological trend apparent from these data.

E. Liver Function Tests:

At 4 weeks increased levels of glutamate-oxaloacetate transaminase (GOT) in 10 to 60 ppm males and 25 to 60 ppm females, also increased levels of glutamate-pyruvate transaminase (GPT) in 25 to 60 ppm male and, dose related, 25 to 60 ppm females were noted. See Table III.

The investigators stated that the "levels in the rats of all dose groups were within the normal range".

At 3 months increased GOT levels in 25 to 60 ppm males, variable GPT levels in males, decreased GPT levels, in a dose-related manner, in females and increased sorbital dehydrogenase (SDH) levels in all treated animals (dose related in males) were observed. See Table III.

Table III: Liver Function Tests at 1 and 3 Months

<u>Dose (ppm)</u>	<u>in mU/ml.</u>		<u>GOT</u>	<u>GPT</u>	<u>SDH†††</u>
	<u>GOT†</u> <u>at 1 month</u>	<u>GPT††</u>			
MALES					
Control	32.0	14.1	31.3	13.0	1.5
10	39.7	14.2	31.4	7.1	1.6
25	42.0	17.6	45.7	16.6	2.3
60	41.6	18.9	40.0	9.9	2.2
FEMALES					
Control	40.4	14.4	28.5	13.2	1.2
10	35.7	13.9	21.1	11.1	1.9
25	45.2	16.0	26.9	10.7	2.6
60	42.4	18.4	30.3	8.8	2.3

† - GOT = glutamate-oxaloacetate transaminase

†† - GPT = glutamate-pyruvate transaminase

††† - SDH = sorbital dehydrogenase

Data extracted from Farbenfabriken BAYER AG Report No. 2150 Tables 5 and 6.

The investigators stated that they did not see "any dose-dependent" changes.

F. Urinalysis and Kidney Function Tests:

According to the investigators, there was no sugar or blood, as analyzed by "clinical sticks" in the urine and no evidence of urobilinogen or differences in the evidence of protein between any of the study groups. No data was provided for any of these parameters.

At 4 weeks and 3 months there were no remarkable differences noted in urea or creatinine levels.

The investigators stated that levels were "within the normal range".

Protein determinations conducted at the end of the study found increases in 60 ppm males and 10 to 60 ppm females but the investigators stated that all findings were "within the physiological range". See Table IV.

Table IV: Protein Levels in Urine (24 hour)
in mg/100ml.

<u>Dose (ppm)</u>	<u>MALES</u>	<u>FEMALES</u>
Control	31.5	22.5
10	25.0	25.1
25	31.7	29.3
60	41.5	28.8

Data extracted from Farbenfabriken BAYER AG Report No. 2150 Table 8.

G. Blood Sugar and Cholesterol:

At 4 weeks and 3 months there were no remarkable differences seen in measured blood sugar. Although, at 4 weeks a dose-related increase in cholesterol in 10 to 60 ppm animals of both sexes were noted and at 3 months the increase in cholesterol, in 10 to 60 ppm males was still observed, however the female levels were less consistent. See Table V.

Table V: Cholesterol Levels at 1 and 3 Months
in mg/100 ml.

Dose (ppm)	1 month		3 months	
	MALES	FEMALES	MALES	FEMALES
Control	75	72	64	58
10	77	81	68	69
25	82	84	79	63
60	90	93	71	57

Data extracted from Farbenfabriken BAYER AG Report No. 2150 Table 9.

According to the investigators the blood sugar and cholesterol levels were "not within the pathological range".

III. Necropsy Data:

The investigators stated that "none of the autopsied rats showed any macroscopic changes of the inner organs attributable to inclusion of the active ingredient in the diet", however no data was provided to support this statement.

A. Organ Weights:

In a previous study (Farbenfabriken BAYER AG Report No. 1719), the liver, thyroid glands, heart, lungs, spleen, kidneys and gonads showed changes in weight, relative to this study only the liver showed an increase in weight in both sexes with 60 ppm females statistically significant at 0.05 level. See Table VI below.

