2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ATRAZINE IN THE UNITED STATES

Atrazine is a white, odorless powder (when pure) that is used as an herbicide to stop the growth of broadleaf and grassy weeds in crops such as corn, sugarcane, sorghum, pineapples, and macadamia nuts. It is not found naturally in the environment. It is moderately soluble in water, but is more soluble in organic solvents such as acetone, chloroform, and ethyl acetate. More than 37,000 tons of atrazine were used in agricultural and weed control settings in the United States in 1997.

Atrazine is released to the environment during its production and use, with the vast majority being released as a result of its application to soils as an herbicide. Atrazine that remains in the soil degrades with half-lives of a few weeks to several months. Atrazine may migrate out of the soil in surface runoff to streams, rivers, or lakes, or it may migrate deeper into the soil and become associated with groundwater. No significant degradation of atrazine has been observed in groundwater. Half-lives of atrazine in surface waters are generally >200 days. Relatively large amounts of atrazine may volatilize from the soils into the atmosphere. In the atmosphere, no direct photolysis degradation of atrazine is expected to occur, but oxidation in the presence of hydroxyl radicals is expected, with an estimated half-life of 14 hours. Most of the atrazine found in the atmosphere is expected to be sorbed to particulates; it can be transported significant distances in the atmosphere, and has been detected >180 miles from the nearest application site.

The general population may be exposed to atrazine found in water or air, but it is rarely found in foods. When the general population is exposed to atrazine, exposure levels are expected to be very low. Maximum seasonal and average atrazine concentrations of 61.6 and 18.9 ppb, respectively, were detected during a 1993–1998 monitoring program of community water systems in the United States. Air concentrations of atrazine vary with application season; concentrations usually range from just above the detection limit of approximately 0.03 to 0.20–0.32 $\mu g/m^3$ during the application period. The concentrations of atrazine detected in foods were low (0.001–0.028 ppm) in the few samples where it was detected.

Populations residing near crops where atrazine is applied or hazardous waste disposal sites or manufacturing and processing plants may be exposed to higher than average levels of atrazine in ambient air or drinking water. As mentioned above, atrazine is mobile in soils and has been detected in a high percentage of the drinking water wells near crops where atrazine has been used. Atrazine has also been identified in at least 20 of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of sites evaluated for atrazine is not known.

2.2 SUMMARY OF HEALTH EFFECTS

Atrazine is a widely used herbicide. The general population, especially people living in the vicinity of farms, may be exposed to low levels in the air and drinking water. Occupational exposure is a concern for farmers, as several routes of exposure are likely to occur. The primary adverse health effects of atrazine exposure are reproductive/developmental effects following inhalation, oral, and dermal exposure. Data on the carcinogenicity of atrazine are inconclusive. Data regarding the health effects of atrazine in humans are limited to ecological, case-control, and cohort mortality cancer studies and reproductive/ developmental toxicity studies. The bulk of the available toxicity data is from oral exposure studies in animals.

The reproductive system and the developing organism are primary targets of atrazine toxicity. There was a possible association between atrazine use/exposure of male farmers and increased pre-term delivery, but not decreased fecundity. The lack of information on exposure levels and the concomitant exposure to other pesticides makes these studies inadequate to assess the contribution of atrazine to these effects. Several animal studies have shown that atrazine exposure disrupts estrus cyclicity and alters plasma hormone levels; these effects appear to be mediated by changes in the gonadal-hypothalamic-pituitary axis. Epidemiological studies, examining developmental end points, have found an association between Iowa communities exposed to atrazine in the drinking water and an increased risk of small for gestational age babies and other birth defects. Farm couples living year-round on farms in Ontario, Canada did not have altered sex ratios, and the risk of small for gestational age deliveries was not increased in relation to pesticide exposure. Developmental effects have been observed following pre-gestational, gestational, and lactational exposure of rat and rabbit dams or post-weaning exposure of rat pups to atrazine. The observed effects included post-implantation losses, decreases in fetal body weight, incomplete ossification, neurodevelopmental effects, and impaired development of the reproductive system.

A few epidemiology studies suggest evidence of a possible association between atrazine exposure and increased cancer risk, but many others do not, and the data are insufficient to adequately assess atrazine's carcinogenic potential. The animal data associate atrazine with early onset of mammary tumors believed to be the result of atrazine-induced acceleration of reproductive senescence. It is unlikely that the mechanism by which atrazine induces mammary tumors in female Sprague-Dawley rats is operational in humans.

