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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: January 5, 2001

SUBJECT: Mesotrione (ZA 1296). Tyrosine-mediated toxicity in mice and rats.

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AND

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Mechanism of Toxicity Science Assessment Review Committee
Health Effects Division (7509C)

TO: Sarah Levy, Risk Assessor
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The Health Effects Division (HED) Mechanism of Toxicity Science Assessment Review Committee is asked to evaluate the mechanism of toxicity of mesotrione in rats and mice in regards to tyrosine-mediated effects and assess the relevance of the two animal models to human health.

cc: Anna Lowit (RRB2), Clark Swentzel (RAB1), James Stone (RD)

I. BACKGROUND

Mesotrione (ZA 1296) is one of a new class of triketone chemicals. It is an herbicide that acts by inhibiting the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD) in plants. This enzyme is also present in mammals, primarily in the liver, and its inhibition may result in accumulation of high levels of tyrosine in the blood. Mesotrione has been noted to adversely affect body weight, pup survival, and litter size and produce effects in the eye, kidney, and liver in the rat. The registrant of mesotrione has attempted to demonstrate that tyrosine is the mediator of the toxic effects observed in rats and that the species (rat vs. mouse) and sex differences in the toxicology of the compound are due to the excess levels of tyrosine that occur uniquely in the rat. The registrant believes the mouse is a better model for assessing mesotrione toxicity in humans than the rat since the enzymes involved in tyrosine metabolism and the pathological process have similar activities in mice and humans and the severe tyrosinemia associated with rats does not develop in mice or humans. Some of the questions that need to be addressed include: 1) Is the toxicity associated with the administration of mesotrione in rats mediated by tyrosine? 2) Are the sex and species differences in the toxic response to mesotrione predominantly a result of different HPPD and TAT (tyrosine aminotransferase) activities? 3) Is the mouse a better model than the rat for assessing mesotrione toxicity in humans and the disposition of tyrosine during a compound-induced tyrosinemia?

Attachment A is the concise report submitted by the registrant explaining their view of the mechanism of toxicity of mesotrione and the rationale behind their request to use the mouse findings and effect levels when assessing the hazards of mesotrione to humans. A summary of their report is given later in this memo. Attachment B is a summation of the deliberations and conclusions on the data presented by the registrant at the national meeting of the Society for Integrative and Comparative Biology held in Denver, Colorado on January 6-10, 1999.

