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MEMORANDUM

SUBJECT: ***ATRAZINE/DACT*** - Reassessment Report of the FQPA Safety Factor Committee.

NOTE: THIS REPORT REPLACES THE PREVIOUS REPORT OF THE FQPA SAFETY FACTOR COMMITTEE DATED NOVEMBER 14, 2000 (HED DOC. NO. 014375).

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Catherine Eiden, Risk Assessor
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PC Code: 080803

The Health Effects Division (HED) FQPA Safety Factor Committee (SFC) met on March 25, 2002 to re-evaluate the hazard and exposure data for Atrazine and its chlorometabolites (represented by DACT) with regard to making a decision on the additional safety factor for the protection of infants and children. The SFC determined that there is not sufficient reliable data to assign a different safety factor than10X default factor to dietary exposure scenarios but that there is reliable data demonstrating that the safety of infants and children will be protected by use of an additional safety factor of 3X for residential exposure scenarios. This report replaces the previous report of the FQPA Safety Factor Committee dated November 14, 2000 (HED Doc. No. 014375).

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I. HAZARD ASSESSMENT

(*Correspondence:* C. Eiden to C. Christensen dated March 22, 2002)

Since the last FQPA SFC meeting (November 8, 2000), the toxicology data for Atrazine and DACT were re-evaluated by the HED Hazard Identification Assessment Review Committee (HIARC) on March 19, 2002.

1. Adequacy of the Toxicology Database

Atrazine has been evaluated for potential reproductive effects under the Subdivision F §83-4 guideline 2-generation protocol in rats and for prenatal developmental toxicity in rabbits and rats under the Subdivision F §83-3 guideline protocols. Although these studies/protocols do not include sensitive measures of endocrine disruption, which are included in the 1998 OPPTS guidelines, there are several non-guideline studies conducted with Atrazine available which do assess endocrine-related toxicity. In a study protocol designed for endocrine disruptors (pubertal assays in rats), Atrazine was positive in both sexes (delayed preputial separation and delayed vaginal opening). There is not information on Atrazine concerning exposure throughout all critical developmental periods (i.e., gestation through puberty in both sexes), in particular, early in development and therefore, Atrazine's CNS mode of action (effects on neurotransmitters/peptides) has not been fully characterized in the young.

Previously, HIARC determined that a developmental neurotoxicity study (DNT) is not required but it was suggested that special studies be conducted to further examine Atrazine's associations with delayed puberty and prostatitis in offspring of dams exposed shortly after parturition, as well as special studies to examine the CNS alterations (neuroendocrine potential of Atrazine). However, during the most recent HIARC meeting (03/19/02), it was discussed that such studies are more research-oriented, and there was no particular study protocol that could be envisioned that would address the residual concerns identified in the studies in the open literature for Atrazine.

2. Determination of Susceptibility

On March 19, 2002, the HIARC concluded that there is no increased quantitative or qualitative susceptibility in any of the guideline studies conducted with Atrazine in the rat, and there was no increased quantitative susceptibility in the rabbit prenatal developmental study. However, there is evidence of increased qualitative susceptibility in the rabbit study (increased resorptions at a dose level that resulted in decreased body-weight gain and clinical signs in the maternal animal).

There are other studies on Atrazine that do show evidence of endocrine disruption including a prostatitis study, a delayed puberty study, and data on LH surge attenuation, and estrous cycle alterations. The primary underlying events that lead to mammary and pituitary tumor formation following Atrazine exposure of Sprague-Dawley female rats involve disruption of the hypothalamic-pituitary-ovarian axis. Since aspects related to

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this axis are involved in reproductive and developmental competency, there is a concern for adverse reproductive and developmental effects in maternal animals and their offspring. Several special studies have been performed that show that treatment of pregnant rats with Atrazine can lead to reproductive and developmental effects that may be associated with endocrine alterations. Additionally, the neurotoxicity seen in the non-guideline studies with Atrazine is a central nervous system (CNS) toxicity - specifically, neurotransmitter and neuropeptide alterations at the level of the hypothalamus.

3. Degree of Concern and Residual Uncertainties

Since there is evidence of increased susceptibility of the young following exposure to Atrazine in the rabbit developmental study and in several special studies conducted to evaluate endocrine effects, HIARC performed a Degree of Concern Analysis to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual concerns after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. If residual concerns are identified, HIARC examines whether these residual concerns can be addressed by a special FQPA safety factor and, if so, the size of the factor needed. The results of the HIARC Degree of Concern analyses for Atrazine (and DACT) follow.

A. Prenatal Developmental Study with Atrazine in Rabbits

The HIARC concluded that there is low concern for the qualitative increased susceptibility (increased fetal resorptions at a dose level that resulted in decreased body-weight gain and clinical signs in the maternal animal) because: 1) the NOAELs in the study are well characterized; and 2.) the effects seen occurred at a high dose level (75 mg/kg/day).

The HIARC also concluded that there are no residual concerns for these effects considering that the Acute RfD established for Atrazine/DACT is based on a NOAEL of 10 mg/kg which is protective of the fetal effects observed in the developmental rabbit study.

