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PREVENTION, PESTICIDES AND
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DATE: 8/28/00

MEMORANDUM

SUBJECT: *Atrazine* - 2nd Report of the Hazard Identification Assessment Review Committee.

FROM: Roger Hawks, Toxicologist.
Reregistration Branch III
Health Effects Division (7509C)
Roger Hawks 8/31/00

THROUGH: Jess Rowland, Co-Chair
Jess Rowland 8/31/00
and
Elizabeth Doyle, Co-Chair
E. A. Doyle 8/31/00
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Cathy Eiden, Risk Assessor
Reregistration Branch III
Health Effects Division (7509C)

PC Code: 080803

On May 4, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for atrazine with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. This chemical was evaluated by HIARC in August of 1998. The current reevaluation of atrazine is based on the receipt of additional data pertaining to atrazine's potential effects on infants and children generated by the Agency's National Health Effects Environmental Research Laboratories and by the availability of a draft cancer assesment document - neither of which was available at the August 1998 HIARC meeting. The potential for increased susceptibility of infants and children from exposure to atrazine was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

Members present were:
Elizabeth Mendez, David Nixon, Yung Yang, Beth Doyle, Jonathon Chen, Jess Rowland, Brenda Tarplee, Bill Burnam, Vicki Dellarco, Pam Hurly

Member(s) in absentia: Tina Levine

Data evaluation prepared by: Roger Hawks, Reregistration Branch III

Also in attendance were: Karl Baetcke, HED Richard Hill, OPPTS

Data Evaluation / Report Presentation

Roger Hawks
Roger Hawks
Toxicologist

1. INTRODUCTION

On May 4, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for atrazine with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. This chemical was evaluated by HIARC in August of 1998. The current reevaluation of atrazine is based on the receipt of additional data pertaining to atrazine's potential effects on infants and children generated by the Agency's National Health Effects Environmental Research Laboratories and by the availability of a draft cancer assesment document - neither of which was available at the August 1998 HIARC meeting. The potential for increased susceptibility of infants and children from exposure to atrazine was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

2. HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD) - Female 13-50 Subpopulation

Study Selected: A weight of the evidence consideration using evidence provided by four studies: two developmental toxicity studies in rats; a rabbit developmental toxicity study and a study examining the effects of maternal atrazine exposure during lactation on prostate effects in male offspring.
The actual NOAEL and endpoint upon which the reference dose is calculated is derived from one of the above-mentioned developmental studies in the rat - MRID 40566302.

Study #1 - MRID No.: 40566302

Executive Summary: In a developmental toxicity study (MRID 40566302) atrazine (96.7%) was administered to 104 Charles River CD rats 27/dose by gastric intubation at dose levels of 0, 10, 70, or 700 mg/kg/day from days 6 through 15 of gestation.

Mortality was very high for the 700 mg/kg/day animals in this study. All but 6 of the 27 females in this group died during the gestation period. Other statistically significant findings in this group included: salivation; oral and nasal discharge; ptosis; swollen abdomens; blood on the vulva; enlarged stomachs and adrenal; and discolored lungs. Body weight gains were statistically significantly reduced throughout most of the gestation period. Significant reductions in food consumption were observed. Although mortality was quite high in the high dose group, pregnancy rates were comparable to controls (85.2% for controls *vs* 96.3% high dose) and the numbers of live fetuses at c-section was comparable to controls (mean of 12.7 per litter for controls *vs* 13.4 for the high dose).

There were few findings in either the low or mid dose animals. Alopecia was observed in mid dose animals, but was not considered to be biologically significant. Body weight gain in the mid dose group was significantly reduced for the first 5 days of compound exposure (gestation days 6-10). Food consumption in the intermediate group was reduced, but only at day 17 of gestation. Low dose body weight gain was increased on days 6-10 of gestation and food consumption was increased on gestation day 9.

The maternal LOAEL is 70 mg/kg/day, based on reduced body weight gain. The maternal NOAEL is 10 mg/kg/day.

Fetal weights were statistically significantly reduced in the high dose group. Skeletal examinations were not conducted in the high dose group due to the extremely low fetal weights. Visceral and external examinations were conducted, though, and no group, including the high dose group, displayed any findings significantly different from control values. Skeletal anomalies, however, were observed in the mid dose group. The original reviewers of this study concluded that none of these skeletal anomalies indicated a direct compound related toxic effect to the embryo/fetus (TXR 006131). An evaluation by the Ad Hoc Committee Regarding the Use of Developmental Toxicity Studies (Memorandum- From: Marion Copley. March 25, 1993) focused on findings of delayed ossification at several sites to conclude that atrazine *did* induce delayed ossification.

The developmental LOAEL was found to be 70 mg/kg/day, based on delayed or no ossification at several sites. The developmental NOAEL is 10 mg/kg/day.

The developmental toxicity study in the rat is classified **Acceptable-Guideline** and does satisfy the guideline requirement for a developmental toxicity study §83-3a in rats.

Study #2 - MRID No.: 41065201

Executive Summary: In a developmental toxicity study (MRID 41065201) atrazine (97.6%) was administered by gavage to 104 mated female Sprague-Dawley rats, 26/dose, at dose levels of 0, 5 (LDT), 25 (MDT), 100 (HDT) mg/kg/day from days 6 through 15 of gestation.

Maternal toxicity findings were almost exclusively confined to the high dose group. Compared to controls high dose dams displayed: reduced food consumption (decreased 13%, $p \leq 0.5$); reduced total body weight gain (reduced 18% during dosing period, $p \leq 0.5$); reduced corrected (minus uterine weight) weight gain (reduced 20% for entire gestation, $p \leq 0.5$); and increased alopecia 1/26 controls vs 5/26 high dose). One high dose animal died on gestation day 20 and salivation was noted as an observation in 18/26 high dose animals. The only observations seen outside the high dose group were: an abortion from one of the mid-dose animals on gestation day 19; a fluid-filled hollow right kidney in a mid-dose animal; and hollow discolored kidneys in a low dose animal.

The maternal LOAEL is 100 mg/kg/day based on reduced body weight gain and food consumption. The maternal NOAEL is 25 mg/kg/day.