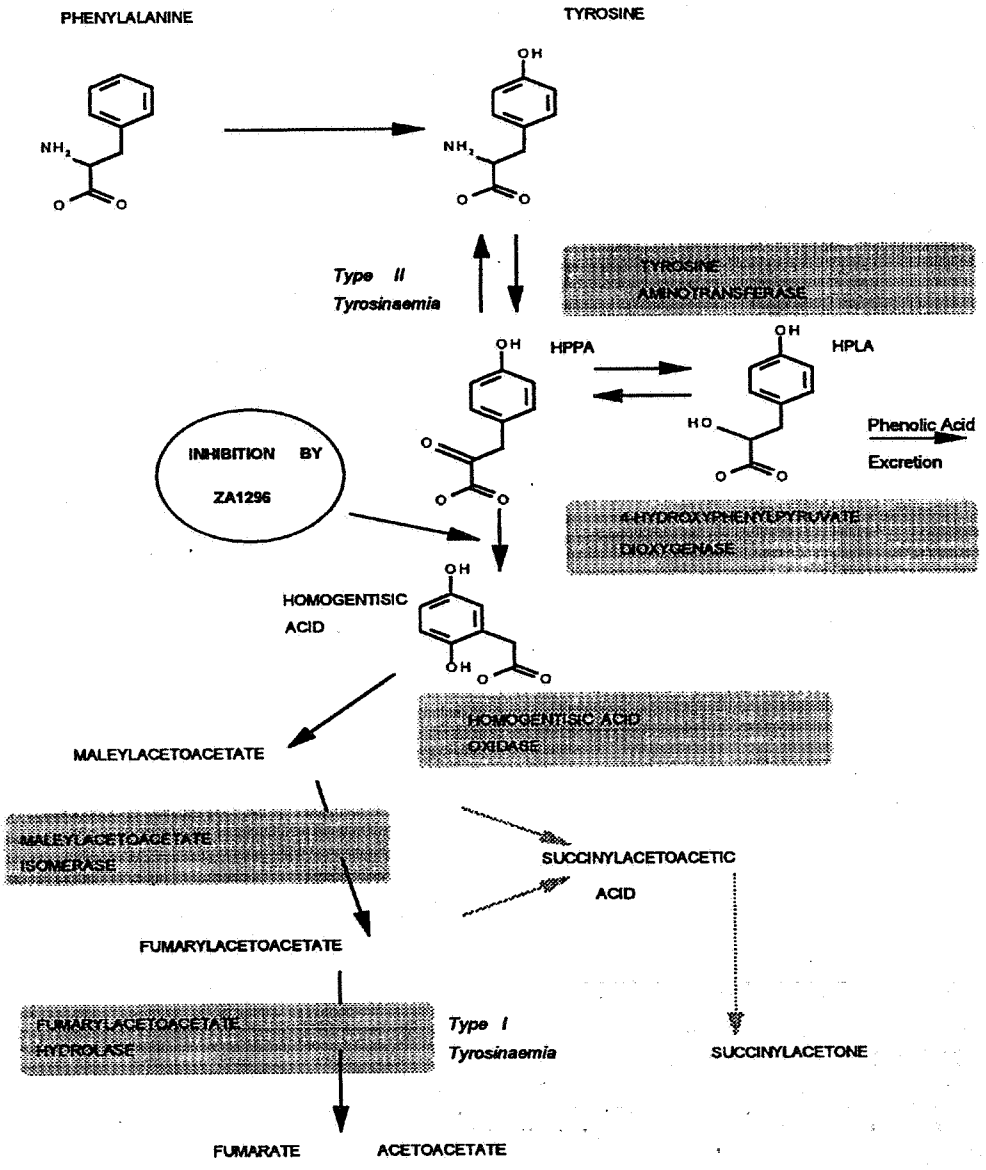
II. PROPOSED MECHANISM OF ACTION

A. Tyrosine Metabolism

Tyrosine metabolism occurs primarily in the liver. Tyrosine is converted to 4-hydroxyphenylpyruvic acid (HPPA) by tyrosine aminotransferase and then to homogentisic acid by HPPD. It then goes on to ultimately form fumarate and acetoacetate. If HPPD is inhibited, HPPA will not be converted to homogentisic acid, but can be converted to phenolic acids and excreted in the urine. If HPPD inhibition is severe, tyrosine levels may increase dramatically depending on the activity of TAT. If the activity of TAT is low, as in the rat, tyrosine cannot be converted quickly to HPPA and excreted so that levels in the blood rise and result in toxicity to the rat. The registrant points out that the TAT activity in the mouse is much higher in the rat so that tyrosine concentrations do not reach high enough levels in the blood that result in toxicity. Hence, the basis for the claim that the mouse is a better model for assessing mestrione toxicity in humans than the rat is that humans have similar TAT activities as the mouse and are not likely to have the adverse effects associated with toxicity in the rat.

Figure 1

Catabolic Pathway for Tyrosine



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B. Comparison of rat, mice and human data

Registrant's Assessment

1. Mesotrione toxicity in rats

Signs of toxicity observed in adult rats administered mesotrione include ocular effects such as corneal opacity, increased kidney and liver weights, and decreased body weight and body weight gain. The ocular and organ weight effects are reversible after the compound is no longer administered to the rat (MRIDs 44537103, 44537104). In multi-generation rat studies, decreased litter size and pup weights, and an increased incidence of hydronephrosis have been noted.

