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Atrazine

Guideline

The interim maximum acceptable concentration (IMAC) for atrazine in drinking water is 0.005 mg/L (5 µg/L). The guideline is applicable to the sum of atrazine and its N-dealkylated metabolites.

Identity, Use and Sources in the Environment

Atrazine ($C_8H_{14}ClN_5$) is a chloro-N-dialkyl-substituted triazine herbicide with a molecular weight of 215.7. Technical atrazine is a colourless crystalline powder with a melting range of 175–177°C and a moderately low solubility in water of 30 mg/L at 20°C.[1] Its vapour pressure is 3×10^{-7} mmHg (0.4×10^{-7} kPa) at 20°C, and its volatility is low, with a Henry's law constant of less than 10^{-7} atm•m^3/mol.[2] Its log octanol–water partition coefficient is reported as 2.75,[3] and it appears not to bioaccumulate to any great degree in the food chain.[4]

Atrazine is used extensively in Canada as a pre- and post-emergence weed control agent, primarily for corn but also for rapeseed, and for total vegetation control in non-cropland and industrial areas. Nearly 2 million kilograms of active ingredient (a.i.) were sold in Canada in 1988, about 70% of this being sold in Ontario.[5]

Atrazine degrades slowly in acidic waters via hydrolysis and N-dealkylation, with a half-life of about 12 weeks at pH 5 and 20°C; breakdown is negligible in neutral or somewhat alkaline waters, with a half-life of two years or more.[2] Atrazine is moderately long-lived in soils in temperate climates; it persists for up to a full season under average field conditions[6] and even longer under some circumstances.[2] The mean soil adsorption coefficient K was reported to be 163 ± 80 for 56 types of soil (K values below 300 to 500 are considered to indicate high potential for migration through soil). The soil–water distribution coefficient K_d is low, ranging between 0.4 for sands and 8 for other soils.[2] Atrazine was therefore considered to be a Priority A chemical for potential groundwater contamination by the U.S. Environmental Protection Agency (EPA)[7] and was ranked highest of 83 pesticides in the Agriculture Canada priority scheme for potential groundwater contaminants.[8]

Exposure

Water

In areas where atrazine is used extensively, it (or its dealkylated metabolites) is one of the most frequently detected pesticides in surface and well water. Atrazine contamination has been reported in British Columbia,[9] Nova Scotia, Prince Edward Island, Quebec, Ontario and Saskatchewan.[10] In 1985, 85% of ambient water samples in one area of southwestern Ontario were found to be contaminated with traces of atrazine.[11] Similar results have been reported for surface waters in Quebec.[10]

In Ontario farm wells, atrazine was detected at levels at or above 1 µg/L in 17% of 351 wells monitored during the 1985 Alachlor Monitoring Survey by the Ontario Ministry of the Environment.[12] The maximum recorded concentration was 1200 µg/L, and the median concentration of the 59 positive samples whose concentrations were recorded was 2.5 µg/L (trace concentrations — below 1 µg/L — were not recorded). Only about 100 of these wells were used for domestic water supplies, but two-thirds of these tested positive for atrazine.[11] Nine municipal supplies were also tested. Dresden, Ontario, in the corn-belt region of southwestern Ontario, was the only municipality seriously affected, with positive atrazine results in 39 out of 54 analyses on its raw water supply. The maximum concentration was 6.4 µg/L in raw water, 4.3 µg/L in conventionally treated water (21 detections/48 samples) and 1.4 µg/L in water treated using powdered activated carbon (PAC) (nine detections).[12]

In 1986, the Ontario Ministry of the Environment conducted surveys for atrazine and its metabolite deethylatrazine on 37 representative farm wells and on 30 municipal supplies — 25 supplied from surface water and five from groundwater. Contamination, at least at trace levels, was 100% for farm wells and surface water

municipal supplies and 40% for municipal supplies from wells. However, concentrations were above 1 µg/L in 17% of farm wells and 44% of municipal supplies. For farm wells, the median and maximum concentrations were 0.5 and 10.5 µg/L, respectively; for municipal supplies, the median and maximum concentrations were 0.66 and 29.4 µg/L, respectively.[13]