B. Special Studies with Atrazine

A substantial amount of research has been conducted on the toxicologic effects of Atrazine exposure at the Reproductive Toxicology Division of EPA's National Heath and Environmental Effects Research Laboratories (NHEERL) at Research Triangle Park, N.C. This research includes studies investigating the neuroendocrine basis of the mode of action for Atrazine-associated carcinogenesis as well as studies investigating developmental and reproductive effects associated with Atrazine exposure. Much of these data have been published in the open literature and the abstracts from these publications are shown below (Section I.C.). Several of these studies indicate increased susceptibility of the young following exposure to Atrazine:

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- Stoker, T.E., Robinette, C.L., Cooper, R.L. (1999) demonstrated that Atrazine suppresses suckling-induced prolactin release and that this suppression results in lateral prostate inflammation in the offspring. The critical period for this effect is PND 1-9;
- Laws, S.C., Ferrell, J.M., Stoker, T.E., Schmid, J., and Cooper, R.L. (2000) demonstrated that Atrazine can delay the onset of puberty and alter estrous cyclicity in the female Wistar rat (NOAEL of 25 mg/kg); and
- Stoker, T.E., Laws, S.C., Guidici, D. and Cooper, R.L. (2000) concluded that Atrazine delays puberty in the male rat and its mode of action appears to be altering the secretion of steroids and subsequent effects on the development of the reproductive tract (apparently due to Atrazine's effects on the CNS).

The mode of action for these effects (prostate inflammation and delayed puberty) is believed to be similar to that described for Atrazine-associated cancer in the SD rat and involves the CNS neuroendocrine alterations at the hypothalamus (Refer to HED CARC document; TXR # 014431).

After considering the effects observed in these studies with Atrazine in the context of establishing toxicity endpoints for risk assessment, the HIARC identified the following residual concerns:

> Since the focus of the testing with Atrazine in the young rat has been limited to short periods of dosing to specific developmental periods, uncertainties are raised for susceptibility during earlier developmental periods as well as for consequences of earlier developmental exposure with longer duration of dosing throughout development. The effects of neurotransmitters/peptides (known to be critical for normal development and which could potentially translate into severe effects in children that may not be manifested until later in life) have not been fully characterized. And as the FIFRA Scientific Advisory Panel noted, there are concerns for behavioral effects in the young resulting from Atrazine's CNS mode of action and the dose level at which these effects might occur compared to reproductive/developmental effects[1].

Considering the existing data used for toxicity endpoint selection, the HIARC used the following rationale to conclude that an additional Special FQPA Safety Factor of 3X would be adequate to account for these hazard-based residual uncertainties:

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[1]SAP Report No. 2000-05; Atrazine: Hazard and Dose Response Assessment and Characterization. "Because of the rapid developmental brain changes...the influence of Atrazine on neurotransmitters in the hypothalamus and on GnRH may well have a differential, permanent effect on children. This phenomenon is the basis of the relatively new field of behavioral teratology. Atrazine could influence the migration of cells and the connectivity of the CNS. The influence of Atrazine on the hypothalamus and on GnRH may have a differential effect on children. This effect could be latent, and emerge later during the challenge of puberty, or during senescence. Behavioral alterations may be the most sensitive outcome. This possibility should be addressed...."

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The toxicology endpoints selected for risk assessment are all consistent with Atrazine's mode of toxicity using the most sensitive endpoint with the lowest NOAEL (1.8 mg/kg/day). When comparing the effects observed in adults to those observed in the young, the HIARC considered the results of the pubertal assay because the effect of concern in the young (delayed puberty) was observed in both male and female offspring exposed to Atrazine during the pubertal period (30 days for the males and 20 days for the females) and clear NOAELs were established for this endpoint in both sexes (6.25 mg/kg/day in males; 12.5 mg/kg/day in females). If the lowest offspring NOAEL from this study is protected by a factor of 3X, the extrapolated NOAEL is 2 mg/kg/day. Comparing this value to the adult NOAEL of 1.8 mg/kg/day from the 6-month LH Surge study (used to establish the Chronic RfD and for the intermediate and chronic oral, dermal, and inhalation exposure scenarios) indicates that the young are not likely to be an order of magnitude more sensitive than the adult. A 3X safety factor applied to the NOAEL from the LH Surge study will provide infants and children with an order of magnitude (10X) level of protection from the lowest offspring NOAEL. Therefore, the HIARC concluded that, given the half-log (3X) protection provided children by the more sensitive endpoint in adults and the relatively tight pattern of NOAELs for adults and children from existing studies, a half-log reduction in the default Special FQPA Safety Factor (3X) is considered to be sufficiently protective of the concerns for this CNS mode of action in the young.

HIARC also recommended that the additional Special FQPA Safety Factor of 3X would **not** be required for Acute dietary exposures (aRfD) because the open literature data demonstrate that while the neuroendocrine effects caused by Atrazine's mode of action could result from a single dose, this would only occur at very high doses (200-300 mg/kg which is significantly higher than the 10 mg/kg level used to establish the Acute RfD).

4. Summary of Open Literature Findings

Cooper, R.L., Stoker, T.E., Goldman, J.M., Parrish, M.B., Tyrey, L. (1996). Effect of Atrazine on Ovarian Function in the Rat. Reprod. Toxicol. 1996 Jul-Aug;10(4):257-64.