In male rats, plasma levels of mesotrione increase linearly with increasing dietary concentrations up to 5000 ppm, but tyrosine plasma levels reach a threshold and are maintained at about the same plasma concentration with dietary concentrations of 40 ppm up to 5000 ppm (MRID 44505113). The steady state plasma tyrosine concentrations increase rapidly at dietary doses ranging from 1 to 10 ppm. Above 10 ppm of dietary mesotrione, there is little effect on plasma tyrosine concentrations or on the toxic effect response in the animal. Also, HPPD activity is completely inhibited at 10 ppm even though plasma levels of mesotrione continue to increase as dietary levels increase. In female rats, steady state plasma tyrosine concentrations occur at higher doses. Excess tyrosine in the blood is metabolized to phenolic acids and excreted in the urine. The shape of the dose-response curve for the excretion of phenolic acids in the urine is similar to the shapes of the dose-response curves for tyrosinemia, HPPD inhibition and liver and kidney weight changes (MRIDs 44537106, 44537107).

Male rats achieve a maximal level of plasma tyrosine concentration approaching 3,500 nmol/ml while female rats achieve a maximal level of around 1,800 nmol/ml. In female rats, HPPD activity is completely inhibited at 1000 ppm, which is two orders of magnitude greater than males. Also, signs of toxicity occur at higher dietary levels of mesotrione in the female than in the male. Females have similar shaped dose-response curves for HPPD inhibition, tyrosinemia, signs of toxicity and excretion of phenolic acids in the urine like male rats, but over a different dose range. The registrant claims that this difference in dose levels between the sexes where toxicity occurs is due to a higher basal HPPD activity, a higher Vmax for TAT, and a lower Km for TAT in females as compared to males. As mesotrione levels increase in the blood, HPPD in female rats will be able to metabolize HPPA more efficiently to homogentisic acid than males because the enzyme activity is greater. Also, due to the kinetics of TAT in females, any tyrosine buildup can be effectively metabolized to phenolic acids and excreted in the urine, thus, preventing presentation of clinical signs at lower doses as observed in males (MRIDs 44537106, 44537107).

The registrant has demonstrated a threshold tyrosine concentration after which adverse effects begin to appear. Liver weight changes appear in both sexes of the rat when plasma tyrosine levels reach about 800 - 1,000 nmol/ml. In male rats, this level is reached at about 5 ppm of mesotrione in the diet, while in females the same effect does not appear until around 100 ppm.

Ocular effects begin to occur at 1,000 nmol/ml of plasma tyrosine which is reached at about 7.5 ppm in males and 1,000 ppm in females (MRIDs 44537106, 44537107).

Other evidence in rats that tyrosine is the mediator of mesotrione toxic effects.

Feeding high concentrations of tyrosine alone to rats results in a tyrosinemia that can elicit the same toxic signs as administration of mesotrione such as increased liver and kidney weights, decreased body weight gain, and ocular effects. When mesotrione is added to the tyrosine-enriched diet, the effects are exacerbated (MRID 44505111).

A more potent triketone, NTBC, affects HPPD like mesotrione and will produce the same adverse ocular effects in rats as mesotrione but at lower doses (Robinson 1995).

2. Mesotrione toxicity in mice

The registrant states that the only effect seen in adult mice when administered mesotrione up to 7,000 ppm is increased liver weight. Decreased pup weights were seen in the reproduction study. The registrant alleges that the mouse reaches a steady state plasma tyrosine concentration around 800 nmol/ml in both sexes which is below the threshold where ocular, kidney weight, body weight, and litter effects appear, but liver weight increases are noted (MRIDs 44505116, 44505022). This difference between rats and mice is attributed to the higher activity of TAT in mice which results in the ability to excrete tyrosine more effectively as phenolic acids than the rat (MRID 44505116). Since both sexes of the mouse can maintain tyrosine plasma levels at about 800 nmol/ml, ocular effects do not occur even at high dietary dosages of mesotrione. Since mesotrione is excreted unchanged at low and high doses in rats and mice, the registrant alleges that it is highly unlikely that differences in disposition of mesotrione between rats and mice will account for their difference in susceptibility to adverse effects associated with the administration of the compound.