Atrazine was the most common contaminant found in an Ontario farm well survey carried out in 1986 and 1987 on 103 and 76 wells, respectively.[14] In a survey of pesticides in 1285 representative Ontario farm wells carried out for Agriculture Canada in 1991, atrazine (or deethylatrazine) was found in 7.1% of wells and was by far the most commonly found of the four pesticides detected. The median concentrations were 0.4 and 0.35 µg/L for atrazine and its metabolite, respectively, and the maximum concentrations were 18.0 and 4.4 µg/L, respectively. One percent of the concentrations measured were above 3 µg/L.[15] In a repeat of this study, carried out during summer 1992, the incidence of detection of both atrazine and its metabolite was significantly greater than in the previous fall (10.5% or 126 wells and 6.3% or 76 wells, respectively). The median and maximum concentrations of atrazine were not significantly different but were higher for deethylatrazine (0.7 and 8.2 µg/L, respectively).[16] In a groundwater and well water survey around Abbotsford, B.C., 31% of the wells were found to be contaminated with atrazine.[9]

In one municipal supply in Quebec that was monitored weekly between 22 April and 31 August 1987, concentrations of atrazine were above 1 µg/L for 11 weeks between May 28 and August 17 and above 4 µg/L for two weeks, peaking on 8 June.[17]

Atrazine has also been found frequently in surface water and groundwater samples in the United States. Positive results were found in surface water in 31 states and in groundwater in 13 states. Overall, almost 40% of surface water and 10% of groundwater samples were contaminated.[18]

Food

No residues of atrazine were found in a Canadian national surveillance study of 1075 food samples from 1984 to 1989[19] or in U.S. surveys of 19 800 samples from 1981 to 1986.[20] A recent report of atrazine contamination of milk in Wisconsin could not be verified after more extensive sampling.[21] A "worst case" estimate of intake from food would be the theoretical maximum dietary intake of atrazine, which is estimated to be 0.0003 mg/kg bw per day for an adult Canadian, based on negligible residues (0.1 mg/kg food) in all barley, corn, oats and wheat consumed in the average diet.

Total Daily Intake

Most of the total daily intake of atrazine would be supplied from contaminated water. Extensive surveys of food have failed to find any residues, and intake from this source is therefore considered negligible. No air monitoring reports were found; atrazine is unlikely to be found in air, except immediately after application to crops, because of its low volatility.

Analytical Methods and Treatment Technology

Atrazine may be monitored in water using gas chromatography (GC) and various detector systems, including flame ionization, electron capture, mass spectrometry (MS) and nitrogen–phosphorus. For the GC/MS method, the sample is extracted in a liquid–solid extractor, eluted with dichloromethane, and concentrated by evaporation before measurement by ion trap mass spectrometer (detection limit [d.l.] 0.1 µg/L) or magnetic sector mass spectrometer (d.l. 0.3 µg/L) (U.S. EPA Method 525). For the nitrogen–phosphorus method, the sample is extracted with dichloromethane, dried, concentrated with methyl tertiary-butyl ether and measured by nitrogen–phosphorus detection (d.l. 0.13 µg/L) (U.S. EPA Method 507). The average quantitation limit would be approximately 0.2 to 1.3 µg/L for these methods. The electron capture detection method (U.S. EPA Method 505) using hexane extraction gives a detection limit of 2.4 µg/L, too high for environmental monitoring.[23] The detection limits in a number of monitoring surveys ranged between 0.02 and 1 µg/L, with 0.05 µg/L being most commonly reported.

