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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Amitraz (Baam)
N-(2,4-dimethylphenyl)-N-[[(2,4-dimethylphenyl)imino]methyl]-N-methyl methanimidamide. TOX CHEM 374A

TO: Jay Ellenberger, PM #12
Registration Division (TS-767)

THRU: Robert B. Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769) RBJ 1/23/85 WOB

FROM: Ray Landolt
Review Section #1
Toxicology Branch/HED (TS-769) 1-23-85

The Toxicology Chapter to the Registration Standard for Amitraz is enclosed. A two year mouse oncogenic study, reviewed by R. Landolt, May 22, 1984, demonstrated an increase in the incidence of hepatocellular tumors in female B6C3F1 mice. This two year mouse oncogenic study and mutagenicity data were sent to CAG for an up-dated risk assessment. CAG's evaluation is not expected before February 1985 and will therefore follow as an addendum to this RS for amitraz.

Attachment

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Tolerances

Tolerances have been established for residues of amitraz and its metabolites containing the 2,4-dimethylaniline moiety (calculated as the parent compound) on pears at 3 ppm (40 CFR 180.287). The toxicity data considered in support of this tolerance are a two year rat feeding and oncogenicity study with a no observed effect level of 50 ppm, a two year dog oral (capsules) study with a no observed effect of 0.25 mg/kg, b.wt., an 80 week mouse oncogenicity study with a no observed effect level of 100 ppm (positive for lymphoreticular tumors in female mice at 400 ppm, highest level tested), a three generation rat reproduction study with a no observed effect level of 15 ppm, a rat teratology study with a no observed effect level of 12 mg/kg b.wt., and a rabbit teratology study with a no observed effect level of 5 mg/kg b.wt.

The acceptable daily intake (ADI) for humans is calculated to be 0.0025 mg/kg b.wt. based on the dog 2-year oral study with a no observed effect level of 10 ppm and a safety factor of 100. The maximum permitted intake (MPI) for a 60 kg human is calculated to be 0.15 mg/day. The published tolerances in or on pears account for 7.66 % of the acceptable daily intake with theoretical maximal residue contribution (TMRC) to the daily diet of 0.0115 mg/day (for an average 1.5 kg daily diet).

Acute Toxicity

Amitraz has a low acute toxicity as demonstrated in mice, rats, guinea pigs, rabbits, dogs, baboons and domestic pigs by the oral, dermal and inhalation routes of exposure. A pharmacotoxic profile of reactions suggest a depression of hypothalmic function (Patton, D.S.G., 1971). The signs of toxicity include central nervous system depression, ataxia, ptosis, emesis, labored respiration, muscular weakness, tremors, hypothermia and bradycardia. These signs varied in severity among different species. The dog was reported to be the most sensitive species to single oral doses of amitraz (Patton, D.S.G. 1971) with the baboon approximately 2.5 times less sensitive (Patton, D.S.G. 1973) followed by the rat and guinea pig being 5 times less sensitive than the dog. The mouse was observed to be the least sensitive to single oral doses of amitraz by a factor of greater than 15 (Patton, D.S.G. 1971) as compared to the dog.

The acute oral LD_{50} in rats with technical material was 531 mg/kg b.wt. for males and 515 mg/kg b.wt. for females (Shaw, J.W. 1973). Dermal penetration was investigated by the application of 200 mg/kg b.wt. of undiluted technical material to a 400 cm^2 dermal area of the White Thornber Hybrid Pig. There were no effects during the six hour observation period. When oral doses of 1, 10, 25, 50 and 100 mg/kg b.wt. were administered in capsules to White Thornber Hybrid Pigs the signs of toxicity at 25, 50 and 100 mg/kg b.wt. were consistent with those reported for acute exposure to amitraz with no effects observed for the 1 and 10 mg/kg b.wt. dose levels. An eight fold difference between the acute oral and acute dermal toxic dosages was noted (Morgan, H.E. 1975). Topical aplication of a 40% solution of amitraz in acetone applied to rabbits at 200 mg/kg b.wt. was without gross signs of toxicity during the five hour exposure period. (Patton, M.M. 1972). The rat inhalation LC_{50} for a six hour exposure to the technical material is approximately 2.4 mg/l actual concentration with 97% of the dust particles in the respirable range. Toxic signs were similar to those observed in the other acute studies with eye irritation, aggressive behavior, sensitive to touch and sound, polyurea and dyspnea also reported by the inhalation route of exposure (Berczy, Z.S. 1972).

The technical material is nonirritating to the rabbit eye (Sutton, M.M. 1972).

Hematological and clinical blood chemistry values in the acute oral toxicity studies using the baboon and dog were reported to be similar. Neutrocytosis was observed in baboons following oral doses of 100 and 250 mg/kg b.wt., but not at the 20 mg/kg b.wt. level. An increase in blood urea nitrogen and alkaline phosphatase concentration were observed in the baboon at the 250 mg/kg b.wt. level but not at the 100 mg/kg b.wt. level. Oral doses of 20 mg/kg b.wt. administered to baboons were without affects on hematological and clinical blood chemistry values (Patton, D.S.G. 1973). Dogs receiving acute oral doses at 100 mg/kg b.wt. showed an increase in RBC, WBC, hemoglobin, and packed cell volume accompanied by an increase in blood urea nitrogen, potassuim and alkaline phosphatase concentrations. An increase in blood urea nitrogen, blood sugar and alkaline phosphatase levels were reported for dogs receiving the 20 mg/kg b.wt. level but not at the 4 mg/kg b.wt. level. Hematological and clinical blood chemistry values were unaffected at 4 mg/kg b.wt. doseage level (Patton, D.S.G. 1971). No microscopic lesions were observed in either the dog or baboon which were related to the oral administration of the technical material (Patton, D.S.G. 1971 and 1973).

Human Exposure

During the period of 1969 to 1972, personnel involved in laboratory research and development of amitraz complained of flushing (capillary dilatation) of the skin within several hours after exposure to the technical material. The reaction lasted one to two hours, did not respond to antihistamines and was characterized as being sensitized to trauma (flare response to scratching) and radiant heat (Moore, W.K.S. 1973). No symptoms have been reported by spray operators during field applicaton of the formulated products. To reproduce the incidence of flushing, amitraz in acetone was applied to the forearm of nine human subjects then allowed to dry and wrapped with "Saran wrap" for six hours. There was no reaction in 7/9 subjects. One of the subjects, with prior exposure, exhibited slight erythema and the response of the other subject was questionable. When amitraz was applied in a paraffin base ointment to the forearm of three human subjects, 2/3 showed no reaction and 1/3 responded with flushing of the chest area after 14 hours which cleared within 24 hours (Boots Hercules, 1971). In another study, repeated applications of 7 hours/day for 4 days to the forearm of 10 subjects resulted in slight to moderate irritation but no flushing reaction (Moore, W.K.S. 1973). A number of studies were undertaken to reproduce the flushing response of amitraz in experimental animals. Amitraz was not a skin sensitizer in the guinea pig sensitization studies (Sutton 1971). No erythema was reported from ultra violet light exposure to guinea pigs pretreated with amitraz. No cutaneous vascular reactions were observed from oral doses of amitraz to rats, guinea pigs, rabbits, dog, pig or baboon. Vasoconstriction was observed in the cat. (Parkinson 1971).