3. Human data

Cytosolic TAT activity in the human liver has been reported to be 4.5 - 7.3 nmol HPPA/mg cytosolic protein/min. This value is similar to the TAT activity in mice and 3 - 4 times the activity in male rats (Furukawa *et al* 1984, Giardini *et al* 1983).

Steady state plasma tyrosine levels have been demonstrated in humans in which HPPD activity was deficient (Endo *et al* 1982, Giardini *et al* 1983). Humans with a low TAT activity (type II tyrosinemia) have been reported to have severe tyrosinemia with associated ocular effects. If the tyrosine plasma levels fall to about 800 nmol/ml, ocular effects resolve, thus, providing evidence that humans have a threshold plasma tyrosine level above which toxic signs develop. Human volunteer studies with mesotrione revealed that doses up to 4 mg/kg produced only a mild, transient tyrosinemia (MRID 44505114).

Sex differences (MRID 44901720)

There are no differences in the incidence or effects between male and female humans affected by the condition of hereditary tyrosinemia.

The available literature shows no differences in hepatic TAT activity measurements between males and females.

The incidence pattern for neonatal tyrosinemia does not suggest that one sex is more vulnerable than the other.

Humans treated with NTBC, a triketone drug about 40 times more potent than mesotrione, for type I tyrosinemia have maintained tyrosine levels less than 1,000 nmol/ml. Treatment resulted in ocular irritation only. Infants administered NTBC for type I tyrosinemia have not had treatment withdrawn due to adverse effects (Ellis *et al* 1995, Lindstedt *et al* 1992).

4. Registrant's Conclusions

The data presented appears to show that the mouse is the best model for assessing mesotrione toxicity in humans due to similarities in steady state plasma tyrosine levels, threshold levels for adverse effects, TAT activity, and the response of both sexes to the compound.

Agency's Findings on Submitted Toxicity Studies of Mesotrione

1. Rat

Subchronic Studies

In two rat subchronic studies, a LOAEL/NOAEL of 11/0.09 mg/kg/day based on corneal abnormalities and decreased body weight gain (MRID 44505019) and a LOAEL/NOAEL of 0.63/0.41 mg/kg/day based on corneal lesions (MRID 44505020) were determined.

Chronic Study

In a rat combined chronic toxicity/ carcinogenicity study, a LOAEL/ NOAEL of 0.48/0.16 mg/kd/day based on corneal lesions, increases in kidney and liver weights, and hepatocyte fat vacuolation was determined (MRID 44505035). However, the NOAEL only applies to the corneal lesions since the lower doses were part of a special study to ascertain ocular toxicity only and not other organ effects, including the kidney and liver.

Developmental

In a rat developmental study, a maternal toxicity LOAEL of 100 mg/kg/day was determined with no NOAEL based on decreased body weight gain during treatment and reduced food consumption. The developmental LOAEL was also 100 mg/kg/day based on delays in skeletal ossification and changes in manus/pes ossification assessments. No NOAEL was determined

(MRID 44920801).

Reproduction

In a rat reproduction study, a parental systemic LOAEL of 0.3 mg/kg/day based on significantly increased plasma tyrosine levels and increased liver weights in F_2 males, and an offspring systemic LOAEL of 0.3 mg/kg/day based on significantly increased plasma tyrosine levels in F_2 male pups. No NOAEL was determined for parental or offspring effects. At the next highest dose (1.1 mg/kg/day) increased ocular and renal lesions in both sexes and decreased food consumption in females was observed in the parents and increased ocular lesions in males and increased renal lesions in both sexes was observed in the offspring. A reproductive LOAEL/NOAEL of 1.1/0.3 mg/kg/day based on decreased mean F_2 litter size was determined.