The few malformations seen upon external examination of the fetuses were seen only in the control groups and clearly could not be compound related. Likewise, there was no increased incidence of visceral malformation in dosed groups *vs* control groups. There were no skeletal malformations observed but there was an increased incidence of incomplete ossification of various bones in the HDT. Hyoids (control fetal incidence of 11% *vs* 21.7% HDT), occipitals (7.7% *vs* 21.1%) and parietals (2.2% *vs* 8.4%) showed incomplete ossification. There was also an increased incidence ($p \leq 0.05$) of incomplete ossification of the interparietals in all dose groups compared to controls.

Fetal body weight, number of resorptions and implantations, and live fetuses/litter were not significantly affected by atrazine treatment.

Exposure of gravid Sprague-Dawley rats to atrazine under the conditions described in this study seemed to have few embryo/fetotoxic effects.

The developmental LOAEL is 100 mg/kg/day, based on increased incidence of delayed ossification of skull bones. The developmental NOAEL is 25 mg/kg/day.

The developmental toxicity study (MRID 41065201) in the rat is classified **Acceptable-Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3a) in the rat.

Study #3 - MRID Nos.: 00143006, 40566301

Executive Summary: In a developmental toxicity study (Acc. No. 254979; MRIDs 00143006, 40566301) atrazine (96.3%) was administered by gavage to 76 mated female New Zealand White rabbits, 19/dose, at dose levels of 0, 1, 5, or 75 mg/kg/day, from days 7 through 19 of gestation.

Clinical signs seen in 75 mg/kg/day (HDT) animals that were considered to be related to compound treatment were stool changes (none, little or soft stool; 9/19 controls *vs* 19/19 HDT), and the appearance of blood in the cage or on the vulva (0/19 controls *vs* 4/19 HDT). Body weight gain was reduced in high dose dams and, at many time points, body weight was below day zero values. At gestation days 14, 19, 21 and 25, mean maternal body weights were 12%, 19%, 18%, and 10% below control values($p \leq 0.01$ for all four of these time points).

High dose animals displayed significantly reduced food consumption during treatment. During gestation days 12 to 17 the HDT average feed consumption was only 1-6 grams of feed per animal per day compared to 175-182 grams for the controls.

The mid and low dose groups had no alterations that could be attributed to atrazine exposure. **The maternal toxicity LOAEL is 75 mg/kg/day based on decreased body weight, food consumption and increased incidence of clinical signs. The maternal toxicity NOAEL is 5 mg/kg/day.** Increased resorptions - mean of 1.3/dam in controls *vs* 4.8/dam in HDT - ($p \leq 0.01$), reduced live fetuses per litter - mean of 8.8/dam in controls *vs* 5.9/dam in HDT - ($p \leq 0.05$), and increased delayed ossification of appendicular elements were observed in the high dose group.

The low and intermediate groups had no fetal findings that could be attributed to compound exposure.

The findings in the high dose group were determined to be secondary to maternal toxicity and thus the LOEL and NOEL for embryo/fetotoxicity match the maternal LOEL and NOEL.

The developmental toxicity LOAEL is 75 mg/kg/day based on reduced litter size, increased resorptions and delayed ossification. The developmental toxicity NOAEL is 5 mg/kg/day

The study is considered **Acceptable-Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3b) in rabbit.

Study #4 - MRID No.: 45166902

Executive Summary: Hyperprolactinemia prior to puberty in male rats has been shown to lead to lateral prostate inflammation in young adult rats. One possible cause of hyperprolactinemia in immature male rats is a deficiency in milk-derived prolactin. Milk-derived prolactin plays a critical role in the development of the tuberoinfundibular dopaminergic neurons (TIDA) of the hypothalamus of a developing rat. The TIDA neurons function to inhibit prolactin secretion from the anterior pituitary. Organization and development of these neurons occurs mainly during the first postnatal week in the rat

(Ojeda and McCann, 1974).

Thus, if developing rats do not receive a sufficient amount of prolactin from their mothers milk during the first week after birth, the TIDA neurons will not develop properly and may not be able to sufficiently provide an inhibitory check to prolactin secretion in the adult animal. The resultant hyperprolactinema is associated with development of prostatitis in the adult.

Atrazine has been shown to depress the secretion of prolactin. The role of milk-derived prolactin in development of the TIDA neurons in the neonatal rat hypothalamus, and the resulting hyperprolactinmia followed by lateral prostatitis that is the consequence of incomplete development of these neurons is described above. To summarize these points: without early lactational exposure to PRL, TIDA neuronal growth is impaired and elevated PRL levels are present in the prepubertal male. Hyperprolactinemia in the adult male rat has been implicated in the development of prostatitis.

Thus, early lactational exposure of dams to agents that suppress suckling-induced PRL release (possibly atrazine) could lead to a disruption in TIDA development in the suckling male offspring, followed by altered PRL regulation and subsequent hyperprolactinemia and prostatitis in these male offspring.

To test the hypothesis that atrazine exposure of dams during lactation could initiate the above-described sequence of events, suckling-induced PRL release was measured in Wistar dams treated with atrazine (by gavage, twice daily on PND 1-4 at 0, 6.25, 12.5, 25, and 50 mg/kg) or the dopamine receptor agonist bromocriptine (BROM, sc, twice daily at 0.052, 0.104, 0.208 and 0.417 mg/kg). BROM is known to suppress PRL release. Serum PRL was measured on PND 3 using a serial sampling technique and indwelling cardiac catheters.

A significant rise in serum PRL release was noted in all control females within 10 minutes of the initiation of suckling. Fifty mg/kg ATR inhibited suckling-induced PRL release in all females, whereas 25 and 12.5 mg/kg ATR inhibited this measure in some dams and had no discernible effect in others. The 6.25 mg/kg dose of ATR was without effect. BROM also inhibited suckling-induced PRL release at the two highest doses.