The effect of the chlorotriazine herbicide, Atrazine, on ovarian function was studied in Long-Evans hooded (LE-hooded) and Sprague-Dawley (SD) rats. Atrazine was administered by gavage for 21 d to females displaying regular 4-d estrous cycles. In both strains, 75 mg/kg/day disrupted the 4-d ovarian cycle; however, no distinct alteration (*i.e.*, irregular cycles but not persistent estrus or diestrus) was apparent at this dose. At 150 mg/kg/day, Atrazine induced repetitive pseudopregnancies in females of both strains. The highest dose tested (300 mg/kg/day) also induced repetitive pseudopregnancies in the SD females, while the ovaries of the LE-hooded female appeared regressed and the smear cytology was indicative of the anestrous condition. Although a NOAEL was not established, the doses employed in this experiment were in excess of those used in chronic feeding studies in which an early onset of mammary gland tumors was noted. These data demonstrate that Atrazine can disrupt ovarian function and bring about major changes in the endocrine profile of the female.

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Stoker, T.E., Robinette, C.L., Cooper, R.L. (1999) Maternal Exposure to Atrazine During Lactation Suppresses Suckling-Induced Prolactin Release and Results in Prostatitis in the Adult Offspring. Toxicol Sci 1999 Nov;52(1):68-79 MRID 45166902

The availability of prolactin to the neonatal brain is known to affect the development of the tuberoinfundibular (TIDA) neurons and, as a consequence, lead to alterations in subsequent PRL regulation. Without early lactational exposure to prolactin (derived from the dam's milk), TIDA neuronal growth is impaired and elevated prolactin levels are present in the prepubertal male. These observations, combined with the finding that alterations in prolactin secretion (*i.e.*, hyperprolactinemia) in the adult male rat have been implicated in the development of prostatitis, led us to hypothesize that early lactational exposure to agents that suppress suckling-induced prolactin release would lead to a disruption in TIDA development, altered prolactin regulation, and subsequent prostatitis in the male offspring. To test this hypothesis, suckling-induced prolactin release was measured in Wistar dams treated twice daily with the herbicide Atrazine (by gavage, on PND 1-4 at 0, 6.25, 12.5, 25, and 50 mg/kg body weight), or twice daily with the dopamine receptor agonist bromocriptine (BROM, sc, at 0.052, 0.104, 0.208, and 0.417 mg/kg); BROM is known to suppress prolactin release. Similarly, Atrazine has also been reported to suppress prolactin in adult females. Serum prolactin was measured on postnatal day [PND] 3 using a serial sampling technique and indwelling cardiac catheters. A significant rise in serum prolactin release was noted in all control females within 10 min of the initiation of suckling. Fifty-mg/kg Atrazine inhibited suckling-induced prolactin release in all females, whereas 25 and 12.5 mg/kg Atrazine inhibited this measure in some dams and had no discernible effect in others. The 6.25 mg/kg dose of Atrazine was without effect. BROM, used here as a positive control, also inhibited suckling-induced prolactin release at doses of 0.104 to 0.417 mg/kg, with no effect at 0.052 mg/kg. To examine the effect of postnatal Atrazine and BROM on the incidence and severity of inflammation 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 Atrazine-treated dams (25 and 50 mg/kg). The 12.5 mg/kg Atrazine and the two highest doses of BROM increased the incidence, but not the severity, of prostatitis. Combined treatment of ovine prolactin and 25 or 50 mg/kg Atrazine on PND 1-4 reduced the incidence of inflammation observed at 120 days, indicating that this increase in inflammation, seen after Atrazine alone, resulted from the suppression of in the dam.

To determine whether or not there is a critical period for these effects, dams were dosed with 25 and 50 mg/kg on PND 6-9 and PND 11-14. Inflammation was increased in those offspring from dams treated on PND 6-9, but this increase was not significant. Dosing on PND 11-14 was without effect. These data demonstrate that Atrazine suppresses suckling-induced prolactin release and that this suppression results in lateral prostate inflammation in the offspring. The critical period for this effect is PND 1-9.

Cooper, R.L., Stoker, T.E., Tyrey, L., Goldman, J.M., McElroy, W.K. (2000) Atrazine Disrupts the Hypothalamic Control of Pituitary-Ovarian Function. Toxicol Sci 2000 Feb;53(2):297-307. MRID 45166901

The chloro-S-triazine herbicides (*i.e.*, Atrazine, simazine, cyanazine) constitute the largest group of herbicides sold in the United States. Despite their extensive usage, relatively little is known about the possible human-health effects and mechanism(s) of action of these compounds. Previous studies in our laboratory have shown that the chlorotriazines disrupt the hormonal control of ovarian cycles. Results from these studies led us to hypothesize that these herbicides disrupt endocrine function primarily through their action on the central nervous system. To evaluate this hypothesis, we examined the estrogen-induced surges of luteinizing hormone (LH) and prolactin in ovariectomized Sprague-Dawley (SD) and Long-Evans hooded (LE) rats treated with Atrazine (50-300 mg/kg/day, by gavage) for 1, 3, or 21 days. One dose of Atrazine (300 mg/kg) suppressed the LH and prolactin surge in ovariectomized LE, but not SD female rats. Atrazine (300 mg/kg) administered to intact LE females on the day of vaginal proestrus was without effect on ovulation but did induce a pseudopregnancy in 7 of 9 females. Three daily doses of Atrazine suppressed the estrogen-induced LH and prolactin surges in ovariectomized LE females in a dose-dependent manner, but this same treatment was without effect on serum LH and prolactin in SD females. The estrogen-induced surges of both pituitary hormones were suppressed by Atrazine (75-300 mg/kg/day) in a