Metabolism studies conducted with two adult male human volunteers showed clinical effects as the result of ingestion of 0.25 mg/kg b.wt. of ^{14}C labeled amitraz. The clinical effects which were reported within 90 to 160 minutes after ingestion included sedation, dry mouth, disorientation, bradycardia, hypertension and hypothermia persisting up to 12 hours after dosing. No flushing was observed in these test subjects (Campell, J.K. 1984). These observations in humans compare favorably to those observed in the dog at 0.25 mg/kg b.wt. (Hall, J.E. 1975).

Dermal Absorption

The back of the weanling pig has been used as an indicator of the percutaneous absorption likely to occur via dermal exposure of the human forearm to pesticides. The application of 18 mg of (^{14}C) amitraz (2 mg ai/kg) as a water diluted EC to a 100 cm^2 area of skin on the back of four weanling pigs resulted in an absorption of 6.7% of the applied dose over a 60 hour period (Campbell, J.K. 1984).

Dermal absorption was determined by the application of 20 mg/kg b.wt. ^{14}C labeled amitraz to the shaven backs of beagle dogs (an area of approximately 460 cm^2, 20-25% of the dogs body surface). Within 3 days approximately 7% of the applied dose was recovered in the urine and feces with 24 to 40% of the dose accounted for over a 10 day period. Metabolism by either the oral or dermal route is similar with 4-formamido 3-methyl benzoic acid (BTS 39098) identified as the metabolite recovered in the urine (Hornish, R.E. 1983).

Urine samples from four spray applicators were analyzed over a 24 hour period following a day work exposure to 10 ounce ai/100 gal. dilution of amitraz. Levels of the metabolite BTS 28869 were reported to be less than the limit of detection (0.01 ppm) for these applicators (Hughes, K.W. 1975).

A single dermal application of 5.3 mg/kg b.wt. amitraz (^{14}C) in acetone to the shaven backs of rats for 24 hours resulted in approximately 50% of the dose accounted for on the skin and in the wrapping material. After 24 hours 25.3 to 31.5% of the dose was recovered in the urine and 2.8 to 12.9% in the feces with the remainder in the tissues. Tissue residues levels recovered were 0.88% and 0.12% of the administered dose in the liver and kidneys, respectively. (Lewis, D.K. 1971).

To determine effects from the topical application of a 21.3% EC formulation to beagle dogs, concentrations representing the use concentration (0.025%), five times the use concentration (0.125%) and ten times the use concentration (0.25%) were applied by wetting the entire body surface with a sponge to the point of runoff. The topical application of the dose concentrations 0.025%, 0.125% and 0.25% were equivalent to 16, 68 and 136 mg/kg b.wt. active ingredient, respectively. Following the application of the use concentration (0.025%) sedation was observed by within 8 hours accompanied by transient hyperglycemia within 4 hours, both of which were reversible within 24 hours. At five times the use concentration (0.125%) sedation was observed within 8 hours accompanied by transient hypothermia and hyperglycemia within 4 hours all of which were reversible within 24 hours. Sedation, ataxia and salivation were observed within 8 hours at ten times the use concentration (0.25%), accompanied by transient hypothermia and hyperglycemia within 4 hours post treatment, reversible within 24 hours (Kakuk, T.J. 1976).

Pharmacology Studies

The mode of action of amitraz in experimental animals was characterized by clinical signs of ataxia, sedation with periods of hyperexcitability and aggression, hypothermia, and bradycardia at toxic dosage levels.

Hypothermia was observed in mice receiving oral doses of amitraz that were consistent with the hypothermic effects reported for chlorpromazine (Sutton 1972). The hypothermic effect of amitraz was observed to be of a longer duration in female mice than in male mice (Berry 1976). Amitraz (BTS 27419) and its metabolite (BTS 27271) at near toxic doses, antagonized reserpine induced ptosis in the rat and extended the pressor response to tyramine in the rat suggestive of monoamine oxidase inhibition activity with a potency in the order of BTS 27271 (metabolite) > BTS 27419 (Amitraz > BTS 21103 (Chlordimeform). However, unlike monoamine oxidase inhibitors these compounds also induce aggressive behavior in rats (Parkinson 1974).

Depression of the central nervous system, suggestive of a tranquil effect was observed at 10 ug/kg b.wt. (administered intravenously) in the conscious dog accompanied by bradycardia and a fall in blood pressure at 20 ug/kg b.wt. level. No changes in rectal temperature were reported at these levels (Parkinson 1971 and Patton 1973).

Recent studies on the hepatic function in B6C3F1 mice, from the oral administration of amitraz at the maximum tolerated dose twice daily for four days resulted in a significant increase in liver weight without evidence of liver microsomal enzyme induction (Needham, D. 1984).

Alterations in the estrous cycle of B6C3F1 female mice were reported (Hounsell, I.A. 1984) from feeding dietary levels of amitraz at 25, 100 and 400 ppm for 28 weeks. Prolonged proestrus and reduced duration of dioestrus with no effect on the length of the estrus cycle were observed at the 400 ppm level. Also at the high level a decrease in weight gain, blood urea and glucose levels were reported. At the 100 and 400 ppm levels a decrease in progesterone, an increase in dehydroepiandrosterone sulphate levels and liver weights were observed. The low level (25 ppm) was without effects.

Metabolism

The metabolic fate of amitraz (BTS 27419) and its metabolites N-(2,4-dimethyl-phenyl)-N-methylformamidine (BTS 27271), 2,4-dimethylformanilide (BTS 27919), 2,4-dimethylaniline (BTS 24868), 4-amino-3-methylbenzoic acid (BTS 28369) 4-formamido-3-methyl benzoic acid (BTS 39098) 4-acetamido-3-methyl benzoic acid (BTS 31158), N,N-bis-2,4-dimethylphenylformamidine (BTS 28037) have been investigated in the mouse, rat, cat, dog, baboon and man. Urinary excretion of amitraz ^{14}C labeled in the 2 methyl position is summarized in the following table as the percent of the administered dose recovered within 48hours.

Human	Baboon		Dog		Rat		Mouse	
Male	Male	Female	Male	Female	Male	Female	Male	Female
77.7	62.3	79.6	74.4	81.9	81.5	79.5	69.8	63.8

Elimination in the feces of amitraz ^{14}C labeled in the 2 methyl position, is summarized in the following table as the percent of the administered dose recovered within 48 hours.

Human	Baboon		Dog		Rat		Mice	
Male	Male	Female	Male	Female	Male	Female	Male	Female
No data	24.1	9.1	13.0	11.6	17		30.9	39.4

Dietary levels of 400 ppm fed to male and female B6C3F1 mice for 3 weeks followed by a single oral dose of 10 mg/kg b.wt. ^{14}C labeled amitraz resulted in 72.3 and 75.7% of the total dose eliminated in the urine within 48 hours of males and females respectively with 21% accounted for in the feces of both sexes (Campbell 1983, 1984 and Hornish, 1983).