Granular activated carbon (GAC), PAC, reverse osmosis, ion exchange, ozone oxidation and ultraviolet radiation have all been used successfully to remove atrazine and its metabolites from drinking water.[22] Although not as efficient as GAC unless used in large quantities, PAC is partially effective in removing atrazine from water, based on limited testing in Ontario and Quebec. An average of 43% reduction was observed over 12 weeks in the Ste. Hyacinthe, Quebec, treatment plant.[17] Effective removal of pesticide residues requires up to 40 to 50 mg/L of PAC,[13] and up to 91% removal has been reported.[22]

A number of point-of-use home water treatment systems based on activated charcoal are available and are suitable for use in individual homes served by well water that may be contaminated with atrazine. These systems can, however, themselves become sources of chemical and microbial contamination. Over time, as the absorptive capacity of the filter is used up, the accumulated chemicals may be released into the treated water, possibly in higher concentrations than were originally present. The accumulation of organic matter on the filter can also lead to bacterial growth. To reduce the potential

health risks associated with these problems, it is essential that these systems be used only on microbiologically safe drinking water, that the devices be well flushed before each use and that the filters be changed frequently.

Health Effects

Metabolism

Atrazine is almost completely absorbed from the gastrointestinal tract, based on 93 to 100% recovery of orally administered radiolabelled material in rats.[23,24] Absorption from the skin may be relatively low: in adult (female) rats, dermal penetration was 3 to 8%; in young (33-day-old) rats, absorption was 16 to 49% higher than that for adults at the same concentration. In both cases, dermal absorption was concentration-dependent and was proportionally higher for dilute solutions.[25] In *in vitro* studies using human skin, about 16% of the applied dose of atrazine was absorbed by the skin.[26]

In six human volunteers who were occupationally exposed dermally and via inhalation, metabolism was rapid, with production of equal amounts of the deisopropyl metabolite (2-chloro-4-ethylamino-6-amino-s-triazine, or deisopropylatrazine) and the fully N-dealkylated metabolite (2-chloro-4,6-diamino-s-triazine).[27] In six workers engaged in the manufacture of atrazine, the doubly dealkylated metabolite comprised 80% of urinary metabolites, whereas only 2% was unchanged atrazine.[28] In *in vitro* studies on human skin, three-quarters of the applied dose was still retained by the skin after 20 hours, and some metabolism took place *in situ*; 50% of the total metabolites formed consisted of deisopropylatrazine, with a smaller amount of the diamino derivative and traces of the deethyl derivative in skin or receptor fluid.[26]

In male Wistar rats administered atrazine in drinking water for one or three weeks, the only metabolite found was deisopropylatrazine.[27] In Fischer-344 rats given 30 mg/kg bw radiolabelled atrazine by gavage, 93% was recovered after 72 hours — 67% in urine, 18% in faeces and <10% in tissues. The plasma absorption and elimination half-lives were three and 11 hours, respectively. The major metabolite, at 64 to 67% of the total, was the N-dealkylated product 2-chloro-4,6-diamino-s-triazine, with 5% present as the deethylated metabolite. The mercapturic acid conjugates of these two compounds formed 13 and 9%, respectively, of the total metabolites.[24]

In rats, mice, rabbits, pigs, goats, sheep and chickens, *in vitro* Phase I metabolism of atrazine via cytochrome P-450 yielded the mono- or di-N-dealkylation products.[29] Species and strain differences were noted in the ratios of metabolites formed and in the rates of metabolism, but there were no appreciable sex differences in two strains of rats and in mice or chickens. Strain differences were observed between Sprague-Dawley and Fischer rats: Fischer rats possessed three times the amount of microsomal protein and P-450 per gram of liver as Sprague-Dawley rats, and their rate of metabolism was correspondingly higher. In both strains, the products and their ratio (deisopropyl metabolite three to four times greater than deethyl metabolite) were similar. Further metabolism to the di-N-dealkylation product was highly specific in this *in vitro* system, with 100% metabolism of the deisopropyl compound and 3 to 4% metabolism of the deethyl compound. Metabolic Phase II conjugation to glutathione compounds was much slower than Phase I dealkylation.[29]