dose-dependent manner in females of both strains evaluated after 21 days of treatment. Three experiments were then performed to determine whether the brain, pituitary, or both organs were the target sites for the chlorotriazines. These included examination of the ability of (1) the pituitary lactotrophs to secrete prolactin, using hypophyosectomized females bearing pituitary autotransplants (ectopic pituitaries); (2) the synthetic gonadotropin-releasing hormone (GnRH) to induce LH secretion in females treated with high concentrations of Atrazine for 3 days; and (3) Atrazine (administered in vivo or in vitro) to suppress LH and prolactin secretion from pituitaries, using a flow-through perifusion procedure. In conclusion, the results of these studies demonstrate that Atrazine alters LH and prolactin serum levels in the LE and SD female rats by altering the hypothalamic control of these hormones. In this regard, the LE female appeared to be more sensitive to the hormone suppressive effects of Atrazine, as indicated by the decreases observed on treatment-day 3. These experiments support the hypothesis that the effect of Atrazine on LH and prolactin secretion is mediated via a hypothalamic site of action.

Cummings, A. M., Rhodes, B.E., and Cooper, R.L. (2000). Effect of Atrazine on Implantation and Early Pregnancy in Four Strains of Rats. *Tox. Sci.* Nov. 58: 135-143.

Atrazine is an herbicide that has been shown to have adverse reproductive effects including alterations in levels of pituitary hormones such as prolactin and luteinizing hormone (LH) in female LE rats when administered at doses of 200 mg/kg/day for 1 and 3 days. Since prolactin's action to promote progesterone secretion is essential for the initiation of pregnancy in rats, this study was designed to examine the effect of exposure to Atrazine during early pregnancy on implantation and short-term pregnancy maintenance. Rats were divided into two groups representing periods of dosing with AtrazineTR prior to the diurnal or nocturnal surges of prl. Within each group, four groups consisting of four strains of rats (Holtzman, HLZ; Sprague Dawley, SD; Long Evans, LE; Fisher 344, F344) were each further subdivided into four Atrazine dosages. Rats were dosed by gavage with 0, 50, 100, or 200 mg/kg/day Atrazine on days 1-8 of pregnancy (day 0 = sperm +). All animals were necropsied on day 8 or 9 of pregnancy. The 200 mg/kg dose of Atrazine reduced body weight gain in all but one group. Two groups of animals dosed at 100 and 200 mg/kg/day in the nocturnal dosing period showed an increase in percent preimplantation loss, and both of these were F344 rats. Holtzman rats were the only strain to show a significant level of postimplantation loss and a decrease in serum progesterone at 200 mg/kg/day both following diurnal and nocturnal dosing. Doses of 100 mg/kg/day also produced postimplantation loss following diurnal and nocturnal dosing, but progesterone levels were only decreased after nocturnal dosing. Alterations in serum LH were seen in several groups. Serum estradiol was significantly increased only in Sprague Dawley rats dosed at the diurnal interval with 200 mg/kg Atrazine. We conclude that F344 rats are most susceptible to preimplantation effects of ATR and that HLZ rats appear most sensitive to the postimplantation effects of the chemical. LE and SD rats were least sensitive to effects of Atrazine during very early pregnancy.

Narotsky M. G., Best, D.S., Guidici, D. L., and Cooper, R.L. (2000). Strain Comparisons of Atrazine-Induced Pregnancy Loss in the Rat. *Repro Toxicol.* 15, 61-69.

Atrazine was administered by gavage, in 1% methylcellulose, to F344 Sprague-Dawley (SD), and Long Evans (LE) rats at 0, 25, 50, 100, or 200 mg/kg/d on gestation days 6 through 10. The dams were allowed to deliver and litters were examined postnatally. The F344 strain was the most sensitive to Atrazine's effects on pregnancy, showing full-litter resorption at ≥50 mg/kg. In surviving F344 litters, prenatal loss was increased at 200 mg/kg. In SD and LE rats, full-litter resorption occurred only at 200 mg/kg. Delayed parturition was seen at ≥100 mg/kg in F344 and SD rats. Regarding maternal toxicity, the SD dams were the most sensitive, with weight loss at ≥25 mg/kg. When 200 mg/kg was administered to F344 rats on days 11 through 15 (after the LH-dependent period of pregnancy), no full-litter resorption was seen. These findings suggest that Atrazine-induced full-litter resorption is maternally mediated, and consistent with loss of LH support of the corpora lutea.

Laws, S.C., Ferrell, J.M., Stoker, T.E., Schmid, J., and Cooper, R.L. (2000). The Effect of Atrazine on Puberty in Female Wistar Rats: An Evaluation in the Protocol for the Assessment of Pubuertal Development and Thyroid Function. *Tox. Sci.* 58 366-376.