To examine the effect of postnatal ATR and BROM on the incidence and severity of inflammation (INF) of the lateral prostate of the offspring, adult males were examined at 90 and 120 days. While no effect was noted at 90 days of age, at 120 days, both the incidence and severity of prostate inflammation was increased in those offspring of ATR-treated dams (25 and 50 mg/kg). The 12.5 mg/kg ATR and the two highest doses of BROM increased the incidence, but not severity, of prostatitis. Combined treatment of ovine prolactin (oPRL) and 25 or 50 mg/kg ATR on PN1-4 reduced the incidence of inflammation observed at 120 days, indicating that this increase in INF seen after ATR alone resulted from the suppression of PRL in the dam. Testing to determine whether or not there is a critical period for these effects revealed that the critical period for this effect is PND1-9.

Summary/conclusion

These data demonstrate that ATR suppresses suckling-induced PRL release and that this suppression results in an increase in lateral prostate inflammation in the offspring and that the critical period for this effect is PND1-9.

<u>Dose and Endpoint for Establishing RfD:</u> 10 mg/kg/day based on delayed or lack of ossification of several sites at 70 mg/kg/day (LOAEL).

Uncertainty Factor (UF): 100

Comments about Study/Endpoint/Uncertainty Factor: Any of the four studies described above may be appropriate for selection of an endpoint for acute risk assessment. The developmental effects seen in the two rat and one rabbit developmental study are assumed to have the potential to occur after a single dosing. The effects seen in the open literature prostatitis paper occurs after only 4 days of dosing.

The lowest NOAEL seen in the above studies was 5 mg/kg/day, which is the developmental NOAEL from the rabbit developmental toxicity study (MRID 41065201). Though the NOAEL from this study would be acceptable for use as an acute RfD, HIARC notes that there was a large dose spread in this study. The mid-dose tested (and the NOAEL) in this study was 5 mg/kg/day while the next highest dose tested (the highest dose tested and the LOAEL) was 75 mg/kg/day. This dose is a full 15 times higher than the mid-dose tested. The large spread between 5 and 75 mg/kg/day raises the possibility that had intermediate doses between 5 and 75 been used then the NOAEL would have been higher.

Examination of the rat developmental toxicity studies indicates that intermediate doses in the rabbit study between 5 and 75 may not have shown any adverse effects. The NOAEL in both the rat studies are greater than 5 mg/kg/day (10 mg/kg/day for 40566302 and 25 mg/kg/day for 41065201). The effects seen in the rabbit and two rat developmental toxicity studies are similar with all three studies seeing delayed or no ossification in certain cranial bones at their respective LOAELS of 75 (rabbit), 70 (40566302) and 100 mg/kg/day (41065201). Other effects on which the developmental NOAEL were based in the rabbit study - reduced litter size and increased resorptions - were not seen either of the rat studies and are not considered to be frank malformations, or even variations. In this respect it should be noted that maternal effects were more severe at the LOAEL in the rabbit study than at the LOAELs in either of the two rat studies. The maternal LOAELs in the two rat studies were based on decreased food consumption and body, while the maternal LOAEL in the rabbit study was based on clinical signs such as none, little or soft stool, blood on the vulva, in addition to decreased food consumption and body weight.

HIARC also notes that an acute RfD based on a NOAEL of 10 mg/kg/day would be protective of the prostatitis effects seen in the open literature study at a NOAEL of 12.5 mg/kg/day.

$$\textbf{Acute RfD} = \frac{10\ \text{mg/kg}}{100} = \textbf{0.1 mg/kg}$$

Dose/endpoint for General Population including infants and children:

An appropriate end point for the general population attributable to a single exposure was not available from the oral toxicity studies including the developmental toxicity studies in rats and rabbits.

2.2 Chronic Reference Dose (RfD)

Study Selected: Six-month LH surge study § Special study

MRID No.: 44152102

Executive Summary: In a study to evaluate the effect of long-term atrazine exposure on the proestrus afternoon luteinizing hormone (LH) surge (MRID 44152102) atrazine, 97.1% a.i., was administered to 360 female Sprague Dawley rats in the diet. Dose levels were 0 (negative control), 25, 50, and 400 ppm (0, 1.80, 3.65, 29.44 mg/kg/day) for 26 weeks (approximately six months).

Body weight, body weight gain and food consumption were significantly ($p \leq 0.05$) decreased in HDT animals compared to controls (body weight decreased 8.5% at the end of the study and food consumption decreased 3.75% for the entire study). The percentage of days in estrus were significantly increased ($p \leq 0.01$) during the 21-22 and 25-26 week time periods at the HDT. Percent days in estrus were also increased during the 21-22 and 25-26 week time periods at the MDT, but the increase was only significant ($p \leq 0.05$) for the 21-22 week time period. The proestrus afternoon LH surge was severely attenuated at the HDT (LH levels at most sampling time points were actually decreased compared to baseline) and less so at the MDT (maximum increase over baseline was 157% compared to maximum increase over baseline in controls of 273%). Pituitary weight were increase at the HDT (absolute weight increased 22% and weight relative to body weight was increased 28%). Pituitary weights at the other two doses were not affected. There was a slight increase at the HDT of animals displaying enlarged pituitaries (0% in controls compared to 3.4% at 29.44 mg/kg/day) and thickened mammary glands (0% in controls compared to 6.7% at 29.44 mg/kg/day). There were no other gross necropsy findings in the HDT that could be attributed to compound exposure and there were no compound-related gross pathology findings at the MDT or LDT. Selected tissues were saved for histopathology but those results have yet to be reported.
There were no compound related effects in mortality or clinical signs. The proestrus afternoon prolactin surge was not affected by compound exposure at any dose. The LDT had no effects on the estrous cycle, LH or prolactin surges.

The LOAEL is 3.65 mg/kg/day, based on estrous cycle alterations and LH surge attenuation. The NOAEL is 1.8 mg/kg/day.

This special study in the rat is **Acceptable-nonguideline**. this study does not satisfy any guideline requirements and was not submitted with the intention of satisfying a guideline requirement.