Health Effects in Humans

In humans, nausea and dizziness were reported after ingestion of contaminated well water containing an unspecified concentration of atrazine.[30]

The association between herbicide use and ovarian cancer was investigated in a hospital-based case–control study in northern Italy. Sixty cases (January 1974 to June 1980) were matched with 127 controls with other non-ovarian malignancies. Exposure was divided into three categories — “definite,” “probable” and “no” exposure, as ascertained by interview. The use of triazine herbicides (90% of which was atrazine[31]) had been extensive in corn crops in this region since 1960; exposure was considered “probable” if the person had farmed and resided in an area with known herbicide use. The relative risk associated with “probable” exposure was 2.2 (confidence interval [CI] 0.77 to 6.3; 10 cases, 14 controls), and the relative risk for combined “definite” and “probable” exposure was 4.4 (CI 1.9 to 16.1; 18 cases). As 69% of the controls had malignancies of the breast (45.7%) or uterus (endometrium: 12.6%; cervix: 11%), which were also possibly endocrine- and herbicide-related, a separate analysis eliminating breast cancer controls was performed, which yielded a statistically significant relative risk of 3.5 (CI 1.4 to 8.4).[32]

A second case–control study, this time population-based, was performed in the same area, covering the succeeding period July 1980 to June 1985 and focusing on the use of triazine herbicides, the most frequently used herbicides in the previous study. Sixty-five cases with histologically confirmed diagnoses and 126 randomly selected controls were enrolled. The relative risk for ovarian neoplasms was increased to 2.7 (CI 1.0 to 6.9; seven cases) for women definitely exposed to triazines; there were significant positive trends for increased exposure (“possible” and “probable”) and for increasing length of exposure (>10 years).[31] It was noted that the 90% confidence

interval was given rather than the more usual 95% confidence interval, which reduces the significance of the observations. The low number of cases in most categories also broadened the confidence interval, thus reducing confidence in the significance of the results.

In a population-based case–control study to investigate the relationship of pesticide use to lymphomas in Kansas, a significantly increased risk of non-Hodgkin's lymphoma (NHL) was reported for farmers who used triazine herbicides (odds ratio [OR] = 2.5, CI 1.2 to 5.4; 14 cases, 43 controls). The risk was no longer significant when those who also used chlorophenoxy herbicides were removed from the analysis (OR = 2.2, CI 0.4 to 9.1; three cases, 11 controls). No further information was given about the frequency of use of atrazine and five other triazines listed.[33] In a second case–control study in Nebraska, to investigate risk factors for NHL among farmers, the use of atrazine was associated with a slight (non-significant) increased risk for NHL (OR = 1.4, CI 0.8 to 2.2). The increase in risk became significant for those who had used atrazine for 16 or more years (OR = 2.0, CI not given) and for increasing frequency of yearly use, but it was not significant after adjustment for use of 2,4-D and organophosphate pesticides (OR = 0.6 to 0.8).[34,35]

In a further analysis of the previous two case–control studies and a third similar study carried out in Iowa and Minnesota, atrazine use was associated with an odds ratio of 1.4 for NHL (CI 1.1 to 1.8; 130 cases, 249 controls), but the increase was not significant after adjustment for use of 2,4-D and organophosphate pesticides. Although detailed analysis of the three studies indicated an increased response with increasing frequency and dose, it revealed inconsistencies and confounders, suggesting that there was no real increase in the risk of NHL.[36]

An increased risk of leukaemia was not found to be associated with triazines (or with any of nine families of herbicide compounds) in a similar large population-based case–control study carried out in Iowa and Minnesota (OR = 1.1, CI 0.8 to 1.5; 67 cases, 172 controls).[37]