No differences were evident between species or sexes for total urinary excretion. Peak levels of radioactivity reported for all species examined occur in the urine within 24 hours (Campbell, J.K. 1984). However, for those studies where plasma levels were monitored for males and females immediately following the oral administration of the labeled amitraz, peak plasma levels were reached within 1.5 hours for female mice and dogs and within 3 to 6 hours for male mice and dogs, respectively (Hamilton, D.Y. 1974, 1976).

The highest levels of ^{14}C tissue residues were reported in the liver-bile, pigmented area of the eye, adrenals and kidneys within 72 to 96 hours of oral dosages to mice, rats, dogs and baboons. Dermal application to weanling pigs resulted in tissue residue levels in the eye within sixty hours with the other tissues below the level of detection (Campbell, J.K. 1984). Beagle dogs treated with ^{14}C amitraz by either the oral or dermal route metabolized amitraz essentially the same via either route of exposure (Hornish, 1983).

The pattern of metabolites formed in rat and dog were reported to be similar (Lewis 1975 and Jones 1973).

Proportion of various metabolites in the urine of rats, mice, baboons and humans given a single oral dose of (^{14}C)-amitraz, expressed as a percentage of the radioactivity in urine, are indicated in the following table.

Metabolites	Human 0.25 mg/kg	Rat 10 mg/kg		Mouse 10 mg/kg		Baboon 10 mg/kg	
	M	M	F	M	F	M	F
BTS 24 868	1.4	1.7	2.1	1.9	1.8	1.9	2.2
BTS 27 919	3.6	1.5	1.6	1.4	1.7	2.0	1.8
BTS 28 369	3.8	1.9	2.0	2.5	2.8	2.8	2.7
BTS 39 098 + BTS 31 158	27.1	26.6	6.4	15.4	19.0	26.0	19.3
BTS 27 271	5.8	3.1	4.6	5.1	5.7	4.1	6.5
Polar material	59.6	55.6	53.6	64.4	59.1	51.8	55.1
Remainder	1.5	9.6	9.7	9.4	10.1	11.4	12.4

Results for human males are the mean of 2 determinations. All other results are single determinations.

The polar metabolites in the above table were identified as acid-labile conjugates of BTS 27271, BTS 39098, FBC 31158 and BTS 28369 (Campbell, J.K. 1984).

In all of the species studied, both sexes rapidly hydrolysed amitraz in the stomach to (BTS 27271) N-(2,4-dimethylphenyl)-N-methyl formamidine and (BTS 27919) 2,4-dimethylformanilide with conjugates of (BTS 28369) 4-amino-3-methylbenzoic acid reported in the urine (Somerville 1973). The concentration of the metabolite BTS 27271 excreted in the urine was observed to be dose dependent (Campbell 1984) with its degradation products of BTS 27271 in the urine similar to amitraz (Knowles 1981).

Metabolite BTS 28369 was recovered in the urine within 24 hours from two female and four male human volunteers dosed with a capsules containing 2.0 mg of BTS 27271 (Hall, J.E. 1975).

Radioactivity was excreted almost entirely in the urine and feces of rats receiving single oral doses of amitraz labeled (^{14}C) in the 2 methyl positions with less than 0.1% of the dose recovered in the expired carbon dioxide. The urine did not contain amitraz either unconjugated or as a glucuronide or sulphate. The feces contained 50% of the labeled (^{14}C) activity identified as BTS 27271 (Thomas 1984).

When single oral doses of ^{14}C labeled BTS 28369 were administered to dogs, female plasma levels peaked at 0.75 hours and male levels at 3 hours with the highest tissue levels occuring in the pigmented part of the eye, liver-bile and kidney (Hamilton 1974).

The metabolite N-(2,4-dimethylphenyl)-N'-methyl-formamidine (BTS 27271) is reported to be 2 to 4 times more toxic orally to rats and dogs, respectively, than the parent material with the signs of toxicity similar for both materials (Sutton 1970 and Morgan 1973). Metabolites, 2,4-dimethylformanilide (BTS 27919) and N,N-bis-2, 4-dimethylphenylformamidine (BTS 28037) are similar in toxicity and less toxic than the parent material with the signs of toxicity comparable to the parent material (Morgan 1973). The metabolite, 4-amino-3-methylbenzoic acid (BTS 28369) is the least toxic. (Morgan, H.E. 1973).

Subacute Studies

Daily oral doses of 0, 3, 12, 50 and 200 mg/kg b.wt. administered by gavage to male and female rats for 90 days resulted in a no effect level of 3.0 mg/kg. At the 12 mg/kg level the animals were excitable, showed depressed weight gain and a decrease in liver weights. No hematological, biochemical or histological changes were observed at the 12 mg/kg level. The two higher dose levels (50 and 200 mg/kg) were terminated after seven days. At these levels chromodacryorrhea, excitability and aggressive behavior were observed, accompanied by depressed weight gain, congestion of major organs, periportal vacuolation of the liver and lipid infiltration of the adrenal cortex (Sutton, M.M. 1973).

Daily oral doses of 0, 3, 12, 50 and 200 mg/kg b.wt. were administered by gavage to male and female mice for 90 days. The 3.0 mg/kg level was considered a no effect level with slight transient decrease in weight gain during the first week of the study. At the 12 mg/kg level a slight transient decrease in weight gain, an increase in plasma GPT and liver organ weights were reported accompanied by slight hepatocyte enlargement and areas of focal necrosis of the liver (Shaw, J.W. 1974).

Rats exposed to a dust (with 88 to 100% of the particles within the respirable range) at 0.01, 0.1 and 1.0 mg/l six hours per day for fourteen days exhibited no effects at the low level. At the 0.1 mg/l level dyspnea, eye irritation, hyperactivity, aggressive behavior and decreased weight gain were observed. In addition to the signs observed at the mid level, ataxia, tremors, and coma were reported at the 1.0 mg/l level accompanied by decrease in packed cell volume, hemoglobin, RBC, and plasma protein levels, along with neutrophilia. No treatment related histopathology was observed (Berczy, Z.S. 1973).

Dermal application of 50 and 200 mg/kg b.wt. of amitraz in acetone to the unoccluded skin of rabbits, six hours per day for 15 exposures over a 21 day period resulted in sedation, local skin reactions, decreased weight gain and elevated blood sugar and neutrophilia at both levels. Heart rate and rectal temperature were not affected. There were 1/8 deaths at 50 mg/kg and 4/8 deaths at the 200 mg/kg levels. Testes of males at the 200 mg/kg level were underweight accompanied by variable tubular degeneration (Sutton, M.M., 1973).

Daily oral doses of 0, 0.25, 1.0 and 4.0 mg/kg b.wt. of amitraz were administered in gelatin capsules to male and female beagle dogs for 90 days. The 0.25 mg/kg level was considered a no effect level with transient central nervous system depression and elevated blood sugar observed in one animal. At the 1.0 mg/kg level transient central nervous-system depression, decrease in pulse rate and rectal temperature with an increase in glucose in the urine was reported. In addition to the signs reported for the mid dose level, ataxia, emesis, catarrhal conjunctivitis were observed at the 4.0 mg/kg level. Neutrophilia of the bone marrow was reported for the 1.0 and 4.0 mg/kg levels. At the 1.0 mg/kg level a slight enlargement of the central and midzonal hepatocytes of the liver with slight hyperplasia of the zona glomerulosa of the adrenals were reported (Patton, D.S.G. 1971).