Dose and Endpoint for Establishing RfD: 1.8 mg/kg/day based on estrous cycle alterations and LH surge attenuation at 3.65 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100

Comments about Study/Endpoint/Uncertainty Factor: The attenuation of the LH surge is deemed to be a critical event in the mode of action of atrazine-associated carcinogenesis. This six-month study is considered adequate for use in selecting a chronic endpoint without an additional safety factor being added to account for study duration of less than 12 months. An LH surge study of longer duration may be of limited value given that the attenuation of LH surge occurs in normally aging Sprague-Dawley rats.

Though this endpoint (LH surge attenuation and estrous cycle disruption) is applicable only to females 13-50, HIARC notes that this dose is the lowest NOAEL available in the toxicology database and therefore would be protective of other adverse effects, including those occurring in males, infants and children. Therefore, a separate endpoint is not needed for this population (i.e., males, infants and children).

This dose and endpoint replaces the previous dose and endpoint of 3.5 mg/kg/day based on decreased body weight gain and food consumption in a two-year rat bioassay selected by HIARC in 1998. The dose of 1.8 mg/kg/day for use in risk assessment would be protective of effects that occur at the higher dose of 3.5 mg/kg/day as well as protective of effects such as LH surge attenuation and estrous cycle alterations, and any effects that may be associated with alteration of these parameters.

$$\textbf{Chronic RfD} = \frac{1.8 \text{ mg/kg/day}}{100} = \textbf{0.018 mg/kg/day}$$

2.3 Occupational/Residential Exposure

2.3.1 Short-Term (1-7 days) Incidental Oral Exposure

Study Selected: Developmental toxicity in rats § 83-3a

MRID No.: 40566302

Executive Summary: See Study #1 above under "Acute RfD"

Dose and Endpoint for Risk Assessment: 10 mg/kg/day based on statistically significant decrease in body weight gains at 70 mg/kg/day (LOAEL).

Comments about Study/Endpoint: Decreases in body weight gain was seen during the first 5 days of dosing. The endpoint is indicative of general or systemic toxicity and is thus appropriate for the population (infants and children) of concern.

2.3.2 Intermediate-Term (7 Days to Several Months) Incidental Oral Exposure

Study Selected: Developmental toxicity in rats §83-3a

MRID No.: 40566302

Executive Summary: Same as for short term-incidental oral

Dose and Endpoint for Risk Assessment: 10 mg/kg/day based on statistically significant decrease in bodyweight gain at 70 mg/kg/day (LOAEL).

Comments about Study/Endpoint: Decreases in body weight gain was seen during the first 5 days of dosing. The endpoint is indicative of general or systemic toxicity and is thus appropriate for the population (infants and children) of concern.

2.3.3 **Dermal Absorption**

Dermal Absorption Factor: The HIARC considered a rat (MRID 43314302) and human dermal penetration study (MRID 44152144) in determining the appropriate dermal absorption factor. A comparison of the two studies reveals a similar dose used in each study. The rat study had dose of 0.1 mg/kg left on the skin for 10 hours with measurement of the percent absorbed at 82 hours following the start of exposure (10/82). The human study had a similar dose of 0.067 mg/kg/ left on the skin for 10 hours with measurement 168 hours following the start of exposure (10/168).

The dermal penetration seen at 0.1 mg/kg with 10/82 hours was 13.32%. Were dermal penetration between the rat and human similar then the human percent absorbed at 0.067 mg/kg with 10/168 hours would be expected to somewhat greater since, in the human study, the dose is lower and the time before measurement is longer (both factors would be expected to increase the percent absorbed). The percent absorbed in the human study is lower (less than half) the percent absorbed in the rat study though. Higher absorption in the rat compared to the human is not uncommon as the stratum corneum is known to absorb many compounds and serve as a sink from which compound steadily diffuses across the epithelium into the dermis. Rat stratum corneum is much thicker than human stratum corneum resulting in this sink being a much greater factor to the rat than to the human. Thus, rat dermal absorption frequently is much greater than human dermal absorption.

Comparison of the penetration achieved following these two doses indicates that the absorption factor seen at this dose in the human study (6%) is an appropriate value to use for risk assessment. Measurement of percent absorbed was not conducted until 168 hours following exposure in the human study. This is ample time to allow any atrazine associated with unexfoliated skin to be absorbed. The higher absorption seen in a rat study with a similar dose is what would be expected and indicates that the 6% value seen in the human study is a reasonably accurate estimate of human dermal absorption at this dose.

The committee recommended a dermal absorption factor of 6% (rounded up from 5.6%). This factor is based on a human study (MRID 44152114) in which 10 human volunteers were exposed to a single topical dose of [triazine ring-U-^{14}C]atrazine (94.3-96.3% a.i., 98.0-98.4% radiochemical purity) at 6.7 (4 volunteers) or 79 µg/cm^2 (6 volunteers) for 24 hours; equivalent to 0.1667 and 1.9751 mg of [14C] atrazine for the low and high doses, respectively. After 24 hours the atrazine was removed and determination of percent absorbed occurred was determined 168 hours (7 days) after the commencement of exposure. The maximum percent absorbed in this study was 5.6% of the dose in the lower dose group. Because the maximum percent absorbed is being used and because an ample amount of time (168 hours) was allowed for absorption to occur, 6% is deemed to be a protective estimate of dermal exposure.

Because both rat and human dermal absorption studies are available, a "Rat:Human Dermal Penetration Factor" can be calculated. As noted above, humans would be expected to have lower skin permeability of many compounds. The available data indicates that skin permeability of atrazine is indeed lower in humans than in rats. To account for this species difference, dermal NOAELs may be multiplied by a rat:human dermal penetration factor. The rat:human dermal penetration factor is calculated by dividing the dermal absorption in the rat by the dermal absorption in the human. In this case the dermal absorption in the rat is taken to be 22% (the 21.6% from the 0.01 10/82 hours dose in the above described rat dermal penetration study [MRID 43314302] rounded up to 22%). This value is selected because it represents the highest dermal absorption value seen following a 10 hour exposure (approximating a tyical workday) in the rat study. The value selected for the denominator for the ratio (the human portion) was 6%. This was the highest percent absorbed in this study (MRID 44152144).

$$\text{Rat:Human Dermal Penetration Factor} = \frac{22}{6} = \mathbf{3.6}$$

This factor is multiplied by the NOAEL for exposure scenarios in which endpoints from a dermal study are used. Exposure scenarios whose endpoints are derived from oral studies will use a 6% dermal absorption factor.