A limited number of animal studies have shown that atrazine exposure may affect other end points, including systemic effects, and damage to the heart, liver, and kidneys. The primary effects are discussed in greater detail below. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on the health effects resulting from exposure to atrazine.

Reproductive Effects. Results of a survey of farm couples in Ontario, Canada, conducted to assess reproductive effects of pesticides, indicated a weak to moderate association between atrazine use in the yard and an increase in preterm delivery. Other results from this survey indicated that atrazine was not associated with any decrease in fecundity as a result of effects on spermatogenesis.

Animal studies have shown that atrazine disrupts estrus cyclicity (i.e., irregular ovarian cycling and changes in the number and/or percentage of days in estrus and diestrus) and alters plasma hormone levels in rats and pigs. These effects appear to be mediated by changes in the gonadal-hypothalamic-pituitary axis that are species-, and even strain-, specific. In Sprague-Dawley rats, atrazine accelerates the normal process of reproductive senescence, which is initiated by a failure of the hypothalamus to release levels of gonadotropin releasing hormone (GnRH) that are adequate to stimulate the pituitary to release luteinizing hormone (LH). Without sufficient LH, ovulation does not occur, estrogen levels remain high, and persistent estrus results. In other strains of rats, atrazine causes elevated progesterone levels, which leads to pseudopregnancy and persistent diestrus. In pigs, atrazine exposure decreased serum estradiol-17β (E_2) concentrations resulting in a short-term delay in the onset of estrus.

The mechanism of reproductive senescence in humans does not involve disruption of hormonal regulation, but is initiated by depletion of ova in the ovaries, which ultimately results in decreased plasma estrogen levels. Therefore, disruption of the menstrual cycle or acceleration of reproductive senescence is not anticipated to occur in humans as a result of atrazine exposure. However, it is not known whether atrazine will cause other perturbations in the hypothalamus-pituitary-gonad axis results in reproductive effects in humans.

Atrazine exposure significantly reduced serum and intratesticular levels of testosterone and ventral prostrate and seminal vesicle weights in juvenile male Sprague-Dawley rats. Female Wistar and Sprague-Dawley rats had delayed vaginal opening, and delayed uterine growth was observed in female Wistar rats.

Developmental Effects. Atrazine exposure has been associated with developmental effects in both humans and animals. An association was found between Iowa communities exposed to an average of 2.2 µg/L atrazine in the drinking water in 1984–1990 and an increased risk of intrauterine growth retardation and cardiac, urogenital, and limb reduction defects. The results of a survey of farm couples living year-round on farms in Ontario, Canada indicate that the sex ratio was not altered and the risk of small for gestational age deliveries was not increased in relation to pesticide exposure (atrazine exposure level not available).

Developmental effects in response to oral exposure to atrazine have been demonstrated in laboratory animals. Studies have shown that gestational and peripubertal exposure to atrazine has an effect on reproductive development in rats and rabbits. The effects of gestational exposure to atrazine in rats and rabbits include increased post-implantation losses, full-litter resorptions, decreased live fetuses/litters, increased prenatal loss, decreased litter size, and reduced pup weights, which could be attributed to severe maternal toxicity. Atrazine exposure in rats is also associated with delayed vaginal opening, first estrus cycle, and uterine growth for female rats and decreased prostate weight, increased incidence and severity of inflammation of the lateral prostate, increased myeloperoxidase levels in the prostate, and increased total DNA in the prostate for male rats.

Atrazine has also been shown to have an effect on the development of the nervous system in rats. Mild neurobehavioral effects were observed in female offspring of Fischer rat dams exposed to atrazine pre-mating, including increased spontaneous activity level, and male offspring had improved performance (decreased latency and increased avoidance) in avoidance conditioning trials.

Other developmental effects include incomplete ossification of the skull, hyoid bone, teeth, forepaw metacarpals, and hindpaw distal phalanges in the offspring of exposed Sprague-Dawley rats, and nonossification of forepaw metacarpals and middle phalanges, hindpaw talus and middle phalanges, and patella in the offspring of exposed rabbits. No developmental effects were noted in a two-generation study in which rats were exposed to atrazine in the diet.