The comparable effect induced by amitraz (BTS 27419) and its metabolite (BTS 27271) were determined by the oral administration of 4 mg/kg b.wt. and 0.5 mg/kg of each compound respectively in gelatin capsules to groups of male and female beagle dogs daily for 14 days. Both compounds induced signs of sedation, ataxia, protrusion of tongue, bradycardia and hypothermia subsiding within 24 hours after treatment. Bodyweight and food consumption were not affected even though sporadic incidence of emesis was reported (Morgan, H.E. 1975).

The metabolite 4-amino-3-methyl benzoic acid (BTS 28369) administered orally by gelatin capsule to male and female beagle dogs at 0, 16, 40 and 100 mg/kg b.wt. for 90 days produced emesis, increased liver weight and a slight elevated urinary excretion of a total reducing substance (other than glucose) at the high level. No effects were observed at the 16 and 40 mg/kg levels for behavior, heart rate, rectal temperature, bodyweight, hematology, clinical biochemistry, organ weight or histopathology (Morgan, H.E. 1974).

Male and female rats dosed orally by gavage with the metabolite 4-amino-3-methyl benzoic acid (BTS 28369) in acacia at 40, 100 and 250 mg/kg b.wt. for 21 days produced a decrease in weight gain in males and an increase in female spleen weight at the high dosage level. No effects were observed at the 40 and 100 mg/kg/day levels for behavior, growth, hematology, clinical biochemistry, organ weights or histopathology (Shaw, J.W. 1974).

Reproduction and Teratology

Amitraz was reported to be without effects in the rat three generation reproduction study at 15 ppm and the teratogenic studies in the rat at 12 mg/kg b.wt. and rabbit at 25 mg/kg b.wt. (Sutton, M.M. 1973). There were no effects on the reproduction indices at the 15 ppm dietary level in the rat reproductive study. There was an increase in pup mortality during the lactation period reported for the two higher dietary levels of 50 ppm (5 mg/kg) and 200 ppm (20 mg/kg). A rat teratology and a rat postnatal teratology study were conducted at the dosage levels of 1, 3 and 12 mg/kg b.wt. Both of these studies were deficient in the number of pregnant females dosed oraly per level tested. However, when these two studies are considered together, it is apparent that amitraz is not teratogenic in the rat when administered orally at 12 mg/kg during days 8 through 20 of gestation. At the 12 mg/kg level a decrease in maternal and fetal body weights accompanied by a decrease in litter size were reported (Sutton 1973). There were no teratogenic effects in the rabbit at 25 mg/kg b.wt. (the highest level tested), although maternal and fetal toxicity were observed at this level. There was a decrease in maternal body weight and an increase in the number of abortions on days 17-20 at the 25 mg/kg level. Fetal toxicity at the 25 mg/kg level included a decrease in mean litter size, litter weight, and a decrease in implantation and viability indices (Sutton 1973).

A prolonged period of estrus (average of 6.1 days) was observed for female rats fed a dietary level of 200 ppm BTS 27419 for 18 weeks when compared to an estrus period average of 4.3 days in control rats. Rats were 8 weeks old at the start of dosing (Merryman, D.C. 1972).

The toxic effects observed from feeding amitraz at 400 ppm for 18 weeks to CFLP male mice and for 33 weeks to CFLP female mice resulted in fighting behavior among males accompanied by a decreased in body weight gain and an increase in food consumption for both sexes. A significant increase (1/3) in the estrus period was observed for the amitraz treated female mice as compared to controls, without an effect on the circulating levels of estradiol. At the termination of the study a significant sex difference was observed for thymus weights in the test and control mice with female thymus weights greater than males. A significant decrease in thymus weight for both sexes was reported for test and control mice. No histological changes were evident in the lymphorecticualar system. As compared to controls a high incidence of foci of inflammatory cells in the liver of females was reported. (Channon, E.J. and Brown, D. 1978).

In a recent study where female B6C3F1 mice were fed dietary levels of 0, 25, 100 and 400 ppm for 28 weeks similar results were observed. At 400 ppm an increase in proestrus, a decreased duration of dioestrus without an effect on the length of the estrus cycle was reported. A dose related decrease in blood levels of progesterone and prolactin and an increase in dehydroepiandrosterone sulfate levels were reported. At the 400 ppm level, glucose and urea levels were reduced as well as decrease in body weight. An increase in liver weight was observed at the 100 and 400 ppm level. The low level (25 ppm) was without an effect (Hoansell, I.A. 1984).

Genotoxicity

The mutagenic potential of amitraz has been reported to be negative in the gene mutation, hostmediated and dominant lethal test systems (Everest, R.P. 1976; Wilcox, P. 1976 and Palmer, A.K. 1977). Metabolites, BTS 27271, BTS 27919 and BTS 28369 have been reported to be without mutagenic activity in the gene mutation system (Everest, R.P. 1976). The weak mutagenic activity of the manufacturing impurity BTS 33220 was not apparent in the gene mutation studies with the technical material (Wilcox, P. 1979, Everest 1979).

Additional negative mutagenic studies were conducted on amitraz in the Mouse Lymphoma Mutation Assay (MCGregor, D.B. 1984), Ames Bacterial Mutagenicity Test (McGregor, D.B. 1983), Unscheduled DNA Synthesis in Human Embryonic Cells (McGregor, D.B. 1983), and for metabolites BTS 24868 in the Mouse Lymphoma Mutation Assay (McGregor, D.B. 1983), BTS 27271 in the Ames Bacterial Mutagenicity Test (Richold, M. 1983), and BTS 27919 in the Ames Bacterial Mutagenicity Test (Richold, M. 1983).

Chronic - Oncogenic Studies

Stability

The stability of amitraz in the diet during the chronic rat and mouse feeding/oncogenic studies showed a degradation of 70% of the original concentration occurred within seven days with 27271 and 27919 identified as the degradation products (Somerville, L. 1976).

Two Year Dietary - Rat

Four groups of 40 male and 40 female Ash Wistar pathogen free rats were fed dietary levels of 15, 50 and 200 ppm for 2 years. There was a temporary reduction in food intake and depressed growth rate in rats fed 200 ppm of BTS 27419. They also tended to be nervous, aggressive and excitable. No hematological or biochemical change was detected; terminal plasma biochemistry and organ weights were no different from control values. No dose related histopathological changes were reported.

Signs of ill-health, such as red tears (chromodacryorrhea), fur loss, skin abscesses, swelling and cornified skin on the feet, glomerulonephritis, etc., were seen in a similar proportion of rats in control and treated groups, which compromise the interpretation of the results and are therefore somewhat less than optimal for purposeful experimental technique.

Pathological examination demonstrated no dose-related response. There were also no significant changes in the incidence, type or time or appearance of tumors in the treated groups as compared to the control group (Sutton, M.M. 1973).

NEL 50 ppm

LEL 200 ppm	At the highest level fed a decrease in body weight and food consumption were reported accompanied by excitable and aggressive behavior. Not oncogenic at the dietary levels fed.