The effects of Atrazine , a chlorotriazine herbicide, on the onset of puberty were evaluated in Wistar rats. Female rats were dosed by oral gavage from postnatal day (PND) 22 through PND 41 with 0, 12.5, 25, 50, 100 or 200 mg Atrazine /kg. Vaginal opening was significantly delayed 3.4, 4.5 or greater than 6.8 days by 50, 100 and 200 mg/kg,

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respectively. Vaginal opening did not occur in 4 of 15 females in the 200 mg/kg group by the time of necropsy (PND 41). Body weight at necropsy was reduced in the 200 mg/kg group by 11.6%, but was not different from the control (0) in the 50 and 100 mg/kg groups. To examine the influence of reduced body weight on pubertal development, a group of pair-fed controls was included whose daily food intake was dependent upon the amount consumed by their counterpart in the 200 mg/kg group. Although necropsy body weight was reduced to the same extent as the Atrazine females, vaginal opening in the pair-fed controls was not significantly delayed. Adrenal, kidney, pituitary, ovary and uterine weights were reduced by 200 mg/kg Atrazine. Serum T3, T4 and TSH were unaltered by Atrazine which were consistent with no histopathologic/morphologic changes in the thyroid. Estrous cyclicity was monitored in a second group of females from vaginal opening - PND 149. The number of females displaying regular 4 or 5-day estrous cycles during the first 15-day interval after vaginal opening, was lower in the 100 and 200 mg/kg Atrazine and pair-fed controls. Irregular cycles were characterized by extended periods of diestrus. By the end of the second 15-day interval (PND 57-71), no effects on estrous cyclicity were observed. These data show that Atrazine can delay the onset of puberty and alter estrous cyclicity in the female Wistar rat (NOAEL of 25 mg/kg). Reduced food consumption and body weight did not account for the delay in vaginal opening because this effect was not observed in the pair-fed controls. In addition, the effect on estrous cyclicity was observed in the 100 mg/kg Atrazine group where no significant reduction in body weight was observed.

Stoker, T.E., Laws, S.C., Guidici, D. and Cooper, R.L. (2000) The Effect of Atrazine on Puberty in Male Wistar Rats: An Evaluation in the Protocol for the Assessment of Pubertal Development and Thyroid Function. *Toxicol. Sci.* Nov. 58: 50-59.

Since Atrazine, a chlorotriazine herbicide, has been shown previously to alter the secretion of luteinizing hormone (LH) and prolactin through a direct effect on the central nervous system (CNS), we hypothesized that exposure to Atrazine in the EDSTAC male pubertal protocol (juvenile to peripubertal) would alter the development of the male rat reproductive system. We dosed intact male Wistar rats from postnatal day (PND) 23 to 53 and examined several reproductive endpoints. Atrazine (0, 12.5, 25, 50, 100, 150 or 200 mg/kg) was administered by gavage and an additional pair-fed group was added to compare the effects of any decreased food consumption in the high dose group. Preputial separation was significantly delayed in the 12.5, 50, 100, 150 and 200 mg/kg Atrazine dose groups. Preputial separation was also delayed in the pair-fed group, although significantly less than in the high dose Atrazine group. The males were killed on PND 53 or 54 and pituitary, thyroid, testes, epididymides, seminal vesicles, ventral and lateral prostates were removed. Atrazine (50 to 200 mg/kg) treatment resulted in a significant reduction in ventral prostate weights, as did the pair-fed group. Testes weights were unaffected by Atrazine treatment. Seminal vesicle and epididymal weights were decreased in the high dose Atrazine group and the control pair-fed group. However, the difference in epididymal weights was no longer significantly different when body weight was entered as a covariable. Intratesticular testosterone was significantly decreased in the high dose Atrazine group on PND 45, but apparent decreases in serum testosterone were not statistically significantly on PND 53, There was a trend for a decrease in luteinizing hormone (LH) as the dose of Atrazine increased, however, dose group mean LH were not different from controls. Due to the variability of serum prolactin concentrations on PND 53, no significant difference was identified. Although prolactin is involved in the maintenance of LH receptors prior to puberty, we observed no difference in LH receptor number at PND 45 or 53. Serum estrone and estradiol showed dose-related increases that were significant only in the 200 mg/kg Atrazine group. No differences were observed in thyroid stimulating hormone (TSH) and thyroxine (T4) between the Atrazine groups and the control, however tri-iodothyronine (T3) was elevated in the high dose Atrazine group. No differences in hormone levels were observed in the pair-fed animals. These results indicate that Atrazine delays puberty in the male rat and its mode of action appears to be altering the secretion of steroids and subsequent effects on the development of the reproductive tract, which appear to be due to Atrazine's effects on the CNS. Thus, Atrazine tested positive in the pubertal male screen that EDSTAC is considering as an optional screen for endocrine disruptors.

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II. EXPOSURE ASSESSMENT

1. Dietary (Food) Exposure Considerations
(*Correspondence:* C. Eiden to C. Christensen dated March 22, 2002)

Although there are some post-emergence uses, the triazines in general are primarily used in early spring preplant and pre-emergence soil applications. Uses for Atrazine exist on corn, sorghum, sugarcane and wheat, guava, and macadamia nuts. Corn is treated with Atrazine preplant, pre-emergence and post-emergence (before corn is 12 inches tall). About 70% of corn is treated pre-plant or pre-emergence and about 30% is treated post-emergence. Average treatment rates are 1 - 1.5 lbs ai/A with a maximum treatment rate of 2.5 lbs ai/A. Sorghum use is similar, at an average 1.2 lbs ai/A/year and a maximum use rate of 1.8 lbs ai/A. About 75% of the use on sorghum is pre-emergence and 25% is post-emergence. Atrazine is used both pre- and post-emergent on sugarcane at an average 4 lbs ai/A/year. On wheat, Atrazine can be applied to fallow fields up to 1 lb ai/A/year. Atrazine is used on macadamia nuts at a maximum 2 - 4 lbs/year as needed, and on guava at a maximum 8 lbs ai/A/year. No Codex MRL's have been published for Atrazine, nor are any triazines under review for an MRL at this time.