2. Mouse

Subchronic Study

In a mouse subchronic study, a NOAEL of 1212 mg/kg/day was determined with no LOAEL due to no systemic effects observed at the highest dose tested (MRID 44505022).

Chronic Studies

In a mouse carcinogenicity study, a LOAEL/NOAEL of 898/49.7 mg/kg/day based on decreases in body weight, body weight gain, and food efficiency was determined (MRID 44505028). In a mouse chronic toxicity study the LOAEL/NOAEL was 1114/56.2 mg/kg/day based on decreases in body weight gain and food utilization (MRID 44505026).

Developmental

In a mouse developmental study, a maternal NOAEL was set at 600 mg/kg/day based on lack of systemic effects at the highest dose test. A developmental LOAEL/NOAEL of 600/150 mg/kg/day based on decreased ossification of cervical vertebrae centra was determined (MRID 44920802).

Reproduction

In a mouse reproduction study, a parental systemic LOAEL/NOAEL of 71.4/10.1 mg/kg/day based on increased kidney weights and tyrosinemia in the F_0 males and F_1 males and females and an offspring systemic LOAEL/NOAEL of 2.1/<2.1 based on tyrosinemia and ocular discharge in the F_1 and F_2 offspring were determined (MRID 44505034).

III. DISCUSSION

The registrant's postulated mechanism of action for mesotrione appears to be sound. Plasma levels of mesotrione increase linearly with increased dietary intake. However, the clinical signs

associated with administration of this compound appear to be mediated by plasma tyrosine levels which ultimately reach a steady-state level and do not continue to rise as dietary concentration increases. Different organs are affected at various threshold levels, but most of the toxic effects are reversible once the tyrosine levels are reduced below the associated threshold level. The same toxic signs can be experimentally induced by feeding a high tyrosine diet alone or can be exasperated by adding tyrosine to a diet containing mesotrione.

Basically, ocular effects are the initial clinical manifestation in rats and appear at lower doses of mesotrione in males than in females. In the rat subchronic study, ocular effects and body weight changes were noted at the LOAEL. In the rat chronic study, no NOAEL was determined for liver and kidney effects in the male rat, but was probably close to the ocular toxicity NOAEL. In the mouse, the reviewer differs from the opinion of the registrant in that body weight decrements and decreased food efficiency appear before liver effects. However, both occur at much higher doses than in either sex of the rat. In the rat reproduction study, tyrosinemia and increased liver weights were observed in adults at the lowest dose tested, while in the mouse reproduction study, tyrosinemia and increased kidney weights were noted at the LOAEL (71.4 mg/kg/day) which was higher than the rat LOAEL (0.3 mg/kg/day). In the rat developmental study, maternal effects included body weight and body weight gain decrements with decreased food consumption at the LOAEL in the absence of any ocular effects. No maternal effects were noted in the mouse developmental study. From these data, it seems that the predictive sequence of adverse effects using threshold levels is not precise, but the proposed mechanisms in the rat and mouse appear to hold true in adult animals.

In the developmental studies, the rat appears to be more sensitive to developmental effects when administered mesotrione than the mouse due to the fact that no NOAEL was established for maternal or developmental effects (the lowest dose tested was 100 mg/kg/day) in the rat and the mouse had developmental effects at 600 mg/kg/day (the highest dose tested) in the absence of any maternal effects

Young animals appear to be more sensitive to the effects of mesotrione administration than adults. In the mouse reproduction study, parental effects seen at the highest dose tested (71.4 mg/kg/day) included increased kidney weights and tyrosinemia while offspring effects of tyrosinemia and ocular discharge were noted at the lowest dose tested (2.1 mg/kg/day). In the rat reproduction study, both parental and offspring systemic LOAELs were observed at the lowest dose tested (0.3 mg/kg/day). The parental effects included tyrosinemia and increased liver weights, while the offspring effect was tyrosinemia alone; however, the tyrosinemia in the pups was 10X that of the adults at the same mesotrione dietary level. Such high levels of an amino acid in the plasma over several years may cause organ damage due to osmotic imbalances. The effects at the next highest dose for both offspring and parents included increased ocular and renal lesions plus increased liver weights in the parents. Young animals may tolerate higher plasma tyrosine levels in the short term than adults, but long-term effects (several years) of a severe tyrosinemia in the young are not adequately assessed by the guideline studies.