Health Effects in Animals

The acute toxicity of atrazine is low to moderate, with oral LD_{50} values for adult rats reported to range from 700 mg/kg bw[38] to 1870 to 3080 mg/kg bw.[1] For weanling rats aged four to six weeks, the LD_{50} was about 2300 mg/kg bw and was about one-third the acute toxicity observed in 90-day-old rats in the same series of experiments.[38] Dermal LD_{50} values were >2500 mg/kg bw.[38] In the Microtox test for acute toxicity, the metabolites deethylatrazine and deisopropylatrazine, frequently found in water along with the parent atrazine, were less toxic than atrazine.[39]

Long-Term Studies

In a two-year dietary study on beagle dogs carried out in the early 1960s, atrazine was administered in the diet at 0, 15, 150 or 1500 ppm, approximately equivalent to doses of 0, 0.35, 3.5 and 35 mg/kg bw per day. A decrease in food intake as well as increased heart and liver weights were noted in females at 150 ppm; in the 1500 ppm group, decreases in food intake and body weight gain, increased heart and liver weights, a decrease in haematocrit and occasional tremors in the rear limbs were observed. The no-observed-adverse-effect level (NOAEL) was 15 ppm or 0.35 mg/kg bw per day.[40] Atrazine has also been tested in a more recent one-year oral study, in which beagle dogs (six per sex in control and high-dose groups, and four per sex in two mid-dose groups) were administered 0, 15, 150 and 1000 ppm (0, 0.5, 5.0 or 34 mg/kg bw per day) in the diet. The major target organ for atrazine toxicity in this species was the heart, with myocardial atrial degeneration and severe dilatation of the left atrium being observed. Clinical signs including ascites, cachexia and abnormal electrocardiogram were noted in both sexes at the highest dose, as early as the 17th week of the study. The high-dose group also had reduced body weights and, in males, changes in haematological values (statistically significant reductions in red cell counts, haemoglobin and haematocrit) and in biochemical values (decreases in total serum protein and albumin). In the 5.0 mg/kg bw per day group, two males and one female also showed signs of cardiac toxicity.[41] A no-observed-effect level (NOEL) of 0.5 mg/kg bw per day was selected by the World Health Organization,[42] whereas Ciba-Geigy (the registrant) presented additional information to the EPA that resulted in selection of the 5.0 mg/kg bw per day dose as the NOAEL by this agency.[43]

In an early chronic study, atrazine was tested by gavage in two strains of mice at one dose level, 21.5 mg/kg bw per day for one month, followed by 82 mg/kg per day in the diet (approximately 4 mg/kg bw per day) for 17 months, but no significant increases in hepatomas were noted.[44] A recent 91-week study has been carried out in CD-1 mice, 60 animals per sex per dose, with atrazine administered in the diet at levels of 0, 10, 300, 1500 or 3000 ppm, equivalent to 0, 1, 38, 194 and 386 mg/kg bw per day for males and 0, 2, 48, 247 and 483 mg/kg bw per day for females. At the two highest dose levels, decreases in body weight gain, erythrocyte count, haematocrit and haemoglobin were observed in both sexes, as well as an increase in the incidence of cardiac thrombi in females. There was no increase in the incidence of neoplasms. The NOAEL was 300 ppm or 38 mg/kg bw per day for males and 48 mg/kg bw per day for females.[45]