Table VI: Mean Absolute and Relative Organ Weights
Absolute Organ Weights (mg)

Dose (ppm)	Thyroids	Thymus	Lung	Liver	Spleen	Kidneys
MALES						
Control	22.5	312	1198	10844	664	2205
10	25.5	334	1159	12387	680	1976
25	25.1	295	1154	11462	613	2091
60	24.9	273	1106	11337	640	2160
FEMALES						
Control	17.9	307	919	7552	473	1362
10	18.7	269	889	7581	476	1376
25	16.9	272	888	7527	460	1338
60	19.7	306	871	7928*	453	1294

continued

Table VI continued

	Relative Organ Weights (per 100 gm body weight)					
	Thyroids	Thymus	Lung	Liver	Spleen	Kidneys
MALES						
Control	6.4	89	342	3073	189	631
10	7.2	94	327	3485	192	557
25	7.3	86	335	3325	178	607
60	7.1	79	319	3272	185	623
FEMALES						
Control	8.5	147	438	3590	226	649
10	9.0	130	429	3671	231	665
25	8.2	132	431	3655	223	650
60	9.3	145	411	3750*	214	612

*p < 0.05

Data extracted from Farbenfabriken BAYER AG Report No. 2150 Tables 10a and 10b.

B. Histological Evaluation

This study included a histological evaluation of certain organs (see page 2, this review) of 5 rats per sex per study group.

The pathologists found evidence in the respiratory tract of chronic interstitial pneumonitis (not graded, only "minimal degree" or "moderate degree") also parasite granuloma in one male of the 25 ppm test group. Lymphocytic aggregation in the portal tracts of the liver were reported in all test groups. In the kidneys minimal dystrophic mineralization (in all groups), 2 animals with calculi (both 25 ppm females) and occasional small aggregations of lymphocytes were reported. Slight congestion in the adrenals (a 25 ppm male), one female control with lymphocytic aggregation in the pons and occasional hydrometia (one incidence each in the 10, 25 and 60 ppm groups) were also reported.

The increase in the 25 and 60 ppm group of the pigment containing macrophages in the spleen should have been addressed.

Conclusions:

The investigators found no differences between groups "in appearance, behavior, activity and mobility" and also no differences "with respect to consumption of feed and water". There were also no differences in respect to body weight gain and mortality.

The observations in hematological parameters, liver function tests, urinalysis, kidney function tests, blood sugar levels and cholesterol levels were not compound related and were not noted in the earlier study (BAYER AG Study # 1719) at the higher dose levels examined. The investigators did not conduct these measurements on the first day of the study (day 0) and there was a lack of historical control data for comparison.

Necropsy examinations found an increase in liver weight in the females, statistically significant at 60 ppm and a trend in males. Histopathology was unremarkable between groups.

A systemic No Observed Effect Level (NOEL) of 25 ppm can be set as determined by the increase in liver weight at 60 ppm, which is the Lowest Observed Effect Level (LOEL) for this study. The previous subchronic study (BAYER AG Study # 1719) could not establish a NOEL for the study (NOEL < 50 ppm) due to an increase in liver weight that was statistically significant at all 4 dose levels in the females.

Core Classification: Core-Supplementary Data based on the limited organs, the small number of animals examined for histopathology and the limited clinical chemistry that was conducted.

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Pages 108 through 110 are not included.

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Data Review:

Study Identification:

Study Title: The Metabolism and Excretion of SENCOR in Rats.

EPA Identification Numbers:

Sponsor: Mobay Chemical Corporation
Chemagro Agricultural Division
Kansas City, Missouri 64120

Testing Laboratory: Chemagro Division of Baychem Corporation
Research and Development Department

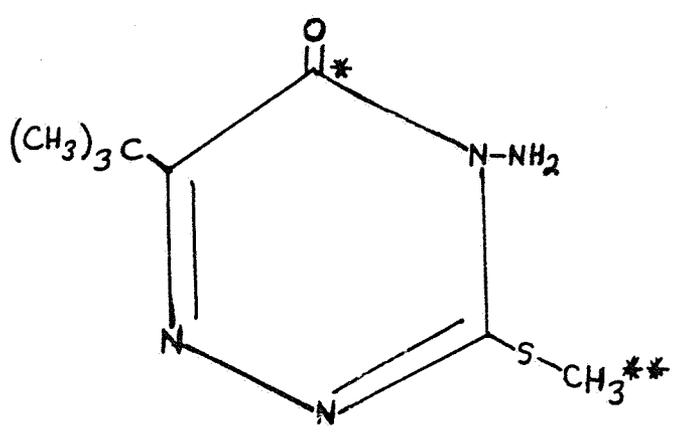
Report Number: 33366

Date of Study: May 1, 1972
Revised July 5, 1973 (to add additional information)

Study Authors: D.R. Flint
R.R. Gronberg
F.E. Sandie

Study Director: T.B. Waggoner

Test Compound: SENCOR [4-Amino-6-t-butyl-3-(methylthio)-1,2,4-triazin-5(4H)-one] (below) initially labeled with carbon-14 in the carbonyl group* and with tritium in the s-methyl group**.