2.3.4 Short-Term Dermal (1-7 days) Exposure

Study Selected: 21-day dermal toxicity in the rat §82-2

MRID No.: 42089902

Executive Summary:

Atrazine technical (97.6%) was administered dermally to 30 New Zealand White rabbits for 6 hours/day for 25 days. Dose levels were 0, 10, 100 or 1000 mg/kg/day. (5 rabbits/sex/dose).
The increased absolute and relative spleen weights in high-dose animals were not accompanied by histological findings; however, statistically significant reductions in red blood cell counts and hematocrit levels were noted in high dose females. Further findings included statistically significant ($p<0.01$) reductions in total protein and chloride in males and significantly increased cholesterol and triglyceride levels in females.

Dermal application of the test material resulted in minimal to moderate acanthosis, hyperkeratosis, and focal subacute inflammation of treated skin in high-dose females. Dermal irritation included limited to slight (grade 1) erythema and scaling in one high dose female at days 17 - 25. erythema (grade 1) was observed in one high dose male at day 18.

The study authors reported a NOAEL of 10 mg/kg/day and a LOAEL of 100 mg/kg/day, based on slight transient reductions in mean percent body weight gain in mid-dose females at days 7 and 14. Because the reductions in female body weight gain at 100 mg/kg/day were slight, not statistically significant, transient, and without significant reductions in food consumption and absolute body weight, the reviewers assessed that the changes were of equivocal biological importance.
Thus, the NOAEL for systemic toxicity is 100 mg/kg/day. The LOAEL is 1000 mg/kg/day based on statistically significant reductions in food consumption, mean body weight, and percent weight gain in both sexes, statistically significantly increased absolute and relative spleen weights in both sexes, and slight changes in excretion (i.e. few and/or mucoid feces). This study is classified **Acceptable- Guideline.** This study satisfies the Guideline series 82-2 requirements for a 21-day dermal toxicity study in the rabbit.

Rat:Human Dermal Penetration Factor: 3.6.

Dose and Endpoint for Risk Assessment: **360 mg/kg/day.**
This value is derived by multipliying the study NOAEL of 100 mg/kg/day (based on reduced food consumption, mean body weight, body weight gain, increased spleen weights at the LOAEL of 1000 mg/kg/day) by the dermal penetration factor of 3.6.

Comments about Study/Endpoint: This study is appropriate because the duration and route of exposure (21-day, dermal) match the duration and route of exposure (up to one week, dermal) in the short-term dermal risk assessment.

2.3.5 Intermediate-Term Dermal (7 Days to Several Months) Exposure

Study Selected: Six-month LH surge study § Special study

MRID No.: 44152102

Executive Summary: See above under "Chronic RfD"

Dose/Endpoint for Risk Assessment: 1.8 mg/kg/day based on estrous cycle alterations and LH surge attenuation at 3.65 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The endpoint of concern was seen after 6 months of exposure and is appropriate for this exposure period of concern. The 21-day dermal study was not selected since estrous cycle evalutions and LH measurements (both of which have been shown to be very sensitive endpoints following atrazine exposure) were not performed in this study. Since an oral NOAEL was selected, the 6% dermal absorption factor should be used in route-to-route extraploation.

2.3.6 Long-Term Dermal (Several Months to Life-Time) Exposure

Study Selected: Six-month LH surge study § Special study

MRID No.: 44152102

Executive Summary: See above under "Chonic RfD"

Dose/Endpoint for Risk Assessment: 1.8 mg/kg/day based on estrous cycle alterations and LH surge attenuation at 3.65 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This study was also used to derive the Chronic RfD. Since an oral NOAEL was selected, the 6% dermal absorption factor should be used in route-to-route extraploation.

2.3.7 Inhalation Exposure (All Durations)

With the exception of an acute inhalation study, no inhalation studies are available for evaluation. Therefore the HIARC selected the oral NOAELs for inhalation risk assessments. Since an oral dose is used, risk assessment should follow the route-to-route extrapolation as below:

Step I. The inhalation exposure component (*i.e* µg a.i./day) using 100% absorption rate (default value) and application rate should be converted to an equivalent oral dose (mg/kg/day).

Step II. The dermal exposure component (mg/kg/day) using a 6% dermal absorption rate and application rate should be converted to an equivalent oral dose. This dose should then be combined with the oral equivalent dose in Step I.

Step III. The combined oral equivalent dose from Step II should then be compared to the oral NOAELs to calculate MOEs. The NOAELs are as follows:

For intermediate term:	1.8 mg/kg/day
For chronic exposures:	1.8 mg/kg/day

NOTE: Route-specific MOE should be used for short-term exposure. Inhalation exposure can not be combined with dermal due to the lack of a common toxicity endpoint via the dermal (decreased body weight gain, and food consumption) and inhalation (attenation of LH surge routes).

2.3.8 Margins of Exposure for Occupational/Residential Risk Assessments

The level of concern for dermal and inhaltion occupational exposure is an MOE of 100.

The MOEs for residential exposure risk will be determined by the FQPA SF committee.

2.3.9 Reccommendation for Aggregate Exposure Risk Assesments

For acute aggregate exposure, the high end value from food plus water should be combined and compared to the RfD.

For short-term aggregate exposure, the oral, dermal and inhalation exposures can not be combined due to the differences in toxicity endpoints via these routes; oral - developmental; dermal - decreased body weight gain, food consumption and spleen weights; and inhalation - attenuation of the LH surge.

For intermediate and long-term aggregate exposures, the three routes can be combined because the dermal and inhalation exposures are corrected to oral equivalent doses and are based on the same endpoint as the RfD

3 CLASSIFICATION OF CARCINOGENIC POTENTIAL

3.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID Nos.: 00158930; 42085001; 42204401; 44544701

Discussion of Tumor Data: Several chronic bioassays in the Sprague-Dawley rat (MRIDs shown above) have demonstrated that chronic atrazine exposure is associated with an increased incidence and/or an earlier onset of mammary tumors. There is also limited evidence (primarily from a single chronic bioassay) that atrazine exposure may be associated with an earlier onset of pituitary adenomas.