In a recent chronic bioassay on Sprague-Dawley rats, 70 animals per sex were fed diets containing 0, 10, 70, 500 or 1000 ppm atrazine (equivalent to 0, 0.5, 3.5, 25 and 50 mg/kg bw per day) for two years. The maximum tolerated dose (MTD) was clearly exceeded at the highest dose; decreases in body weight gain were noted in both sexes (26% in females), and centrilobular necrosis of the liver was noted in females. Other non-neoplastic changes at the highest dose included retinal degeneration in females with a non-significant trend in males, hyperplasia of the renal pelvic epithelium and urinary bladder in females, increases in red cell count, haemoglobin and haematocrit in females and increases in pelvic calculi, mammary acinar cell hyperplasia and epithelial hyperplasia of the prostate in high-dose males. At the two highest doses, bone marrow myeloid hyperplasia and extra-medullary haemato-poiesis of the spleen were significantly increased in females. Dose-related increases in both benign (fibroadenoma) and malignant (adenocarcinoma) mammary gland tumours were observed in females, significant at 3.5 mg/kg bw per day and higher for malignant tumours. The biological significance was unclear (until release of the results from the second bioassay in rats in 1990) because of a high background incidence in both historical (40 to 51%) and concurrent (53%) controls and a slight non-significant increase to 61% in the lowest dose group (0.5 mg/kg bw per day). A NOAEL of 3.5 mg/kg bw per day was observed for systemic effects, based on decreases in body weights and pathological changes in liver and blood-forming elements at higher doses.[46] A NOAEL of 0.5 mg/kg bw per day has also been suggested, based on increased hyperplastic effects at the next highest dose.[42]

A second chronic bioassay using rats has been carried out under the auspices of the International Agency for Research on Cancer (IARC).[47] Atrazine was administered at concentrations of 0, 375 or 750 ppm in the diet to groups of 50 to 56 F344 rats per sex per dose for a lifetime; the experiment was terminated at week 126 for males and week 123 for females. (The dietary concentrations were approximately equivalent to 33 and 35 mg/kg bw per day in high-dose males and females and to 16.5 and 18.5 mg/kg bw per day in low-dose males and females, based on feed consumption and body weights given by the authors.) A dose-related decrease in body weight gain was observed in both sexes, and survival was increased in males but not females. No other treatment-related systemic effects were observed. The incidence of benign mammary tumours was significantly increased in high-dose males but not in females (males: 1/48, 1/51 and 9/53; females: 14/47, 16/53 and 17/54 for the three dose groups). There was also a significant dose-related increase in the incidence of malignant uterine tumours (principally adeno-carcinomas), with 7/45 in controls, 10/52 in the mid-dose group and 14/45 in the high-dose group. Tumours of the haematopoietic system (combined leukaemia and lymphoma) were significantly increased over high control values only for females (incidences in the three groups were 47, 55 and 67% for males and 27, 31 and 43% for females).

Genotoxicity

IARC has recently summarized the information on genotoxicity of atrazine.[48] Atrazine did not induce mutations, with or without mammalian metabolic activation, in bacteriophage or bacterial systems, the yeast *Saccharomyces cerevisiae* or rodent cells *in vitro*. Mutations and chromosomal aberrations were observed in other yeasts and fungi, most plant species tested and *Drosophila*. Additionally, positive results were obtained in several testing systems when they were activated with plant microsomal preparations. An unscheduled DNA synthesis test on human EUE cells was negative with a mammalian activating system and positive with plant microsomes.[49] A positive dose-related increase in chromosomal aberrations was observed in human lymphocyte cultures.[50] *In vivo* test results have been mixed: a host-mediated assay with *Escherichia coli* in mouse gave weakly positive results[49]; in *Drosophila*, aneuploidy, dominant lethal and sex-linked recessive lethal mutations were observed,[51] whereas the latter test was negative in another study[49]; dominant lethal mutations were seen in mouse spermatids after oral exposure at high doses,[49] and DNA strand breaks were observed in rat stomach, liver and kidney but not in rat lung, also after oral administration of high toxic doses.[52] In mice administered doses ranging from 80 to 98 µg/d in drinking water for 30 and 90 days, no increases in chromosomal damage were observed in bone marrow cells after either period; however, the mitotic index was significantly increased at 90 days.[50]