Two Year Oral - Dog

Groups of beagle dogs (4 male/4 female per group) received daily oral doses at 0.1, 0.25 and 1.0 mg/kg b.wt. in gelatin capsules for two years. A similar control group received lactose in gelatin capsules.

All eight dogs given 1.0 mg/kg b.wt. exhibited signs of slight CNS depression 3 hours after dosing on days 1 and 2, and all appeared normal again by the following morning. One male receiving 1.0 mg/kg b.wt. had a slight subnormal temperature at 3 hours which returned to normal within 24 hours. All dogs in this group appeared clinically normal, except for one female that was slightly hypothermic 3 hours after dosing during weeks 52 and 79 (decrease 1° - 2°F). No clinical reaction to treatment was seen in dogs on lower dosage levels.

Blood samples collected during weeks 40 and 53 showed significant increase in mean blood sugar concentration 3 hours after dosing in the 1.0 mg/kg group (Morgan, H.E. 1973).

NEL = 0.25 mg/kg b.wt.

LEL = 1.0 mg/kg b.wt. At the highest dosage level slight depression of the central nervous system and slight hypothermia accompanied by an increase in mean blood sugar levels and plasma GOT levels were observed.

80 Week Oncogenic Study - Mice

Amitraz (BTS-27419) was fed to pathogen free mice of the CFLP strain (50 males and 50 females per group) at dose levels of 25, 100 and 400 ppm in the diet for 80 weeks. A similar number of control mice were fed plain diet. Clinical signs and survival were unaffected by dosing. Weight gain of both sexes was reduced at 400 ppm and temporarily at 100 ppm, in comparison with weight gain of the controls. The only statistically significant pathological finding was a greater number of lymphoreticular tumors in females, but not in males at the 400 ppm level in comparison to the controls. There were no other statistically significant effects related to treatment (Barnett, R. 1976).

Amitraz was referred to the Special Pesticides Review Division in October 1976 for Rebuttable Presumption Against Registration (RPAR) which was issued April 1977. The Agency's Cancer Assessment Group, in their preliminary review of the evidence on experimental oncogencity for amitraz, indicated that it did fulfill the requirements for triggering an RPAR (Albert, R. 1977).

As part of the RPAR process amitraz was reviewed by the Federal Insecticide, Fungicide and Rodenticide Act Scientific Advisory Panel (SAP) in January 1979. The SAP concluded that a statistically significant increase in lymphoreticular tumors in amitraz-treated mice had not been shown. The Panel also stated that it did not agree with the EPA proposal to prohibit the use of amitraz on apples. The oncogenicity of amitraz, was, in the Panel's opinion, sufficiently questionable that the restriction of the use of amitraz on apples was not warranted and that the compound could prove to be of value in mite control on apples in some areas of the U.S.A.

In Februrary 1979, 'the EPA determined in a qualitative sense, amitraz should be regarded as a carcinogen although the existing evidence is relatively weak' (restated in Fed. Reg. 70143, dated 12/6/79).

In an attempt to resolve the position Boots/Upjohn offered to undertake a repeat mouse oncogenicity study. EPA accepted the use of amitraz on pears and agreed to issue a registration for this use on the condition that the mouse oncogenicity study be repeated. The RPAR process was duly completed in October 1979 with the approval of this conditional registration.

Discussions consequently took place between EPA, Boots and Upjohn on the protocol for the repeat mouse study. Two 90-day studies were undertaken to identify the dose levels and the most appropriate strain of mouse to be used in the repeat study since, the CFLP strain used in the original study was no longer available. From these studies the B6C3F1 strain was selected. The results of the 90-day studies indicated that a lower dosing regime should be followed because of significant body weight decrease at the 400 ppm level. The Agency insisted that the same dose levels as in the original 80 week study i.e. up to 400 ppm, should be used.

In January 1980 the EPA issued a conditional registration for the use of amitraz on pears valid for 4 years. During this time the repeat mouse study was completed and reviewed. It is presently undergoing evaluation by CAG.

104 Week Oncogenic Study - Mice

Seventy-five male and 75 female 33 day old B6C3F1 hybrid (Charles River) mice were fed dietary levels of 25, 100, and 400 ppm amitraz for 104 weeks. The untreated controls consisted of 100 male and 100 female B6C3F1 hybrid (Charles River) mice. Males fed the 400 ppm level exhibited hyperactivity and aggressive behavior. The incidences of cutaneous ulceration and inflammation of the perigenital and perianal areas of male mice were greater at the 100 and 400 ppm levels than observed for the 25 ppm and control males. The incidence of urogenital swelling of males fed all three dietary levels was greater than observed for the control males. Incidence of gross adverse effects among females fed all three dietary levels were comparable to the control females. Survival rates for the males and females were similar between the controls, 25 and 100 ppm levels. As compared to the controls, there were 73 and 75% survival among males and females, respectively, fed the 400 ppm level. Body weight gains for the 400 ppm level were comparable to the controls during the initial four weeks for males and initial seven weeks for the female mice, but were significantly lower for the duration of the study. A significantly reduced body weight gain was observed for females fed the 100 ppm level over the later 74 weeks of the study. A decrease in food consumption was observed during the initial 13 weeks for males and initial 19 weeks for females fed the 100 and 400 ppm dietary levels. This was followed by an increase in food consumption for the duration of the study for males and females fed the 400 ppm level. At the termination of the study, an increase in liver and lymph node involvement was apparent from macroscopic examination of males and females fed the 400 ppm level. The incidence of preputial gland enlargement of males fed the 400 ppm level was greater than observed for the control males. A significant decrease in the bone marrow myeloid/erythroid ratio was reported for males fed the 400 ppm level and females fed the 100 and 400 ppm levels. The incidence of hepatocellular tumors (carcinoma and adenoma) in females fed the 400 ppm level were greater than those observed in the control group. Females fed all three dietary levels and males fed 400 ppm exhibited a greater incidence of liver hyperplastic nodules, telangiectatic and basophilic foci than observed for the controls.

The incidence of spleen hematopoiesis of males and stomach focal hyperkeratosis in males and females fed all three dosage levels were greater than those observed in the control groups (Lancaster, 1983).

This study was referred to the Agency's Cancer Assessment Group May 14, 1984 for full risk assessment following the finding of an increase in the incidence of hepatocellular tumors at the 400 ppm level in female B6C3F1 mice.

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Taylor, J.; Somerville, L. (1977) The Conversion of Amitraz to BTS 24 868 in Dog Gastric Juice: AX 77010. (Unpublished study received April 9, 1980 under 43142-EX-1; submitted by Boots Hercules Agrochemicals Co., Wilmington, Del.; CDL:099371-M).

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Wilcox, P.; Oxley, P. (1978) Amitraz Impurity BTS 33220: "In-Vitro" Bacterial Mutagenicity Testing. (Unpublished study received March 5, 1980 under 1023-59; submitted by Upjohn Co., Kalamazoo, Mich.; CDL:241968-C).