Atrazine is 6-chloro-N^2-isopropyl, N^4-ethyl, 1,3,5 triazine-2,4-diamine. In a generalized scheme of metabolism the chloro-atom can be replaced either by a hydroxy- group or by a glutathione conjugate. This leads to three families of metabolites: the chloro metabolites, the hydroxy metabolites, and the glutathione metabolites. Within each family, three additional metabolites can arise by removal of either one or both of the N-alkyl moieties. Other metabolites can also arise within the glutathione family of metabolites by metabolic changes to the glutathione conjugate.

Residues of Atrazine that are soil applied and are absorbed through the root system are systemic, and are translocated throughout the plant. Therefore, residues cannot be removed by simple washing or peeling. Foliar applied residues are apparently not translocated to other parts of the plant but do penetrate into the local tissues and also cannot be removed by simple washing or peeling. All of the major modes of metabolism described above have been identified in plants - replacement of the chloro-atom with a hydroxy- group (hydrolytic dehalogenation), glutathione conjugation, and removal of either one or both of the N-alkyl groups (dealkylation). All routes leave the central triazine ring intact and, since these modes exist in competition, all three families of metabolites (chloro-, hydroxy-, and glutathione conjugate-) can exist in combination with each of the N-dealkylated forms. Metabolism by hydrolytic-dehalogenation dominates for residues absorbed through the roots while metabolism by glutathione conjugation dominates for foliarly applied residues.

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Monitoring data is available for Atrazine, parent compound only , for many foods. The Pesticide Data Program (PDP), Food and Drug Administration (FDA), and Food Safety and Inspection Service (FSIS) have all monitored for Atrazine. In general, this monitoring data suggest that exposure to the parent Atrazine through the diet is small. However, because the parent Atrazine is also not found in the fruiting parts of plants in the metabolism studies, it is difficult to estimate the total chloro- or hydroxy- metabolites in fruits, nuts or grains based upon testing for parent Atrazine, alone. Therefore, for dietary exposure assessments, residues of Atrazine, its chloro-and hydroxy metabolites were estimated from field trial and metabolism study data where possible as these studies included analyses for the chloro- and hydroxy metabolites, as well as the parent compound, in the main crops on which Atrazine is used. Except for sugar cane, all human foods treated with Atrazine are fruits, nuts or grains. Sugar cane, of course, is highly processed before it is consumed by humans.

Extensive field trials, including recently updated trials, exist for Atrazine on corn and sorghum and adequate field trials also exist on sugar cane and wheat. In these field trial, samples were analyzed for residues of Atrazine, each of the three chloro-metabolites, and each of the four hydroxy metabolites of Atrazine. Old, limited field trials exist for macadamia nuts and guava, in which samples were analyzed for Atrazine, per se, only. The guava tolerance is translated from use on other crops (Atrazine alone). Processing studies are available for processing of sugar cane into refined sugar and molasses. Processing studies are available for corn, sorghum, and wheat. Residues do not concentrate in edible portions of corn, sorghum, and wheat commodities. Likewise, adequate metabolism studies were available for corn, sorghum and sugar cane. Samples from the corn, sorghum and sugarcane studies were analyzed for residues of Atrazine, each of the three chloro-metabolites, and each of the four hydroxy metabolites of Atrazine. Metabolism studies were not available for wheat, guava or macadamia nuts.

BEAD has recently updated percent crop treated information for Atrazine. Data is good for the major crops. Uses of Atrazine are 76% average to 100% maximum on sugarcane, approximately 50% to 60% max on sweet corn, 82% to 97% max on other corn, 60 to 74% max on sorghum and less than 1% on wheat. 57% will be used for macadamia nuts based on BEAD use information. Syngenta has suggested that there is not more than 10% use on guava and BEAD has affirmed that this estimate should be conservative.

Using the HED Dietary Exposure Evaluation Model (DEEM), the dietary exposure to Atrazine and its metabolites has been small (<1%) relative to the respective RfDs for all assessments. Because the human food portions of crops treated with Atrazine were generally free of residues, estimated exposure was very predominantly through milk and meat from animals fed the feed and forage portions of crops that did contain residues of Atrazine. These estimates in animals foods, however, are based upon conservative assumptions that may overestimate the residues in these foods.

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2. Dietary (Drinking Water) Exposure Considerations
(*Correspondence:* C. Eiden to C. Christensen dated March 22, 2002)

Exposure to Atrazine in drinking water involves exposure both to the parent compound and several chlorinated metabolites. Known metabolites of Atrazine are deethylatrazine (DEA), deisopropylatrazine (DIA), diaminochlorotriazine (DACT), hydroxyatrazine (HA), deethylhydroxyatrazine (DEHA), and deisopropylhydroxyatrazine (DIHA). DACT is known to form and persist in groundwater as the terminal metabolite.

The parent and several of its metabolites are considered to be highly mobile and persistent due to the wide detections in the monitoring studies. Based on the information of the environmental fate profiles and the results of the monitoring programs, the drinking water exposure potential is high. Up to 75 million pounds of Atrazine are applied in the US each year, in part, accounting for its prevalence in surface water and groundwater. Atrazine and its chlorinated metabolites are the most prevalent pesticide residues detected in finished drinking water from community water systems (CWS) using surface water sources. Atrazine and its chlorinated metabolites have also been detected in rural wells, and to a much lesser degree in CWS using groundwater sources. Based on its prevalence (frequent occurrence) the OW established a MCL of 3 ppb in 1991 and has monitored for Atrazine under the Safe Drinking Water Act (SDWA) for the past 10 years.