Adequacy of the Dose Levels Tested: The dose levels tested were adequate to determine the carcinogenic potential of atrazine.

3.2 Carcinogenicity Study in Mice

MRID No. : 40431302

Executive Summary: In an oncogenicity study (MRID 40431302), atrazine, (purity not given) was administered to CD-1 mice, 59-60/sex/dose, in the diet at dose levels of 0, 10, 300, 1500 and 3000 ppm (male/female mean daily dose 0/0, 1.4/1.6, 38.4/47.9, 194.0/246.9, 385.7/482.7 mg/kg/day) for 91 weeks. Female mice in the 300, 1500 and 3000 ppm groups received a daily atrazine dose about 25% higher than their counterpart males. No dose-related increases in neoplasms were observed. The dose response curve seemed adequate since toxic effects, such as a decrease in mean body weight of both sexes and an increase in cardiac thrombi in the females, are seen at both 1500 and 3000 ppm, while no dose-related toxic effects are seen at 10 and 300 ppm. In addition to the toxic effects just mentioned, the 3000 ppm animals of both sexes also displayed decreases in food consumption and decreases in RBC, hematocrit, and hemoglobin concentration. Female mice, but not males, at 3000 ppm showed decreased mean group brain and kidney weights and decreased percentages of neutrophils and lymphocytes. There was also an increase in mortality ($p < 0.05$) in 3000 ppm females, but not males, with only 25% of the females surviving *vs* 39-43% of the females surviving in the other female dose groups. The cardiac thrombi found at both 1500 and 3000 ppm may have contributed to unscheduled female deaths during the course of the study. The incidence of unscheduled death in mice with cardiac thrombi is statistically significantly different from the incidence of unscheduled death in mice from control groups. The occurrence of cardiac thrombi must be considered a severe effect.

The LOEL is 1500 ppm (222.0 mg/kg/day), based on decreased body weight gain in both sexes and increased cardiac thrombi in the females. The NOEL is 300 ppm (43 mg/kg/day).

At the doses tested, there was not a treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate due to the occurrence of decreased body weight gain and cardiac thrombi.

This carcinogenicity study in the mouse is **Acceptable-Guideline,** and does satisfy the guideline requirement for a carcinogenicity study in the mouse.

Discussion of Tumor Data: There was no evidence of carcinogenicity in CD-1 mice following exposure to atrazine for 91 weeks.

Adequacy of the Dose Levels Tested: Dose levels tested were adequate to determine carcinogenic potential

3.3 Classification of Carcinogenic Potential

In 1987, the HED Cancer Peer Review Committee (CPRC) classified atrazine as a Group "C" carcinogen (possible human carcinogen) and recommended a linear low dose approach (Q_1*) for human risk characterization. The CPRC met again on June 6, 1988 and September 29, 1988 and reaffirmed the Group C classification.

In 1997, the HED Cancer Assessment Review Committee (CARC) evaluated the carcinogenic potential of atrazine and discussed mode of action data submitted by the Registrant in regards to the ability of atrazine to produce mammary tumors in Sprague-Dawley rats. A document from that CARC meeting has been prepared, was evaluated by CARC in the Fall of 1999, and was presented at the Science Advisory Panel (SAP) in June 27, 28 and 29th, 2000. This document may be accessed at *http://www.epa.gov/oscpmont/sap/.* A final Cancer Peer Review Document will not be ready until after receipt of the written SAP evaluation and final approval by CARC.

4 MUTAGENICITY

Atrazine has not been found to be mutagneic in bacteria and does not cause unscheduled DNA synthesis in primary rat hepatocytes. Atrazine did not induce clastogenicity in the mouse micronucleus assay. Atrazine was negative in a mouse Dominant-Lethal Assay.

An extensive review of more than 50 mutagenicty studies using atrazine, and atrazine metabolites is included as a chapter in the most recent cancer peer review document. This document can be accessed at the internet address shown in the previous paragraph.

(I) Gene Mutation

In a reverse gene mutation assay in bacteria (MRID 40246601), strains TA 98, 100, 1535 and 1537 of S. typhimurium were exposed to atrazine (98.2% a.i.), in dimethylsufoxide, at concentrations of 0, 20, 78, 313, 1250, and 5000 μg/plate. Tests were conducted in the presence and absence of mammalian metabolic activation S9 fraction of Tif:RAIf rats treated with Aroclor 1254. Atrazine was tested up to the limit concentration, 5000 μg/plate. The positive controls did induce the appropriate responses in the corresponding strains. **There was no evidence of induced mutant colonies over background.**

This study is classified as **Acceptable-Guideline.** It does satisfy the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

(ii) Structural Chromosomal Aberrations

A mouse bone marrow micronucleus test was conducted using Tif:MAGF mice (MRID 40722301). The test consisted of two parts. The first portion consisted of 24 male and 24 female mice being dosed with 2250 mg/kg atrazine (98.2% a.i.). Eight animals of each sex were then sacrificed at 16, 24 or 48 hours following treatment. The second portion of the study 24 mice, 8/sex/dose, were treated with atrazine (98.2% a.i.) at doses of 562.5, 1175, 2250 mg/kg. Bone marrow cells were harvested at 24 hours post-treatment. The vehicle in both portions of the study was carboxymethyl cellulose. Exposure in both portions of the study was accomplished by a single gastric intubation. There were no signs of cytotoxicity in bone marrow erythropoiesis seen either portion of the study. However, the high dose was clearly toxic since 7 of the 32 females which received the high dose died prematurely. Atrazine was tested at an adequate doses being that these were doses that induced death in mice. The positive control induced the appropriate response. **There was not a significant increase in the frequency of micro nucleated polychromatic erythrocytes in bone marrow after any treatment time or dose.**
This study is classified as **Acceptable-Guideline.** It does satisfy the requirement for FIFRA Test Guideline 84-2 for *in vivo* cytogenetic mutagenicity data.