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TABLE A
GENERIC DATA REQUIREMENTS FOR AMITRAZ

Data Requirement	Composition[1/]	Use[2/] Patterns	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?[3/]
§ 158.135 Toxicology					
ACUTE TESTING:					
81-1 - Oral Toxicity - Rat	TGAI	A	YES	00041539	NO
81-2 - Dermal Toxicity	TGAI	A	YES	00040862	NO
81-3 - Inhalation Toxicity - Rat	TGAI	A	YES	00029963	NO
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI	NA			
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding-Rodent, Non-rodent	TGAI	A	YES	00028712 00028715 00028716	NO
82-2 - 21-Day Dermal	TGAI	A	YES	00029972	NO
82-3 - 90-Day Dermal	TGAI	NA			
82-4 - 90-Day Inhalation Rat	TGAI	NA			
82-5 - 90-Day Neurotoxicity-Hen/Mammal	TGAI	NA			

1/ Composition: TGAI = Technical grade of the active ingredient; PAI = Pure active ingredient; PAIRA + Pure active ingredient, radiolabelled; Choice = Choice of several test substances determined on case-by-case basis.

2/ 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.

3/ Data must be submitte no later than _____.

TABLE A
GENERIC DATA REQUIREMENTS FOR AMITRAZ

Data Requirement	Composition[1/]	Use[2/] Patterns	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?[3/]
§ 158.135 Toxicology (continued)					
CHRONIC TESTING:					
83-1 - Chronic Toxicity - 2 species: Rodent	TGAI	A	YES	00044585	NO
Non-rodent	TGAI	A	YES	00044586	NO
83-2 - Oncogenicity Study - 2 species: Rat and Mouse preferred	TGAI	A	YES	00044484 (Acc. 252098 - 252102)	NO
83-3 - Teratogenicity - 2 species	TGAI	A	YES	00029959 00029960	NO
83-4 - Reproduction, 2-generation	TGAI	A	YES	00029961 00029962	NO
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI	A	YES	00029459 00029953	NO
84-2 - Chromosomal Aberration	TGAI	A	YES	00029954 00029955	NO
84-2 - Other Mechanisms of Mutagenicity - DNA	TGAI	A	YES	00029957 00029958 (Acc. 253 131)	NO

1/ Composition: TGAI = Technical grade of the active ingredient; PAI = Pure active ingredient; PAIRA + Pure active ingredient, radiolabelled; Choice = Choice of several test substances determined on a case-by-case basis.

2/ 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.

3/ Data must be submitte no later than _____.

005633

TABLE A
GENERIC DATA REQUIREMENTS FOR AMITRAZ

Data Requirement	Composition[1/]	Use[2/] Patterns	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?[3/]
§ 158.135 Toxicology (continued)					
SPECIAL TESTING				00028685 00028676 00028667 00041503	
85-1 - General Metabolism	PAIRA	A	YES	00028668 00041497 00028671 00041499 00028669 00041500 00028682 00041498 00028672 00041501 00028674 Acc. 253 130 00028675	NO
85-2 - Domestic Animal Safety	TGAI	-	YES	00041513	NO
	Choice	-	YES	00044591	

1/ Composition: TGAI = Technical grade of the active ingredient; PAI = Pure active ingredient; PAIRA + Pure active ingredient, radiolabelled; Choice = Choice of several test substances determined on a case-by-case basis.
2/ 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.
3/ Data must be submitte no latter than _____.

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3

DATA EVALUATION REPORT

STUDY: Metabolism - Dog, Acute

LABORATORY: Boots Hercules

DATE: 1977

STUDY NUMBER: AX 77010

ACCESSION NUMBER:

MRID NUMBER: 00028676

MATERIAL TESTED: Amitraz ^{14}C (BTS 27419) in the 2 methyl position.

ANIMALS:

METHODS: To determine the degradation of amitraz in stomach, 4 mg/kg b.wt. was adminstered by gavage followed by sampling of stomach contents through a gastric fistula at 0, 1 and 8 minutes after dosing.

RESULTS: Within one minute amitraz was degraded to BTS 24868 (2,4-dimethylaniline), BTS 27271(N-(2, 4-dimethylphenyl)-N-methylformamidine and BTS 27919 (2,4-dimethylformanilide).

CONCLUSIONS: Gastric degradation products have been identified.

TOXICITY CATEGORY:

CORE RATING: Minimum

REPAIRABLITY:

DATA EVALUATION REPORT

STUDY: Metabolism, Rat, Subacute

LABORATORY: Boots Hercules

DATE: 1973

STUDY NUMBER: AX 73011

ACCESSION NUMBER:

MRID NUMBER: 00041492
00028669

MATERIAL TESTED: Amitraz ^{14}C (BTS 27419)
in the 2 methyl positions

ANIMALS: Rat

METHODS: Four pairs of one male and one female per pair were dosed by gavage daily at 4 mg/kg b.wt. for 28 days, followed by a 7 day holding period. The animals were fasted for 17 hours before dosing.

RESULTS:

Mean Tissue Residues (ppm) for Males and Females

	7 Day	28 Day	28+2 Day	28+7 Days
Liver	1.7	2.0	1.0	0.4
Thyroid	6.2	6.3	-	-
Adrenal	2.5	1.5	0.1	0.2
Skin	0.9	0.5	0.3	0.3

CONCLUSIONS: Highest tissue levels were reported in liver and thyroid at 7 and 28 days with residue in the liver detectable 7 days after the last dose was administered.

TOXICITY CATEGORY:

CORE RATING: Mimimum

REPAIRABLITY:

DATA EVALUATION REPORT

STUDY: Metabolism - Rat, Acute

LABORATORY: Upjohn Co.

DATE: 1971

STUDY NUMBER: C 71 011

ACCESSION NUMBER:

MRID NUMBER: 00041490

MATERIAL TESTED: Amitraz ^{14}C (BTS 27 419) in the 2 methyl position.

ANIMALS: Rats - male and female

METHODS: To determine the peak plasma and tissue levels seven pairs of one male and one female per pair were dosed by gavage at 10 mg/kg b.wt. then terminated at 0.75, 1.5, 3, 6, 12, 24 and 48 hours. Four additional rats were dosed by gavage at 10 mg/kg b.wt. for collection of urine and feces at 24, 48 and 72 hours.

RESULTS: ~~Plasma and liver peak levels were reached within 1.5 hours with 1.7 and 9.2 ppm, respectively of the dose recovered.~~ Within 48 hours, 81.9% of the dose was recovered in the urine and 16.7% in the feces.

→ Plasma and liver levels peaked at 1.5 hours post-dosing. amounts of BTS 27 419 equivalents were 1.7 ppm in blood plasma and 9.2 ppm in liver tissue.

CONCLUSIONS: Amitraz is rapidly absorbed and excreted in the urine and feces of rats with peak levels observed in the liver and plasma in 1.5 hours.

TOXICITY CATEGORY:

CORE RATING: Minimum

REPAIRABLITY:

DATA EVALUATION REPORT

005633

STUDY: Metabolism - Rat, Acute

LABORATORY: Upjohn Co.

DATE: 1971

STUDY NUMBER: C7i 015

ACCESSION NUMBER:

MRID NUMBER: 00041491
00055720
00028668

MATERIAL TESTED: Amitraz ^{14}C (BTS 27419) in the 2 methyl position

ANIMALS: Rat

METHODS: To determine the nature of the metabolites, three male and three female rats were dose by gavage at 45 mg/kg b.wt. (C71011)

RESULTS: Principal metabolites found in feces are BTS 27271, (N-(2,4-dimethylphenyl)-N-methyl formamidine, BTS 27919 (2,4-dimethylformanilide) and BTS 24868 (2,4 dimethylaniline).