Cancer. The carcinogenic potential of atrazine has been investigated in a number of epidemiology studies, including cohort studies of workers at triazines manufacturing facilities, case-control studies of farmers using atrazine or triazines, and ecological studies of populations living in agricultural areas with high atrazine use and residents living in areas with atrazine-contaminated drinking water. In most of these studies, it is likely that the individuals were exposed to atrazine via several exposure routes. For example, in the studies of farmers, the likely exposure routes are inhalation during application of atrazine, dermal during handling and use of atrazine, and possible oral exposure due to contamination of groundwater. Epidemiological data are available for a number of types of cancers; however, for most cancer types, only one study investigated the possible association. The most widely studied cancer type is non-Hodgkin's lymphoma. In general, case-control studies of farmers using atrazine (in some studies, data are only available for triazine exposures) found small elevations in the risk of developing non-Hodgkin's lymphoma; typically, the odds ratios were ≤1.5 and the 95% confidence intervals included unity. A small number of cases is a common limitation of these studies. One study pooled the data from three other studies, representing farmers in four U.S. states, to increase the statistical power of the analyses. This study found an odds ratio of 1.4 (95% confidence interval of 1.1–1.8), suggesting a weak association between atrazine exposure and increased risk of non-Hodgkin's lymphoma. To account for possible exposure to other pesticides that have been shown to induce non-Hodgkin's lymphoma, the odds ratio was adjusted for exposure to 2,4-D and organophosphate insecticides. This adjustment resulted in a small decrease in the odds ratio (1.2, 95% confidence interval of 0.9–1.7). A cohort mortality study of workers at two triazines manufacturing facilities also found an increase in the risk of non-Hodgkin's lymphoma (SMR=385; 95% confidence interval of 79–1,124). Collectively, these studies provide suggestive evidence of a possible association between atrazine exposure and non-Hodgkin's lymphoma, but a causal relationship cannot be established.

Evidence on the possible association between atrazine exposure and increased risk of other cancer types is weak. Studies of farmers or possible agricultural workers did not find significant increases in the risk of multiple myeloma, leukemia, soft tissue sarcoma/carcinoma, or Hodgkin's disease. Suggestive evidence between atrazine (or triazines) exposure and an increased risk of prostate cancer, breast cancer, and ovarian cancer have been reported. Although these data provide a suspicion of carcinogenicity, the limited number of investigations and study limitations preclude drawing conclusions regarding these cancer types.

The animal data suggest that the carcinogenicity of atrazine is species-, strain-, and sex-specific. Statistically significant earlier onset of mammary tumors or incidence of mammary tumors were observed

in female Sprague-Dawley rats, but not in female Fischer 344 rats or in female CD-1 mice. An increase in mammary tumors was observed in male Fischer 344 rats; however, it is likely that the increased tumor incidence is due to increased lifespan of the atrazine-treated animals, as compared to the controls (aged Fischer 344 rats have a high rate of spontaneous mammary tumors). The early onset of mammary tumors in female Sprague-Dawley rats is believed to be the result of atrazine-induced acceleration of reproductive senescence. Both the failure to ovulate and the state of persistent estrus lead to constant elevated serum levels of endogenous estrogen, which could result in tumor formation in estrogen-sensitive tissues. Reproductive senescence in humans involves ovarian depletion and decreased serum estrogen levels instead of decreasing hypothalamic function and increased serum estrogen levels. It is unlikely that the mechanism by which atrazine induces mammary tumors in female Sprague-Dawley rats is operational in humans.

IARC has classified atrazine as "not classifiable as to its carcinogenicity to humans" (Group 3) based on inadequate evidence in humans and sufficient evidence in experimental animals.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

There is limited information on the toxicity of inhaled atrazine. Two human studies and no animal studies were identified. The two ecological studies examined reproductive and developmental toxicity end points in farmers using atrazine (Curtis et al. 1999; Savitz et al. 1997). In both studies, the atrazine exposure was poorly characterized; no monitoring data were provided; and exposure likely involved inhalation, oral, and dermal routes. These studies are inadequate for MRL derivation.

Oral MRLs

- An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to atrazine.

Human data on the acute toxicity to atrazine are limited to a report of an individual intentionally ingesting weed killer containing atrazine (Pommery et al. 1993). Acute-duration animal studies have primarily focused on endocrine, reproduction, and developmental end points. The endocrine effects primarily included increases in pituitary weight and alterations in levels of several reproductive hormones. Increases in pituitary weight were observed in rats receiving gavage doses of 120 mg/kg/day for 7 days