There are more monitoring data for Atrazine, *per se*, from studies designed to assess ambient water quality, available for assessing the exposure to Atrazine in ground and surface water than for any other pesticide. Because Atrazine is regulated under the SDWA, there are also more monitoring data on Atrazine, *per se*, in finished drinking water than for any other pesticide. The PRZM/EXAMS modeling and the SCIGROW screening model have not been used to estimate drinking water concentrations of Atrazine, *per se*, from surface water and groundwater sources, respectively, because of the available monitoring data and a concern that the models could not reliably address the large number of chlorinated metabolites involved in an Atrazine exposure assessment. Monitoring databases include: i) Syngenta's PLEX database (population-linked exposure based on SDWA monitoring data from 21 states with major Atrazine use); ii) Syngenta's Voluntary Monitoring Study (9 States); iii) Acetochlor Registration Partnership (ARP) study (12 states); iv) Syngenta's Rural Well Survey (1505 wells in 19 states); and v) monitoring data on Atrazine and the chlorinated metabolites in CWS using groundwater (samples from 204 and 235 CWSs with previous detect's and previous non-detect's, respectively). Data from 17 CWS in which Atrazine and the chlorinated metabolites were measured for approximately one year was used to estimate the chlorinated metabolites in all other CWS using surface water.

At the most, CWS included in the PLEX database were sampled once quarterly (4 times per year) as mandated under the SDWA. Because of the infrequency of the sampling, HED/EFED cannot be certain that all CWS in the 21 selected states with high seasonal

exposures to Atrazine have been identified. In addition, CWS in states not included in the PLEX database may have exposure to Atrazine. Since compliance monitoring data do not include analyses for the chlorinated metabolites of Atrazine, EFED has had to estimate concentrations of the chlorinated metabolites in drinking water from CWS using surface water based on data from only 17 CWS.

The survey of CWS using groundwater was designed to estimate the 95th percentile exposure from two strata of CWS wells: wells with at least one detection of Atrazine prior to 1998 (about 3% of wells in the PLEX system), and wells with no previously detections of Atrazine (about 97% of GW CWSs). Because this is a statistical survey, the one well with the high value of ~10 ppb for total chlorotriazines represents other wells with potentially high exposures.

There are an estimated 13 million rural household wells in the US. The registrant has provided a database containing residue data on Atrazine, its chlorinated metabolites, and its four hydroxy-metabolites for 1505 rural drinking water wells in 19 states with major Atrazine use called the Rural Well Survey. The wells were selected based on their proximity to farms growing corn, and general location in Atrazine use areas, as well as depth to water. Although this database represents rural wells targeted for their location in Atrazine use areas, because of the small number of wells sampled and the infrequency of sampling (one sample per well) HED has high uncertainty regarding the extent of exposures to Atrazine and the chlorinated metabolites in rural wells.

Relative to other pesticides, exposures to Atrazine and its chlorinated metabolites in drinking water are high and widespread. The databases indicate that at least 35 million people in the US on CWS have been exposed to Atrazine above the level of detection (0.01 to 0.5 ppb). However, this population estimate does not include the population on rural wells which are at risk for Atrazine contamination. It also does not include populations on CWS that were not included in the PLEX database, i.e., the remaining 29 states where Atrazine use is not considered major, but where exposures occur (for example, Virginia, Hawaii).

Although the database on Atrazine in finished drinking water is robust relative to other pesticides, the infrequency of monitoring under the SDWA (quarterly), the limited data on the metabolites and rural wells, and the exclusion of CWS in other than 21 major use states and CWS using blended water makes it possible that neither Syngenta nor HED/EFED have identified all CWS with Atrazine exposures of concern. Estimates of metabolites in surface water have been derived from regression equations calculated from data collected for only 17 CWS through only one year of monitoring. In addition, there are an estimated 13 million rural wells in the US; there are only one to two samples from each of only 1505 of these wells. Given the variability over time of Atrazine residues in surface water and groundwater as seen in other monitoring surveys, there is uncertainty that one year of monitoring data for the metabolites in surface water, and one to two

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samples per rural well are adequate to characterize chloro-triazine concentrations in these sources of drinking water.

In summary, although it is known that there is significant, widespread exposure to Atrazine and its metabolites in drinking water, limitations in the extent, frequency, and compounds tested for in the monitoring data raise significant uncertainties regarding the level of exposure to Atrazine and its metabolites.

3. Residential Exposure Considerations
(*Correspondence:* C. Eiden to C. Christensen dated March 22, 2002)

Based on the product labels, meetings with registrants, and usage reports, children and infants would be exposed to Atrazine after application of the herbicide to sod, golf course turf, and residential lawns. The formulated product has a non-restricted label. Atrazine is contained in several homeowner-usable "weed and feed" formulations. There is limited information available, but BEAD estimates the average rate on sod to be 2.3 lb ai per acre annually (typically one application at 2 lbs ai per acre per year).

Three chemical-specific studies were submitted which will be used for residential post-application exposure scenarios: Dissipation of turf transferable residues after application of (1) granular; and (2) dry flowable formulations; and (3) a hand press study of granular residues on turf. For some scenarios, such as soil ingestion, the Residential SOPs will be used. In addition, golfing exposure is assessed using guidelines developed by the Exposure SAC.