Radiolabelled SENCOR

Dosages: First excretion study: 4 mg SENCOR - ^{14}C , ^3H in 0.8 ml 50% aqueous ethanol for a dose rate of 20 mg/kg in a 200 gm rat given orally by gavage (stomach tube).

Second excretion study and tissue residue studies: SENCOR (presumably ^{14}C labelled only, although not clearly stated) administered orally as a suspension in 0.5% aqueous gum tragacanth. For animals weighing 150 to 165 gm, dosage volumes of 0.75 to 1.00 ml per animal were administered (presumably by gavage). The dose rates were calculated as 100 and 50 mg/kg for these studies.

Test Animals: Rats, Sprague-Dawley strain
Sprague-Dawley Company

Experimental: A copy of the experimental section from the investigators report is appended.

There was no clear indication as to how many animals were used at study initiation, however the results section states that one male and one female rat were used for the first excretion study, 2 males for the second excretion study and from the tables, 2 males and 2 females for the tissue residue studies. Also the age and sex of the animals was not given (although the results sections mentions male and female).

Apparently 2 excretion studies were conducted, one using glass metabolism cages with collection of respiratory gases and the other study using plastic with no collection of gases.

There was no mention of the purity of the test compound (a statement was made: "All equipment was standard except as listed and all chemicals were reagent grade or better.").

There was no indication of the time period for observation of animals (Guidelines state 7 days or until 90+% of the administered dose is excreted, with the animals in individual metabolism cages), although the individual tables in the final report state collection times.

The investigators examined expired air (only in the initial study for both ^3H and $^{14}\text{CO}_2$), urine, feces, blood, plasma, liver, kidney, heart, brain, muscle, testes, ovaries and fat. There was apparently no analysis of bone, lungs, spleen or residual carcass.

Results:Excretion Studies:

The first study (using ^{14}C , ^3H labelled SENCOR) involved only 2 animals, one male and one female. The investigators reported sex related differences in excretion where in the male, 60.7% of the recovered radioactivity was found in the feces and in the female, 57.4% of the recovered radioactivity was found in the urine (over 90% of ^{14}C was recovered in urine and feces of both animals over a 16 day period). These values probably include measured ^3H levels as the total values on Table I do not totally agree. They further stated that no ^{14}C was recovered in the expired air. Sex related differences were also seen in the blood and tissue studies (to be discussed later).

The second study used 2 male rats (using only ^{14}C labelled SENCOR). The investigators found 45.89% of the radioactivity in the feces and 56.27% in the urine, from these finding they justified their reason for not collecting expired air, since the total was 102.16% of the administered radioactivity. See Table I. The excretion peak levels from this study were generally in agreement with the earlier study.

Table I: Excretion of Radioactivity (% of administered radioactivity)

Hours Post-Administration	Male		Female		2 Males	
	Urine	Feces	Urine	Feces	Urine	Feces
6.0	-	-	-	-	7.86	-
7.0	8.21	0.08	7.27	0.06	-	-
7.5	-	-	-	-	-	0.75
9.0	-	-	-	-	3.24	-
12.0	4.78	9.21	10.23	0.93	5.09	-
18.0	13.51	4.77	17.70	9.08	-	-
24.0	4.59	6.43	8.50	6.73	18.90	-
30.0	2.42	25.23	2.85	12.73	-	29.80
48.0	1.25	6.38	3.02	7.04	9.52	21.76
72.0	0.52	2.60	1.10	1.78	0.45	2.74
96.0	-	-	-	-	0.47	0.36
100.0	0.26	0.39	0.41	0.05	-	-
120.0	-	-	-	-	0.36	0.87
124.0	0.11	0.10	0.20	0.05	-	-
16 days	0.36	0.34	0.57	0.14	-	-
TOTAL	36.00	55.53	51.85	38.59	45.89	56.27

Data extracted from CHEMAGRO Report No. 33366 Tables I and II.