CONCLUSIONS: The parent material was not apparent in the feces.

TOXICITY CATEGORY:

CORE RATING: Mimimum

REPAIRABLITY:

DATA EVALUATION REPORT

005633

STUDY: Metabolism - Dog, Acute

LABORATORY: Upjohn Co.

DATE: 1974

STUDY NUMBER: AX 74006

ACCESSION NUMBER:

MRID NUMBER: 00041496
00028674

MATERIAL TESTED: Amitraz ^{14}C (BTS 27419) in the 2 methyl position.

ANIMALS:

METHODS: Two dogs, one male and one female were dosed by gelatin capsule at 15 mg/kg b.wt. (following a 17 hour fast) for the collection of blood) at 0.75, 1.5, 3, 6 and 24 hour after dosing. Urine and feces were collected over the 24 hours period. The animals were terminated after 24 hours for tissue residue levels determinations with particular reference to the eye.

RESULTS: Peak plasma levels were read within 1.5 hours (5.66 ppm) for the female as compared to 6.0 hours (5.07 ppm) for the male.

Tissue Residue Levels (ppm) at 24 Hours

	Liver	Bile	Kidney	Eye*	Colon
Male	10.6	178.3	6.1	42.0	2.2
Female	6.7	107.4	9.0	33.0	11.6

*Pigmented Tissue

CONCLUSIONS: Female dog peak blood level lead the male blood levels by 4.5 hours.

TOXICITY CATEGORY: Excretion within 24 hours (ppm)

Male	urine 208.6	Female	urine 130.0
	feces 347.4		feces 1470.5

CORE RATING: Minimum

REPAIRABLITY:

DATA EVALUATION REPORT

005633

STUDY: Metabolism - Dog, Acute

LABORATORY: Upjohn Co.

DATE: 1971

STUDY NUMBER: C 71 014
C 71 018

ACCESSION NUMBER:

MRID NUMBER: 00041494 00041495 00028672
00055724 00028673

MATERIAL TESTED: Amitraz ^{14}C (BTS 27419) in the 2 methyl position

ANIMALS: Beagle Dogs

METHODS: To determine the peak plasma and tissue levels, eight pairs of one male and one female beagle dogs per pair were dosed with geletin capsules at 4 mg/kg b.wt. for collection of blood at 0.75, 1.5, 3.0, 6.0, 24, 48, 72 and 96 hours. Residue tissue levels were determined at 96 hours.

RESULTS: Peak blood levels were reach within 1.5 hours (2.0 ppm) for the male then decreased over the next 1.5 hours (1.75 ppm) and were comparable to the female peak level (1.17 ppm) at 6 hours. Maximum levels were recoverd in urine (53.3%) and feces (21.5%) within 48 hours. Tissue analysis was repeated because of variation in the original results.

Tissue Levels (ppm) at 96 Hours

	Liver	Bile	Kidney	Skin	Eye
Male	1.04	0.52	0.04	0.41	0.37
Female	1.22	0.42	0.11	0.44	2.27

CONCLUSIONS: Male dogs peak blood levels lead the female blood levels by 4.5 hours.

TOXICITY CATEGORY:

CORE RATING: Minimum

REPAIRABLITY:

DATA EVALUATION REPORT

STUDY: Metabolism - Cat, Acute

LABORATORY: Boots Co. Ltd.

DATE: 1974

STUDY NUMBER: AX 74005

ACCESSION NUMBER:

MRID NUMBER: 00041503

MATERIAL TESTED: N-(2,4-dimethylphenyl)-N-methylformamidine (BTS 27271) ^{14}C in 2-methyl position.

ANIMALS: Cat

METHODS: One male (3.9 kg) and one female (3.0 kg) were dosed with gelatin capsules of BTS 27271 at 5 mg/kg b.wt. following a 17 hour fast. Blood was taken at 0.75, 1.5, 3.0 and 6.0 hours. Urine and feces were collected at the termination of the study after 24 hours.

RESULTS: Male cat vomited 18 minutes after dosing with a lose of 8% of the dose. Peak plasma levels were reached in 0.75 hour for the male (2.5 ppm) and 3 hours for the female cat (2.4 ppm). Highest tissue levels in eye pigment (27 ppm), liver (5.5 ppm), bile (69 ppm) and kidney (0.75 ppm).

CONCLUSIONS:

TOXICITY CATEGORY:

CORE RATING: Minimum

REPAIRABLITY:

DATA EVALUATION REPORT

STUDY: Metabolism - Calves, Subacute

LABORATORY: Boots Hercules

DATE: 1979

STUDY NUMBER: Not available

ACCESSION NUMBER:

MRID NUMBER: 00030432

MATERIAL TESTED: N-(2,4-dimethylphenyl)-N-methylformamidine (BTS 27271)

ANIMALS: Weaned calves

METHODS: Twelve weaned calves were dosed with 3 animals per level of 0, 4, 12 and 40 mg/kg b.wt. daily for 21 days with BTS 27271 in gelatin capsules. Blood was drawn six hours after dosing on days 1, 3, 5, 9, 14, 17 and 21.

RESULTS: Plasma levels were below 0.01 ppm for all dose levels. Tissue residue levels for 12 mg/kg b.wt. dose and below were less than 0.01 ppm. At the 40 mg/kg b.wt. level liver and kidney levels were 0.02 ppm.

CONCLUSIONS: Plasma levels were below the level of detection of 0.01 pm. Liver and kidney levels were 0.02 ppm.

TOXICITY CATEGORY:

CORE RATING: Mimimum

REPAIRABLITY:

DATA EVALUATION REPORT

005633

STUDY: Metabolism - Dog, Acute

LABORATORY: Boots Hercules

DATE: 1974

STUDY NUMBER: AX 74012

ACCESSION NUMBER:

MRID NUMBER: 00041501

MATERIAL TESTED: 4-amino-3-methyl benzoic acid (BTS 28369) ^{14}C in the carboxyl group

ANIMALS: Dog

METHODS: One male (6.04 kg) and one female (5.45 kg) were fasted for 17 hr. prior to the oral administeration of gelatin capsules containing 10 mg/kg b.wt. of BTS 28369. Blood samples were collected at 0.75, 1.5, 3.0, 6.0 and 24 hours. Urine was collected at 7 and 24 hours. Feces collected after 24 hours. The animals were terminated at 24 hours for tissue analysis.

RESULTS: Plasma levels peaked at 0.75 hour for females (6.8 ppm) and at 3 hours for males (4.4 ppm). Labeled activity in the urine was not reported separately for each sex. Peak levels of radioactivity in the urine were observed within 7 hours. Highest tissue residue were reported in the pigmented part of the eye and in the liver-bile.