Reproductive and Developmental Effects

In a two-generation, one litter per generation reproduction study on Charles River rats, 30 rats per sex per group were administered technical atrazine (97% a.i.) at 0, 10, 50 or 500 ppm in the diet (equivalent to 0, 0.5, 2.5 and 25 mg/kg bw per day), beginning 10 weeks before mating at age 47 to 48 days in the parental generation. Decreased body weights, body weight gain and food consumption occurred in both sexes at the high dose, 25 mg/kg bw per day. Pup weights were significantly reduced in the F_2 generation at 2.5 and 25 mg/kg bw per day, and a statistically significant increase was seen in relative testes weights in both generations at the high dose. The maternal NOAEL was 2.5 mg/kg bw per day, and the NOAEL for reproductive toxicity was 0.5 mg/kg bw per day.[53]

No teratogenic responses were found in a 1971 rat teratology study,[54] a 1984 rat study[55] or a study on rabbits.[56,57] In the 1971 study, pregnant rats were given atrazine in the diet on gestation days 6 to 15 at 0, 100, 500 or 1000 ppm (equivalent to 0, 4, 20 and 40 mg/kg bw per day). Maternal mortality was 23% at the highest dose, and various (unspecified) toxic symptoms were evident at 100 and 500 ppm. Increased embryonic and fetal deaths, decreased mean fetal weights and retarded skeletal development were observed at the two highest doses. The NOAEL for both maternal and fetotoxic effects was 4 mg/kg bw per day. In the 1984 study, technical atrazine was given by gavage to CR rats, 27 per group, at 0, 10, 70 or 700 mg/kg bw per day on gestation days 6 to 15. Mortality was 78% at the highest dose. At 70 mg/kg bw per day, reduced weight gain and food consumption in the dams and reduced fetal weights as well as inhibition of skeletal development were seen. The maternal and fetotoxic NOAEL was 10 mg/kg bw per day.[55,57] In New Zealand white rabbits, administration of 0, 1, 5 or 75 mg/kg bw per day of technical (97% a.i.) atrazine by gavage on gestation days 7 to 19 resulted in decreased food consumption and body weight in dams of the 5 and 75 mg/kg bw per day groups. In the high-dose group, resorptions were increased, body weights were reduced in fetuses of both sexes and there was delayed ossification. The maternal NOAEL was 1 mg/kg bw per day, and the developmental NOAEL was 5 mg/kg bw per day.[55,57]

Special Studies

Hormonal imbalances in steroid metabolism appear to be induced by atrazine, which exerts its effects through the pituitary gland.[48] It induces increases in some hormones, notably luteinizing hormone and follicle-stimulating hormone,[58] while inhibiting other hormones. Testosterone must be reduced to several metabolites in order to become fully active; reductions in steroid reductase and dehydrogenases result in reduced hormonal activity.[48,59] Effects on testosterone metabolism induced by atrazine and by deethylatrazine, the metabolite that frequently co-occurs in water with atrazine, have been reported in rats that were prenatally treated with these compounds at 16.6 mg/kg bw subcutaneously. There was no alteration of pituitary metabolism in male pups, but an increase in 5α-steroid reductase was noted in female pups. Both pre- and post-natal treatment (with the same protocol) resulted in reductions in 3α-hydroxysteroid dehydrogenase in male pups and in the number of androgen-specific binding sites in the prostate. Atrazine, but not deethylatrazine, also caused a reduction in 5α-steroid reductase in male pups.[60] In male rats administered 120 mg/kg bw atrazine *per os* for seven days, a 60 to 70% increase was noted in the weight of the anterior pituitary, with hyperaemia and hypertrophy of the chromophobic cells. There was also a reduction of 37, 39 and 46% in 5α-steroid reductase, 3α- and 17β-hydroxysteroid dehydrogenase, respectively. Dose-related changes were also seen at 60 mg/kg bw. Deethylatrazine was equipotent for 5α-steroid reductase.[61]