Tissue Residue Studies:

These determinations reportedly involved 2 male and 2 female rats. The investigators stated that the residue levels were "generally similar" between the male and female rats except at 28 hour (after administration) interval which showed the females retaining more of the radioactivity in all tissues examined. After this time point the decline is similar, however the females still show slightly higher levels. There were not enough animals for statistical evaluation. The investigators further state that this was due to "sex-related differences in rates of absorption, metabolism, distribution and/or excretion". The table which they present for "half-lives" compares different interval measurements. See Table II.

Table II: Radioactive Residues in Rat Tissues (estimated "half-lives" of total ¹⁴C in hours)

<u>Tissue</u>	<u>Male†</u>	<u>Female††</u>
Brain	21.1	22.4
Heart	26.4	33.6
Liver	30.4	33.6
Kidney	26.9	31.2
Muscle	21.3	24.5
Testes or Ovaries	18.4	30.4
Fat	25.0†††	24.8
Blood Plasma	19.1	27.2

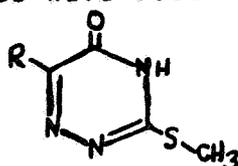
- † - determined over a 24 to 96 hour interval.
- †† - determined over a 48 to 96 hour interval.
- ††† - apparent biphasic decay curve after 24 hours.

Data extracted from CHEMAGRO Report No. 33366 Table III.

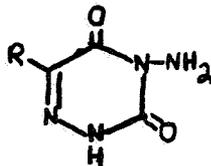
The investigators noted high tissue residue levels in liver and kidney (stated "presumably due to concentration in these organs for detoxification and elimination"). As can be seen in Table II the female rat presented with higher residue levels in heart, kidney, sex organs and blood plasma than the male rat.

Metabolite Identification:

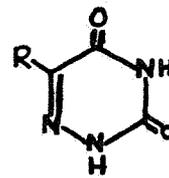
From earlier metabolism studies in the soybean plant, three metabolites have been identified.



A



B



C

R = tertiary butyl

- A - DA, deaminated SENCOR, also called BAY Dic 2058
 B - DK, diketo SENCOR
 C - DADK, deaminated diketo SENCOR, also called BAY Dic 2164

These metabolites were also identified in the animal studies. However, not all the residues were accounted for in the present study and many of the methods employed by the investigators destroyed much of the primary metabolites; this was especially true for the conjugate hydrolysis methods. The investigators should have employed non-harsh methods which could have involved the pre-separation of the metabolites prior to analysis and then study each metabolite separately.

Urine:

The investigators employed thin-layer chromatography (TLC) methods for urine studies. They observed that very polar solvent systems were needed to separate the samples and stated that this indicated that there were "either highly polar metabolites or, more likely, conjugated metabolites".

Enzyme incubation did not substantially change the pattern urine metabolites. The investigators then employed acid hydrolysis and found that one third of the radioactivity in the urine was rendered organoextractable. The organoextractable fraction was submitted to gas chromatographic analysis and SENCOR, DA, DK and DADK metabolites were found.

From other experiments the investigators stated that they found that the conditions of hydrolysis (not given) can affect a near complete de-thiomethylation of SENCOR and the DA metabolite to produce the DK and DADK metabolites, therefore the procedure of using acid hydrolysis after enzyme treatment was not an accurate determination of urine metabolic distribution.

Studies with potatoes found that incubation in buffers of near neutral pH at 37°C could release significant amounts of SENCOR without other treatment.

A pooled 24 hour rat urine specimen was first deproteinized with perchloric acid and then extracted twice with isopropyl ether (IPE). The IPE extracts were analyzed by gas chromatography revealing small amounts of SENCOR and the 3 metabolites. The water soluble portion was analyzed by gel filtration. Two large fractions were found and were further treated by hydrolysis and ion-exchange chromatography. Although the investigators state that work in the area is not complete, they feel that significant amounts of the fractions they found from gel filtration are conjugates of SENCOR and its metabolites.

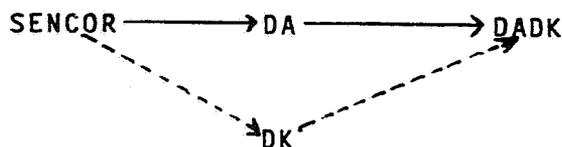
Tissues:

Liver and muscle tissues from male and female rats were homogenized in a two-phase water-chloroform system and each phase was assayed. They found slight differences in liver distribution of the compound between the male and female rats, whereas muscle distribution showed no sex related differences. The insoluble residue from the 28 hour female rat liver tissue extraction was also assayed using various enzymatic and hydrolytic methods (below).