CONCLUSIONS: BTS 28369 is rapidly eliminated in the urine within 7 hours with residues levels in the liver and eye

TOXICITY CATEGORY: Minimum

CORE RATING:

REPAIRABLITY:

DATA EVALUATION REPORT

005633

STUDY: Subactue, Human, Dermal

LABORATORY: Boots Hercules

DATE: 1973

STUDY NUMBER:

ACCESSION NUMBER:

MRID NUMBER: 00044593
00040866
00029973

MATERIAL TESTED: Amitraz 20% EC in xylene

ANIMALS: Human

METHODS: Half ml on 1.0 cm^2 patch exposured 7 hour/day for 4 days to the forearm of 10 subjects.

RESULTS: Slight to moderate irritation. No flushing or sensitization reported.

CONCLUSIONS:

TOXICITY CATEGORY:

CORE RATING: Minimum

REPAIRABLITY:

DATA EVALUATION REPORT

STUDY: Acute, Human - Dermal

LABORATORY: Boots Hercules

DATE: 1975

STUDY NUMBER: F 75012

ACCESSION NUMBER:

MRID NUMBER: 00030436

MATERIAL TESTED: Amitraz 20% EC

ANIMALS: Human

METHODS: Urine sample of four spray applications were analyzed over a 24 hour period after a day of exposure to 10 ounce ai/100 gal. use dilution.

RESULTS: Urinary metabolite BTS 28869 was below limit of detection (0.01 ppm).

CONCLUSIONS:

TOXICITY CATEGORY:

CORE RATING: Minumim

REPAIRABLITY:

DATA EVALUATION REPORT

STUDY: Dermal Absorption, Rat

LABORATORY: Boots Co.

DATE: 1971

STUDY NUMBER: C 71019

ACCESSION NUMBER:

MRID NUMBER: 00041493
00055721
00028670

MATERIAL TESTED: ^{14}C amitraz (BTS 27419)

ANIMALS: Rats

METHODS: Labeled (^{14}C) amitraz in acetone was applied at 5.3 mg/kg to the shaven back of two rats, wrapped with aluminum foil, then placed in metabolism cages for 24 hours.

RESULTS: Approximately 50% of the dose was accounted for on the skin and in the wrapping material. After 24 hours 25.3 and 31.5% of the dose was recovered in the urine and 2.8 and 12.9% in the feces. Tissue residues reported in the liver were 0.87 and 0.88% of the dose with 0.12 and 0.15% in the kidney.

CONCLUSIONS: Approximately 50% of the applied dose was absorbed during a 24 hour dermal exposure to (^{14}C) amitraz.

TOXICITY CATEGORY:

CORE RATING: Minimum

REPAIRABLITY:

DATA EVALUATION REPORT

005633

STUDY: Dermal Absorption - Pig

LABORATORY: Boots Co. Ltd.

DATE: 1975

STUDY NUMBER: TX 75025

ACCESSION NUMBER:

MRID NUMBER: 00041543
00029445

MATERIAL TESTED: Amitraz, BTS 27419

ANIMALS: White X Thornber Hybrid Pigs

METHODS: To compare the effect of dermal to oral exposure, two groups of one male and one female pigs per dose level received gelatin capsules at doses of 1, 10, 25, 50 and 100 mg/kg b.wt. of technical BTS 27419. The other group of one male and one female pigs per dose level received a topical application to a surface area of approximately 400 cm^2 at 10, 20, 50, 100 and 200 mg/kg ai of a 20% EC formulation.

RESULTS: Oral - NOEL 10 mg/kg b.wt. Transient hypothermia was observed at the 25 mg/kg b.wt. level. At 50 mg/kg and above sedation, ataxia, hyperexcitability, hypothermia and emesis were observed by 19 hours after dosing, subsiding within 25 hours.

Dermal - No effects were observed after topical application at doses up to 200 mg/kg. Flushing was not observed.

CONCLUSIONS: An eight fold difference between the oral and dermal effective dose was reported.

TOXICITY CATEGORY:

CORE RATING: Minimum

REPAIRABLITY:

DATA EVALUATION REPORT

STUDY: Dermal Absorption - Dog

LABORATORY: The Upjohn co.

DATE: June 1976

STUDY NUMBER: 527-9610-TJK-76-1

ACCESSION NUMBER:

MRID NUMBER: 00044591

MATERIAL TESTED: Amitraz 21.3% EC

ANIMALS: Beagle Dogs

METHODS: Four groups of 3 male and 3 female beagle dogs were sponged over the entire body with 0, 1 times 5 times and 10 times the use concentration (0.025%) representing dose levels of 16, 68 and 136 mg/kg active material, respectively. Gross observations and rectal body temperature were recorded initially and at 4, 8 and 12 hours and at 5 and 7 days post treatment. Hematology parameters were recorded initially, at 24 hours and 7 days. Clinical chemistry was determined initially, at 8, 24 hours and 7 days post treatment.

RESULTS: Use conc: 0.025% - sedation was observed within 8 hours accompanied by hyperglycemia within 4 hours followed by normal values within 24 hours.
5 X Use Conc: 0.125% - sedation was observed within 8 hours accompanied by hypothermia and hyperglycemia within 4 hours followed by normal values within 24 hours.
10 X Use Conc: 0.25% - sedation, ataxia, salivation were observed within 8 hours, accompanied by hypothermia and hyperglycemia within 4 hours followed by normal values within 24 hours.

CONCLUSIONS:

TOXICITY CATEGORY:

CORE RATING: Minimum

REPAIRABLITY:

DATA EVALUATION REPORT

005633

STUDY: 90 day feeding -rat

LABORATORY: Japan Experimental Med. Res. Co.

DATE: August 20, 1972

STUDY NUMBER:

MRID NUMBER: 00040343
00028713

MATERIAL TESTED: BTS 27419, Amitraz

ANIMALS: Wister rats

METHODS: Dietary levels of 0, 3, 12 and 50 mg/kg (feed) were fed to four groups of 10 male and 10 female rats for 90 days.

RESULTS: The no effect level was reported to be 3 mg/kg. A depressed weight gain and an increase in the brain to body weight ratio was reported for the 12 mg/kg level. No hematological changes were observed at the 12 and 50 mg/kg levels. At the 50 mg/kg level a decrease in alkaline phosphatase and SGOT values were reported accompanied by a increase in urobilinogin in the urine.

CONCLUSIONS:

TOXICITY CATEGORY:

CORE RATING: Supplementary

REPAIRABILITY: The lack of histopathological data at the dose level fed raises questions as to the quality of this study.

DATA EVALUATION REPORT

STUDY: 90 day feeding - mice

LABORATORY: Japan Experimental Med. Res. Co.

DATE: August 22, 1972

STUDY NUMBER:

MRID NUMBER: 00028714
00040344

MATERIAL TESTED: BTS 27419, Amitraz

ANIMALS: ICR mice

METHODS: Dietary levels of 0, 3, 12, and 50 mg/kg (feed) were fed to four groups of 13 males and 13 females mice for 90 days.

RESULTS: The no effect levels was considered to be 3.0 mg/kg with a decrease in body weight gain reported during the first week of the study. At the 12 mg/kg level a decreased in blood GPT, alkaline phosphatase and an increase in urobilinogen in the urine was reported.

CONCLUSIONS:

TOXICITY CATEGORY:

CORE RATING: Supplemental

REPAIRABILITY: The lack of histopathological data at the dosage levels fed raises questions as to the quality of this study.

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