Some interesting observations to note are that exposure to mesotrione throughout the lifespan of the mouse appears to greatly affect the dose level at which adverse effects are seen. In the subchronic, chronic, and carcinogenicity mouse studies, effects were noted near the limit dose or

not seen at all. In the reproduction study, the parental LOAEL/NOAEL was much lower (71.4/10.1 mg/kg/day). Apparently, a lifetime exposure to mesotrione from the womb to reproductive age can increase the sensitivity of the animal to the toxic effects of the compound. It is also noted that the gap in effect levels between the rat and mouse offspring is much smaller than between adult rats and mice in the reproduction study and the other oral studies. This may suggest that enzyme kinetics may differ in the young as compared to adults.

The purpose of this review of rat/mouse toxicity studies and mechanistic data is to determine if the mouse endpoints should be used for human risk assessment rather than the rat even though the rat is the most sensitive species. The mouse and rat, however, are not the only species in which the toxicity of a chemical is assessed. In the dog subchronic study, no effects were seen up to the limit dose of 1000 mg/kg/day, but plasma tyrosine levels were not assessed. In the dog chronic study, no NOAEL was determined and the LOAEL of 10 mg/kg/day was based on increased plasma tyrosine levels and erythrophagocytosis in the mesenteric lymph nodes, suggesting a possible immune system effect. This dose level is between the rat and mouse chronic study effect levels. We have no mechanistic data in the dog on the effects of mesotrione.

IV. CONCLUSIONS

The registrant's proposed mechanisms in the rat and mouse appear to hold true in adult animals as evidenced in the subchronic, chronic, and developmental studies. However, the apparent increased sensitivity of adult mice to mesotrione in the reproduction study plus the increased sensitivity of the young as compared to the adults cannot be explained by the proposed mechanism and may suggest that the enzyme kinetics differ in the young as compared to adults.

For regulatory purposes, studies with species other than the rat or mouse may be used to set endpoints if the Agency determines that they are more appropriate.

TOXICITY PROFILE FOR MESOTRIONE

DER #	STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
1	2-YR FEED/CARCINOGENIC RAT (1997, 1998) MRIDs 44505035, 44505036 Acceptable 0, [1, 2.5], 7.5, 100, 2500 ppm M/F: 0/0, [0.06/0.08, 0.16/0.19], 0.48/0.57, 6.48/7.68, 159.89/189.48 mg/kg/day	0.16/0.19 (M/F) [The NOAEL only applies to ocular lesions; a NOAEL was not determined for kidney and liver weights or hepatocyte fat vacuolation in males]	0.48/0.57 (M/F), based on ocular lesions, increases in kidney and liver weights, and hepatocyte fat vacuolation in males No evidence of carcinogenicity
2	12-MONTH CHRONIC TOXICITY MOUSE (1997) MRID 44505026 Acceptable/guideline 0, 10, 50, 350, 7000 ppm M/F: 0/0, 1.5/2.1, 7.8/10.3, 56.2/72.4, 1114/1494.5 mg/kg/day	56.2/72.4 (M/F)	1114/1494.5 (M/F), based on decreases in body weight gain and food utilization in males
3	80-WEEK CARCINOGENIC MOUSE (1997) MRID 44505028 Acceptable 0, 10, 350, 7000 ppm M/F: 0/0, 1.4/1.8, 49.7/63.5, 897.7/1102.9 mg/kg/day	Males: 49.7 Females: 1102.9	Males: 897.7, based on decreased body weight, body weight gain, and food efficiency Females: not observed No evidence of carcinogenicity
4	1-YR FEEDING DOG (1997) MRID 44505027 Acceptable/guideline 0, 10, 100, 600 mg/kg/day	Not determined	10, based on evidence of tyrosinemia in both sexes and increased incidence of erythrophagocytosis in the mesenteric lymph nodes of females