Dermal postapplication exposure assessments for Atrazine were based on the higher average daily residues from the chemical-specific TTR study data, but also used standard assumptions for transfer coefficients. Incidental oral ingestion scenarios are based on standard assumptions and formulae (Residential SOPs) which are designed to be screening level. Granular ingestion is considered episodic in nature and therefore not aggregated. These risk estimates are considered conservative.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. FQPA Safety Factor Recommendations

For the reasons set forth below, the FQPA SFC recommends that OPP use the default 10X FQPA Safety Factor to protect the safety of infants and children in assessing dietary exposures to Atrazine; and that a 3X Special FQPA Safety Factor is adequate to protect the safety of infants and children in assessing residential exposures to Atrazine.

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A. Traditional Additional Safety Factor (Addressing Data Deficiencies)

On March 19, 2002, the HIARC concluded that no traditional additional safety factors were required to address deficiencies in the databases for Atrazine or DACT.

B. Special FQPA Safety Factors

Taking into account the HIARC recommendation regarding residual concerns for uncertainties associated with Atrazine's neuroendocrine mode of action, the FQPA SFC recommends that the default additional 10X FQPA Safety Factor be used in assessing dietary exposures because reliable data are not available to show a different factor would be safe; and that an additional 3X Special FQPA Safety Factor is adequate to protect the safety of infants and children in assessing residential exposure and risks.

2. Rationale and Findings Regarding Recommendation on Special FQPA Safety Factor

The Committee concluded that, as to dietary risk, the default 10X FQPA safety factor is statutorily required because of the absence of reliable evidence showing that an additional safety factor different than the statutory 10X default would be protective of infants and children. The principal grounds for this conclusion are: 1.) the HIARC identified residual concerns for the of effects of the neuroendocrine mode of action described for Atrazine on the development of the young (Refer to Section I.3.B.). These concerns could not be accounted for in the determination of toxicity endpoints and traditional uncertainty factors to be used in risk assessment; and 2.) residual concerns were also identified with regard to the drinking water exposure assessment. The various water monitoring data sources which exist for Atrazine and its chlorinated metabolites indicate that exposure via drinking water sources is high in some of the systems that have been monitored and widespread low levels are commonly detected. Although it is known that there is significant, widespread exposure to Atrazine and its metabolites in drinking water, limitations in the extent, frequency, and compounds tested for in the monitoring data raise significant uncertainties regarding the level of exposure to Atrazine and its metabolites. Because of these uncertainties, the Committee concluded there is not reliable data to assign an additional safety factor that would adequately protect the safety of children by insuring that exposure in drinking water is not underestimated. The FQPA specifies that in the absence of such reliable data a default value of 10X is to be used as an additional safety factor for the protection of infants and children. As discussed below, the Committee believes there is reliable data to address the residual uncertainties regarding the neuroendocrine mode of action; however, because reliable data is not available as to all of the issues raising residual uncertainties, use of the default 10X factor is appropriate.

The Committee concluded that an additional Special FQPA safety factor of 3X is adequate for assessing residential exposures to Atrazine / DACT because the concerns for drinking water (described above) would have little or no impact on the residential exposure scenarios. The concerns for the effect of the neuroendocrine mode of action on the development of the young remain and the Committee concluded that there are reliable

data to address these concerns through use of an additional Special FQPA Safety Factor of 3X (Refer to Section I.3.B for the rationale that this factor would be adequate to account for these hazard-based residual uncertainties).

3. Application of the FQPA Safety Factors (Population Subgroups / Risk Assessment Scenarios)

The FQPA safety factor recommendation is for the default 10X additional FQPA safety factor for dietary exposure scenarios and 3X for residential exposure scenarios. The default 10X additionalFQPA safety factor should be applied to the Acute and Chronic RfDs (dietary risk assessments). And the 3X additional Special FQPA safety factor should be applied to short-, intermediate-, and long-term residential scenarios (oral, dermal, and inhalation).

4. Summary of FQPA Safety Factors

Summary of FQPA Safety Factors for Atrazine					
	LOAEL to NOAEL (UF_L)	**Subchronic to Chronic (UF_S)**	**Incomplete Database (UF_{DB})**	**Special FQPA Safety Factor (Hazard and Exposure)**	**Default FQPA Safety Factor (Hazard and Exposure)**
Magnitude of Factor	1X	1X	1X	**3X**	**10X**
Rationale for the Factor	No LOAEL to NOAEL extrapolations performed.	No subchronic to Chronic extrapolations performed	All required studies have been submitted	**Residual Concerns for Atrazine mode of action on the development of the young**	**Residual Concerns for Atrazine mode of action on the development of the young and exposure via drinking water**
Endpoints to which the Factor is Applied	Not Applicable	Not Applicable	Not Applicable	**Short-, Intermediate-, and Long-term Residential Exposure scenarios (oral, dermal, and inhalation)**	**Acute and Chronic RfDs (Dietary Exposure)**

FQPA SAFETY FACTOR COMMITTEE MEETING

Mar. 25, 2002

ATRAZINE/DACT

Name	Division/Branch
Edward Zager	HED
John Abbotts	EFED
Jess Rowland	HED CSITS
Susan Makris	HED/TOX
Vicki DeIlosco	HED
Steve Swearman	BEAD
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TINA LEVINE	BEAD
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Mike Metzger	HED
Mary Frankenberry	EFED
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Ray Kent	HED
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Richard Dumas	SRRD
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