The investigators evaluated several procedures and decided to employ a pepsin digestion followed by an acid hydrolysis of the aqueous phase. They were able to render 94-96% of the activity in the muscle, 55-78% of the activity in the liver and 43-58% of the activity in the kidney organosoluble. They could also render 63-96% of the activity of the brain and heart organosoluble without acid hydrolysis.

Tissues from male and female rats, collected at 4 and 28 hours after ¹⁴C-SENCOR administration showed similar patterns of metabolites (no sex related differences). They determined that the DA metabolite appears early with the DK and DADK metabolite being produced at later intervals.

The scheme is as follows:



The investigators state that "the solid line indicates the more active pathway". However it is noted that on page 15 of the report both dotted lines point to "DK" and on page 16 one dotted line points to "DK" and the other to "DADK". The latter is consistent with the findings of the report.

Feces:

In a preliminary investigation the investigators tried organic extraction with acetone, methanol and then water. They were unable to extract the isotopes. TLC analysis yielded little information. No other procedures were tried.

Conclusions:

The excretion studies found sex related differences with the males excreting the radiolabel primarily in the feces and the females excreting the label primarily in the urine, however this reviewer feels that an inadequate number of animals was used in this study (one male and one female in one study and two males in another study). Tissue distribution studies also suggested slight sex related differences in distribution up to the 28 hour interval (after administration) with similar patterns of reduction in residue levels after that time point (however the females tended to present with higher overall levels at all time points measured). These studies also used an inadequate number of animals.

The investigators found a metabolic scheme for SENCOR in rats that was similar to what was found in an earlier study in soybeans. The metabolites that were identified are:

- deaminated SENCOR (DA), also called BAY Dic 2058
- diketo SENCOR (DK)
- deaminated diketo SENCOR (DADK), also called BAY Dic 2164

Additional metabolites were not identified.

The following are the study deficiencies:

1. The numbers of animals used was inadequate.
2. The age of the animals was not provided.
3. The purity and clear isotope identification of the test compound was not given.
4. Rationale for time frame used for collection of urine, feces and expired air since there should have been some time points earlier than the 7.0 hour in one study and 6.5 in the other.
5. There was no tissue analysis of bone, lungs, spleen and residual carcass.

Core Classification: Core-Supplementary Data based on above deficiencies.

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Data Review:Study Identification:

Study Title: The Metabolic Fate of Carbonyl ^{14}C -SENCOR in Dogs.

EPA Identification Numbers:

Sponsor: Mobay Chemical Corporation
Chemagro Agricultural Division
Kansas City, Missouri 64120

Testing Laboratory: Chemagro
Division of Baychem Corporation
Research and Development Department

Report Number: 33361

Date of Study: May 1, 1972

Study Authors: A.M. Khasawinah
D.R. Flint
H.R. Shaw
D.D. Cox

Study Director: T.B. Waggoner

Test Compound: Carbonyl carbon-14 label SENCOR with a specific activity of 1.45 mC/mM. Radiochemical purity >99% (determined by thin-layer chromatography). This chemical was diluted with unlabeled pure crystalline SENCOR to give a specific activity of 2273 dpm/ug (0.22 mC/mM).

Dosage: 200 mg oral dose of the labeled material in a gelatin capsule (#000), giving an approximate 10 mg/kg (body weight) dose.

Test Animal: Adult male dogs (3 hounds and 1 mongrel)
Supplier: Mr. George C. Lindquist
Hallsville, Missouri 65255

Experimental: A copy of the experimental section from the investigators report is appended.

No justification/reasoning was provided for the use of dogs in this study (unless this is a preliminary study for developing information on comparative metabolism).

The age of the animals was not provided.

Only one dose level was employed in this study. According to the Guidelines "at least two dose levels should be used, the low dose level should correspond to the no-effect level and the upper dose should produce toxic or pharmacologic signs, but should not produce severe effects or a high incidence of mortality which would prevent a meaningful evaluation."

The 4 dogs were sacrificed at different time periods (4, 24, 72 and 120 hours), these points did not provide much overlap in time periods especially in terms of collection of excretion products.

The expired air from the dogs was not collected. However in a study in rats conducted concurrently with this study, the investigators determined that no radiolabel (^{14}C) was excreted in the expired air.

The following tissue samples were collected: liver; heart; kidney; muscle; fat; brain; skin. There was no evidence that samples of bone, sex organs, lung, spleen or residual carcass were collected.