TOXICITY PROFILE FOR MESOTRIONE

DER #	STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
5	3-GEN REPRODUCTION RAT (1997) MRID 44505033 Unacceptable 0, 2.5, 10, 100, 2500 ppm M/F: 0/0, 0.3/0.3, 1.1/1.2, 11.7/12.4, 287.7/311.4 mg/kg/day	Parental systemic: not established Offspring systemic: not established Reproductive: 0.3 (M/F)	Parental systemic: 0.3 (M/F), based on significantly increased plasma tyrosine levels and increased liver wts. in F_2 males Offspring systemic: 0.3 (M/F), based on significantly increased plasma tyrosine levels in F_2 male pups Reproductive: 1.1/1.2 (M/F), based on decreased F_2 mean litter size
6	2-GEN REPRODUCTION MOUSE (1997) MRID 44505034 Unacceptable 0, 10, 50, 350, 1500, 7000 ppm M/F: 0/0, 2.1/2.4, 10.1/11.7, 71.4/82.5, 306.7/362.7, 1455.5/1652.3 mg/kg/day	Parental systemic: 10.1/11.7 (M/F) Offspring systemic: not established	Parental systemic: 71.4/82.5 (M/F), based on increased kidney weights and tyrosinemia in the F_0 males and F_1 males and females Offspring systemic: 2.1/2.4 (M/F), based on tyrosinemia and ocular discharge in the F_1 and F_2 offspring
7	DEVELOPMENTAL TOX RAT (1999) MRID 44920801 Unacceptable/upgradable 0, 100, 300, 1000 mg/kg/day	Maternal: not established Developmental: not established	Maternal: 100, based on decreased body weights, body weight gains during treatment, and decreased food consumption Developmental: 100, based on delays in skeletal ossification and changes in *manus/pes* ossification assessments

TOXICITY PROFILE FOR MESOTRIONE

DER #	STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
8	DEVELOPMENTAL TOX MOUSE (1997, 1999) MRIDs 44920802, 44901708 Acceptable 0, 10, 60, 150, 600 mg/kg/day	Maternal: ≥600 Developmental: 150	Maternal: not observed Developmental: 600, based on decreased ossification of the cervical vertebrae centra
9	90-DAY FEEDING RAT (1997) MRID 44505020 Acceptable/guideline 0, 2.5, 5, 7.5, 150 ppm M/F: 0/0, 0.21/0.23, 0.41/0.47, 0.63/0.71, 12.46/14.48	Males: 0.41 Females: 0.71	Males: 0.63 Females: 14.48 based on corneal lesions
10	90-DAY FEEDING RAT (1995) MRID 44505019 Acceptable/guideline 0, 1, 125, 1250, 12,500 ppm M/F: 0/0, 0.09/0.10, 11/13, 112/126, 1111/1213 mg/kg/day	0.09/0.10 (M/F)	11/13 (M/F), based on corneal abnormalities in both sexes and decreased body weight gain in males
11	90-DAY FEEDING DOG (1997) MRID 44505023 Acceptable/guideline 0, 100, 600, 1000 mg/kg/day	1000	>1000 No effects noted
12	13-WEEK FEEDING MOUSE (1997) MRID 44505022 Acceptable/guideline 0, 10, 50, 350, 7000 ppm M/F: 0/0, 1.7/2.4, 8.4/12.4, 61.5/80.1, 1212/1537 mg/kg/day	1212/1537	> 1212/1537 No effects noted

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