(Babic-Gomerac et al. 1989; Šimić et al. 1994). Increases in pituitary prolactin levels and decreases in serum prolactin and luteinzing hormone levels were observed in ovariectomized, estrogen supplemented female Long-Evans rats receiving gavage doses of 50 mg/kg/day and higher for 1–3 days (Copper et al. 2000) and Sprague Dawley rats receiving 300 mg/kg/day via gavage for 1–3 days (Cooper et al. 2000). Decreases in serum luteinizing hormone levels were also observed in Holtzman rats receiving gavage doses of 100 mg/kg/day on gestational days 1–8 (Cummings et al. 2000b) and decreases in prolactin release in response to pup suckling was observed in rats receiving 25 mg/kg/day on postpartum days 1–4 (Stoker et al. 1999). Increases in serum estradiol levels were observed in Sprague-Dawley rats receiving gavage doses of 200 mg/kg/day on gestational days 1–8 (Cummings et al. 2000b) and decreases in serum and intratesticular testosterone levels were observed in juvenile (aged 46–48 days) male rats exposed to 50 mg/kg/day for 3 days (Friedmann 2002). There are a limited number of other systemic effects that were reported for acute duration exposure. The most commonly reported effects were decreases in body weight gain or weight loss at doses of 50 mg/kg/day and higher in rats (Cummings et al. 2000b; Santa Maria et al. 1987; Šimić et al. 1994).

The alterations in hormone levels resulted in a number of reproductive and developmental effects including altered estrus cyclicity at 120 mg/kg/day and higher in rats (Cooper et al. 2000; Šimić et al. 1994), decreased fertility in rats at 120 mg/kg/day (Šimić et al. 1994), increased pre- and post-implantation loss in rats administered 100 mg/kg/day and higher (Cummings et al. 2000b; Infurna et al. 1988) and rabbits administered 75 mg/kg/day (Infurna et al. 1988), and delayed ossification in rat and rabbit offspring administered 70 or 75 mg/kg/day on gestational days 6–15 or 7–19, respectively. Additionally, maternal toxicity, as evidenced by decreased food consumption and body weight gain, was also observed in rabbits administered 5 mg/kg/day; at 700 and 75 mg/kg/day severe weight losses were observed in rats and rabbits, respectively (Infurna et al. 1988).

The lowest LOAEL identified in the acute toxicity database is 5 mg/kg/day for maternal toxicity (decreased body weight gain and food consumption) in rabbits receiving gavage doses of atrazine on gestational days 7–19 (Infurna et al. 1988); this study also identified a NOAEL of 1 mg/kg/day for maternal toxicity. Derivation of an acute-duration MRL using this critical effect level would be protective for the endocrine and reproductive effects that are observed at higher doses. The lowest LOAEL values for an endocrine effect or reproductive effect are 25 mg/kg/day for decreases in prolactin release in response to pup suckling (Stoker et al. 1999) and 100 mg/kg/day for pre- and post-implantation losses in rats exposed on gestational days 1–8 (Cummings et al. 2000b), respectively; both studies identified NOAEL values of 12.5 and 50 mg/kg/day, respectively.

An MRL of 0.01 mg/kg/day was derived using the NOAEL of 1 mg/kg/day, with a LOAEL of 5 mg/kg/day, for maternal toxicity (decreased body weight gain and food consumption) in New Zealand White rabbits exposed to atrazine on gestational days 7–19 (Infurna et al. 1988). The NOAEL of 1 mg/kg/day was divided by an uncertainty factor of 100 (10 to account for animal to human extrapolation and 10 for human variability).

- An MRL of 0.003 mg/kg/day has been derived for intermediate-duration oral exposure (15–365 days) to atrazine.

No studies have examined the intermediate-duration oral toxicity of atrazine in humans. In animals, intermediate-duration oral exposure has resulted in reproductive, developmental, immunological, and a variety of systemic effects. Atrazine disrupts the normal functioning of the endocrine system resulting in impaired reproduction and hormone levels. A decrease in pituitary weights were observed in juvenile rats exposed to 12.5 mg/kg/day on postnatal days 22–41 (Laws et al. 2000). Alterations in endocrine hormones included decreases in serum luteinizing hormone levels in rats at 75 mg/kg/day (Cooper et al. 2000); increases in pituitary prolactin levels in rats at 75 mg/kg/day (Cooper et al. 2000); alterations in estradiol levels in rats at 6.9 mg/kg/day and higher (Cooper et al. 2000; Eldridge et al. 1994a; Wetzel et al. 1994) and pigs at 1 or 2 mg/kg/day (Gojmerac et al. 1996, 1999); and decreases in testosterone levels at 50 mg/kg/day and higher (Friedmann 2002; Trentacoste et al. 2001). These hormone alterations resulted in a disruption of estrus cyclicity in pigs exposed to 1 or 2 mg/kg/day (Ćurić et al. 1999; Gojmerac et al. 1999) and rats exposed to 6.9 mg/kg/day and higher (Cooper et al. 1996b; Eldridge et al. 1994a, 1994b; Wetzel et al. 1994). Decreases in ovarian and uterine weights were also observed in rats at 100 mg/kg/day (Eldrigde et al. 1994a) and ovarian lesion were observed in pigs at 2 mg/kg/day (Ćurić et al. 1999; Gojmerac et al. 1996). Postnatal exposure to atrazine also results in impaired development of the reproductive system; delayed vaginal opening and delayed preputial separation were observed in rat offspring at 50 (Laws et al. 2000) and 12.5 mg/kg/day (Stoker et al. 2000), respectively.