Results:

Absorption and Distribution in Tissues:

The investigators state that there was rapid absorption of the ^{14}C label from the gastrointestinal (GI) tract. They claim that maximum absorption from the GI tract occurs at 4 hours after administration of radiolabeled SENCOR. Blood samples were taken at 1, 2, 4 hours and greater intervals and the peak levels were found at the 4 hour period. However, the investigators also state this time point for maximum tissue levels, this claim cannot be made for the tissue levels since the first tissue samples were checked at 4 hours and only in one animal with the next animal sacrificed at 24 hours post administration.

They found 40-99% of the radioactivity as free SENCOR and its metabolites (specifically the deaminated (DA) metabolite). Fat tissue contained mostly non-metabolized SENCOR while liver tissue presented with a greater quantity of metabolites.

The investigators found that radioactive tissue residues declined after 4 hours, again assessed by individual time points in a single dog. They state that the $T_{1/2}$ of the tissue residues was less than 24 hours. However, it appears that the $T_{1/2}$ in the tissues could not be precisely determined due to an inadequate number of animals and time points for collection of tissues.

The investigators reported that the radioactivity in blood was first primarily found in the plasma and later in the red blood cells.

Excretion Studies:

A rapid excretion of metabolites in the urine was not found, however, this conclusion is limited by the small number of animals. Combined urine and fecal radioactivity was 89.4% for animal # 2 (72 hour) and 85.9% for animal # 4 (120 hours). When combined with tissue residue levels, recovered radioactivity for animal # 2 is 94.2% and animal # 4 is 88.0%.

Tissue Metabolite Studies:

The investigators determined that the radioactivity in the tissues could not be extracted by organic solvents after 24 hours, therefore they tried enzymatic and chemical hydrolysis.

Papain and trypsin treatment of tissue from a 24 hour liver helped solubilize the radioactivity in water (66-88%) but no increase in the organoextractable fraction (4-5%) was seen.

Acid hydrolysis of a 24 hour liver sample yielded 92% of the radioactivity in the tissue organosoluble.

Steam autoclaving combined with acid hydrolysis of liver and kidney tissue samples was found to render nearly all the radioactivity organosoluble (liver - 86 to 120%, kidney - 65 to 96%), but the investigators found it did not yield a true pattern of metabolites. One-hundred twenty percent of the radioactivity of the 120 hour liver sample was found to be organoextractible.

Urine Metabolite Studies:

According to the investigators, thin-layer chromatography (TLC) studies at 4, 24 and 48 hours were not successful since they observed no movement of the sample on the plates. Also, since the investigators could not find any organoextractable radioactivity, they concluded that no free SENCOR or metabolites were eliminated in the urine.

Gel permeation chromatography studies yielded 2 peaks. From this finding the investigators then subjected the 24 hour urine samples to "specific enzymatic chemical and general enzymatic (bacterial) hydrolysis". Very little of the radioactivity was found to be organoextractable and they concluded that the metabolites were not o-glucuronide or aryl-sulfate conjugates.

Acid hydrolysis in combination with autoclaving was more successful in releasing radioactivity while incubation of the urine with *E. coli* was not helpful.

Fecal Metabolite Studies:

The investigators determined by TLC that 81% of the fecal radioactivity through 24 hours was unchanged SENCOR, while studies on samples from longer than 24 hours found that little radioactivity was organosoluble. Acid hydrolysis in an autoclave could release 80% of this radioactivity.

Conclusions:

Analysis of blood samples showed a peak level at 4 hours. However due to the small number of animals used, the time of the peak level in the tissues could not be determined. The excretion study data indicated that 52 to 60% of the administered dose was eliminated in the urine and 30% in the feces. The true patterns of metabolites could not be accurately determined. However, it appeared that the same metabolites found in an earlier study in soybeans and a concurrent study in rats were present in this study. They are as follows:

DA - deaminated SENCOR
DK - diketo SENCOR
DADK - deaminated, diketo SENCOR

The deficiencies of this study are as follows:

1. Inadequate number of animals (especially for the tissue distribution studies).
2. At least two dose levels are required (see page 2 of this review).
3. The justification for the use of dogs for this study.
4. The age of the animals in the study was not reported.
5. There was no analysis of bone, sex organs, lung, spleen or residual carcass.

Core Classification: Core-Supplementary Data based on above deficiencies.

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