(iii) Other Genetic Effects

In an unscheduled DNA synthesis assay (MRID 42547105), primary rat hepatocyte cultures were exposed to atrazine, (97.1% a.i.), in dimethyl sulfoxide at concentrations of 15, 46, 139, 417, 835, and 1670 μg/ml for 16-18 hours. Atrazine was tested up to precipitating concentrations, 139 μg/ml. The positive controls did induce the appropriate response. **There was no evidence that unscheduled DNA synthesis, as determined by nuclear silver grain counts, was induced.**

This study is classified as **Acceptable-Guideline.** It does satisfy the requirement for FIFRA Test Guideline 84-2 for other genotoxic mutagenicity data.

In a mouse dominant lethal assay (MRID 42637003), groups of 30 male Tif: MAGf (SPF) mice were treated orally by gavage with Atrazine technical (97.1% a.i., batch #SG8029BA10) at doses of 0, 500, 1000, 2000, or 2400 mg/kg body weight in a volume of 10 mL/kg. The vehicle was corn oil. Starting immediately after dosing, each male was mated with 2 untreated females per interval for days 1-4, days 4-8, and days 8-12. Each male was then mated with 2 untreated females per week for weeks three through eight.

Atrazine technical was tested at an adequate dose. There were signs of toxicity after dosing as evidenced by piloerectiőn and decreased locomotor activity. The females were sacrificed on gestation day 13-15 and the uteri examined for the number of alive, early, and late dead embryos and resorptions. Cyclophosphamide served as the positive control. There was no significant difference between the control group and treated groups with respect to post-implantation mortality of embryos. Under the conditions of this study atrazine technical did not induce dominant lethal mutations in male mice at doses as high as 2400 mg/kg.

This study is classified as **Acceptable-Guideline.** It does satisfy the requirement for FIFRA Test guideline 84-2 for rodent dominant lethal data

5 FQPA CONSIDERATIONS

5.1 Adequacy of the Data Base

The toxicology database for atrazine was considered adequate by the HIARC for consideration of factors under FQPA.

5.2 Neurotoxicity

Acute and subchronic neurotoxicity studies are not available for atrazine and are not required as atrazine is neither a carbamate nor an organophosphate compound. Indications of possible neurotoxicity were not evident in the submitted guideline studies. Special studies submitted by the registrant (MRIDs 44152102 and 43934406) and published in the open literature (Cooper, *et al.* 2000. Atrazine disrupts the hypothalamic control of pituitary- ovarian function. Tox. Sci. 53: 297-307 [MRID 45166902]) provide evidence of atrazine-associated neurotoxicity. The neurotoxicity seen in these studies was a central nervous system (CNS) toxicity (specifically, neuroendocrine alterations at the hypothalamus).

5.3 Developmental Toxicity

One rabbit and two rat developmental studies are available for evaluation. The executive summaries for these three studies are shown above under "Acute RfD: Study #'s 1, 2, and 3".

5.4 Reproductive Toxicity

A two-generation study is available for evaluation.

MRID: 40431303 Guideline no.: §83-4

In a 2-generation reproduction study (MRID 40431303) atrazine, (purity not specified but said to be technical grade) was administered to 240 Charles River (CRCD, VAF/PLUS) rats 30/sex/dose in the diet at dose levels of 0, 10, 50, and 500 ppm. There was very little variation in test article consumption between generations; the F_0 and F_1 males had similar test article consumption during the 70-day premating period as did the F_0 and F_1 females. The average values for the two generations are 0, 0.75, 3.78, 39.0 mg/kg/day for males and 0, 0.86, 3.70, 42.8 mg/kg/day for females. Test article consumption for the F_0 and F_1 generation females during their gestation period did not vary greatly between generation. Mean compound consumption for both generations were 0, 0.66, 3.33 and 35.43 mg/kg/day.

Parental body weights, body weight gain, and food consumption were statistically significantly reduced at the 500 ppm dose (HDT) in both sexes and both generations throughout the study. Compared to controls, body weights for F_0 HDT males and females at 70 days into the study were decreased by 12% and 15%, respectively while F_1 body weight for the same time period was decreased by 15% and 13% for males and females, respectively. The only other parental effect which may have been treatment related was a slight, but statistically significant, increase in relative testes weight which occurred in both generations of the HDT. **The parental LOAEL is 500 ppm (39 mg/kg/day in males, 42.8 mg/kg/day in females) based on decreased body weights, body weight gains and food consumption. The NOAEL is 50 ppm (3.78 mg/kg/day in males, 3.7 mg/kg/day in females).**

There did not appear to be any offspring toxicity in females from compound exposure. Male offspring pup body weight was significantly decreased ($p<0.05$) in males at day 21 in both generations. **The offspring toxicity LOAEL is 39 mg/kg/day based on decreased body weights in both generations of males at PND 21. The offspring toxicity NOAEL is 3.78 mg/kg/day.**

This study is classified **Acceptable-Guideline** and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800, §83-4) in the rat.

5.5 Additional Information from Literature Sources

An open literature publication (MRID 45166902, discussed above under "Acute RfD, Study #4") has demonstrated that exposure of a lactating dam to atrazine during the days shortly after parturition may result in increased incidence and severity of prostate inflammation in male offspring. Other work from the NHEERL laboratories at EPA has

indicated that atrazine exposure to immature rats may delay the onset of puberty (Stoker *et al.*, 2000. The Effects of Atrazine on Puberty and Thyroid Function in the Male Wistar Rat: An Evaluation in the Male Pubertal Protocol. Submitted.; Laws, *et al.* 2000. The effects of atrazine on puberty in female Wistar rats: An evaluation in the protocol for the assessment of pubertal development and thyroid function. Submitted).
The mode of action for these two effects (prostate inflammation and delayed puberty) is believed to be similar to the mode of action described for atrazine-associated cancer and involves the CNS neuroendocrine alterations described in the HED CPRC document (specifically, neuroendocrine alterations at the hypothalamus).

5.6 Determination of Susceptibility

HIARC concluded that an increased quantitative or qualitative susceptibility was not seen in the developmental or two generation reproduction studies. However, the studies mentioned above under section 5.5 provide evidence of increased susceptibility.