Several other effects have been observed in rats and pigs following intermediate-duration oral exposure to atrazine, including degeneration of myocardial fibers and mild degeneration and inflammation and mild chronic interstitial hepatitis in pigs at 2 mg/kg/day (Ćurić et al. et al. 1999), lymphopenia in rats at 15.4 mg/kg/day (Vos and Krajnc 1983), lymphoid depletion in lymph nodes and spleen in pigs at 2 mg/kg/day (Ćurić et al. 1999), and decreases in body weight gain in rats exposed to 2.7 mg/kg/day and higher (Cantemir et al. 1997; Cooper et al. 1996b, 2000; Desi 1983; Eldridge et al. 1994a; Laws et al. 2000; Trentacoste et al. 2001; Wetzel et al. 1994).

These studies clearly identify endocrine disruption, as evidenced by altered hormone levels and disrupted estrus cyclicity, as the most sensitive target of atrazine toxicity; the lowest LOAEL for this effect was identified in pigs. A 19-day exposure to 1 mg/kg/day atrazine in the diet resulted in a short-term delay in the onset of estrus (Gojmerac et al. 1999); a NOAEL was not identified. The delay in estrus was accompanied by significant alterations in estradiol levels, which were measured for 5 consecutive days after exposure termination (beginning 2 days prior to anticipated estrus). As presented in figure 2 of the paper (Gojmerac et al. 1999), the estradiol levels were steadily increasing on days 1 and 2, which is the pattern that would be anticipated if the animals were about to go into estrus.

An intermediate-duration oral MRL of 0.003 mg/kg/day was derived using the LOAEL of 1 mg/kg/day for delayed estrus in pigs (Gojmerac et al. 1999). This LOAEL was divided by an uncertainty factor of 300 (10 to account for the use of a LOAEL, 10 for animal to human extrapolation, and 3 for human variability). An uncertainty factor of 3 for human variability was used instead of 10 because the critical effect was identified in a sensitive population (young, developing female pigs).

Two human studies involving chronic exposure to atrazine were identified (Munger et al. 1992b, 1997). Both studies examined potential developmental effects in residents exposed to elevated triazine levels in drinking water. These studies have limited usefulness for risk assessment because atrazine concentrations were not measured and the community was exposed to a number of chemicals from the drinking water. A number of animal studies have examined the chronic toxicity of atrazine. As with acute- and intermediate-duration exposure, the endocrine/reproductive system is the primary target of toxicity. An increased length of estrus was observed in rats exposed to 6.9 mg/kg/day atrazine in the diet for 18 months (Wetzel et al. 1994); a NOAEL for this end point was not identified.

In addition to the endocrine/reproduction effects, a number of systemic effects have been observed. Decreases in body weight gain were observed in rats exposed to 25 mg/kg/day and higher (EPA 1984f, 1987d, 1987c; Pintér et al. 1990); cardiac effects consisting of increased thrombi in mice at 247 mg/kg/day and EKG alterations, atrial dilatation, fluid-filled pericardium, enlarged heart, and atrophy of atrial myocardium in dogs at 34 mg/kg/day (EPA 1987f); alterations in hepatic and renal clinical chemistry parameters in rats at 52 mg/kg/day (EPA 1984f, 1987d); and hematological alterations in rats at 71 mg/kg/day (EPA 1984f, 1987d), mice at 194 mg/kg/day (EPA 1987b), and dogs at 34 mg/kg/day (EPA 1987f).

The lowest LOAEL identified in a chronic study was 6.8 mg/kg/day for increased estrus cycle length in rats (Wetzel et al. 1994). This study was not selected as the basis for a chronic-duration oral MRL because the resultant MRL would be higher than the MRL for intermediate-duration exposure.