Recommendation for a Developmental Neurotoxicity Study

5.6.1 Evidence that suggest requiring a Developmental Neurotoxicity study:

Special studies and an open literature study mentioned above under section 5.2 indicate a neuroendocrine toxicity in the CNS of rats following atrazine exposure.

5.6.2 Evidence that **do not** support a need for a Developmental Neurotoxicity study:

The avaible studies have not indicated any disruption of thyroid function following atrazine exposure. Evidence of neurotoxicity was seen following atrazine exposure. Evidence of neurotoxicity following exposure to a compound is frequently seen as evidence that supports the need for a Developmental Neurotoxicity study (DNT). However, numerous studies have been conducted which have described and defined this atrazine-associated neurotoxicity. The neurotoxicity seen following atrazine exposure is CNS neuroendocrine toxicity. This CNS neuroendocrine toxicity has been well-defined through a series of registrant submitted studies and studies performed by EPA scientists at NHEERL. Many of the parameters measured in the DNT are behavioral in nature, or are effects on the peripheral nervous system (PNS). Tests conducted in a DNT are those such as motor activity tests, auditory startle tests, and learning and memory tests. The neurotoxicity associated with atrazine exposure has been well-defined, and does not involve these sorts of behavioral alterations or PNS alterations.
Certain measures performed in the DNT (such as determination of onset of developmental landmarks and neuropathology) would be useful in examining this CNS neuroendocrine toxicity. However, special studies designed specifically to examine these endpoints would be much more useful in this regard as protocols could be designed around the desired endpoints.

Therefore, HIARC determined that a DNT is not required. Instead, the HIARC reccommended that studies examining the specific CNS alterations described in the studies conducted by the registrant and the Agency's NHEERL labs, be performed.

6 HAZARD CHARACTERIZATION

Atrazine is herbicide most commonly used on corn and sorghum to control broadleaf grasses. The toxicological database for atrazine is complete, and acceptable. Atrazine has low acute toxicity and is not a dermal sensitizer.

Guideline subchronic, dermal, chronic, developmental, and reproduction studies did not indicate any particular target organ for toxicity though several studies have indicated that atrazine is associated with mammary and pituitary tumors in females of the Sprague-Dawley strain of rat. Special studies designed to elucidate a mode of action of for this carcinogenic effect have demonstrated that the hypothalamus appears to be a target organ. Neuroendocrine alterations of the hypothalamic-pituitary axis of rodents following atrazine exposure have been well-described both in studies submitted by the registrant and in studies conducted by EPA labs. These alterations are seen in chronic studies at low doses and in shorter term studies at higher doses.

The mutagenicity database for atrazine is extensive and has indicated that atrazine is not mutagenic. Special studies have also been conducted to determine the estrogenic potential of atrazine and these studies have demonstrated that atrazine lacks direct estrogenic activity.

The Cancer Assessment Review Committee (CARC) has evaluated atrazine and a draft report from that committee has been prepared. This draft report was presented to the Agency Science Advisory Panel June 28 - 30, 2000.

7 DATA GAPS

There are no datagaps for atrazine according to the Subdivision F Guideline requirements. HIARC reccommends, *but does not require,* that special studies examining atrazine's associations with delayed puberty and prostatitis in offspring of dams exposed shortly after partution, be conducted. Should such studies be conducted, it is reccommended that study protocols be approved by HED prior to commencent of any such study.
In addition, HIARC recommends, but does not require, that special studies examining the CNS alterations following atrazine exposure, be performed.

8 ACUTE TOXICITY

Acute Toxicity of Atrazine

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	Acc 230303	LD_{50} = 1,869 mg/kg (M+F combined)	III
81-2	Acute Dermal	Acc 230303	LD_{50} > 2,000 mg/kg (M+F combined)	III
81-3	Acute Inhalation	430165-02	LC_{50} > 5.8 mg/L (M+F combined)	IV
81-4	Primary Eye Irritation	Acc 230303	PIS= 0.0/110	IV
81-5	Primary Skin Irritation	Acc 230303	PIS= 0.2/8.0	IV
81-6	Dermal Sensitization	001051-31	Non-sensitizing	IV
81-7	Acute Neurotoxicity	none	Not Applicable	—

9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.*

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 10 UF = 100	Delayed ossification of certain cranial bones	Developmental toxicity study in the rat
	Acute RfD = 0.1 mg/kg/day		
Chronic Dietary	NOAEL = 1.8 UF = 100	Attenuation the pre-ovulatory lutenizing hormone (LH) surge	Six-month LH surge study in the rat
		Chronic RfD = 0.018 mg/kg/day	
Incidental Oral, Short-Term	NOAEL= 10	Decreased body weight during the first five days of dosing in the dams	Developmental toxicity study in the rat
Incidental Oral, Intermediate-Term	NOAEL= 10	Same as short term	Same as short term
Dermal, Short-Term[a]	NOAEL= 360 (NOAEL from study was 100 mg/kg/day. Multiplied by the rat:human dermal pentration factor of 3.6 = 360 mg/kg/day)	reductions in food consumption, mean body weight, and percent weight gain in both sexes, statistically significantly increased absolute and relative spleen weights in both sexes, and slight changes in excretion (*i.e.* few and/or mucoid feces).	21-day dermal toxicity study
Dermal, Intermediate-Term[b]	NOAEL= 1.8	Attenuation the pre-ovulatory lutenizing hormone (LH) surge	Six-month LH surge study in the rat
Dermal, Long-Term [b]	NOAEL= 1.8	Same as intermediate term	Same as intermediate term
Inhalation, Short-Term [c]	NOAEL= 10	Delayed ossification of certain cranial bones	Developmental toxicity study in the rat
Inhalation, Intermediate-Term [c]	NOAEL= 1.8	Attenuation the pre-ovulatory lutenizing hormone (LH) surge	Six-month LH surge study in the rat
Inhalation, Long-Term [c]	NOAEL= 1.8	Same as intermediate term	Same as intermediate term

a The rat:human dermal penetration factor of 3.6 is applied to this scenario only.
b Dermal absorption rate = 6% c Convert from oral dose using an inhalation absorption rate= 100% default