The immunotoxic potential of a formulation of atrazine was tested in mice by administration of a sublethal dose (one-half or more of the LD_{50}). No dose-related changes were observed in organ weights, spleen cell number and cell viability, lymphocyte stimulation by various agents, interleukin-2 production, T-cell numbers or responses, mitogen activation or primary humoral IgM response.[62]

Classification and Assessment

Although several analytical epidemiology studies provide some suggestive evidence for an association between exposure to triazine herbicides (largely atrazine) and increased risk of ovarian cancer or lymphomas, the evidence is considered inadequate because of the limited number of studies conducted to date and the methodological limitations of the available studies, including incompletely characterized exposure, presence of mixtures and other confounding factors and small numbers of exposed subjects, which reduce the power of the study to detect excess risk.

Oral administration of atrazine has resulted in mammary, uterine and haematopoietic system tumours in two strains of rats. No tumours were observed in an adequate long-term study in mice. The tumours of the reproductive system, which were observed in animal studies, are known to be associated with hormonal factors that act as tumour promoters. Atrazine is known to act on the pituitary–gonadal system of hormone regulation; the increased incidence of tumours after atrazine administration is therefore consistent with this role. The dose-related increase in leukaemias and lymphomas observed in the F-344 rat also appeared to be due to a promoting effect on an already high background incidence. The weight of evidence indicates that atrazine is not genotoxic, although the evidence is mixed for the few *in vivo* studies that are available. Atrazine has therefore been included in Group III (possibly carcinogenic to humans).

For compounds classified in Group III, the acceptable daily intake (ADI) is derived on the basis of division of a NOAEL by appropriate uncertainty factors. For atrazine, a provisional ADI is derived as follows:

$$\text{provisional ADI} = \frac{0.5 \text{ mg/kg bw per day}}{1000} = 0.0005 \text{ mg/kg bw per day}$$

where:

- 0.5 mg/kg bw per day is the NOAEL in a two-generation rat reproduction study, based on reductions in body weight of offspring in the F_2 generation.[53] This NOAEL is supported by a NOEL of 0.5 mg/kg bw per day in a one-year dog study,[41] based on cardiac toxicity,[42]

and by a NOAEL of 0.5 mg/kg bw per day observed in a two-year feeding/oncogenicity study in rats,[46] based on dose-related increases in mammary neoplasms in females[42]
- 1000 is the uncertainty factor (×10 for interspecies variation; ×10 for intraspecies variation; and ×10 for evidence that atrazine might act as a non-genotoxic carcinogen or as a promoter in rats through interferences in hormonal regulation).

Rationale

Because atrazine has been classified in Group III (possibly carcinogenic to humans), an interim maximum acceptable concentration (IMAC) for atrazine in drinking water may be calculated as follows:

$$\text{IMAC} = \frac{0.0005 \text{ mg/kg bw per day} \times 70 \text{ kg bw} \times 0.20}{1.5 \text{ L/d}} \approx 0.005 \text{ mg/L}$$

where:
- 0.0005 mg/kg bw per day is the provisional ADI, as derived above
- 70 kg is the average body weight of an adult
- 0.20 is the proportion of total daily intake of atrazine allocated to drinking water (the maximum theoretical daily intake from residues in food constitutes about 60% of the provisional ADI)
- 1.5 L/d is the average daily consumption of drinking water for an adult.

This guideline is applicable to the sum of atrazine and its metabolites. Atrazine is frequently found along with the metabolite deethylatrazine and is sometimes accompanied by other N-dealkylated metabolites. Deethylatrazine, although not as acutely toxic as the parent compound, was equally effective in producing hormonal imbalances resulting in changes in enzyme levels and testosterone binding sites in the testes of male rat pups after intake by the pregnant female and the pups via milk.[60]

Although the guideline was derived using adult consumption, it was based on a NOAEL at which no reproductive consequences of lifetime consumption were observed in a two-generation reproduction study, and to which a 1000-fold uncertainty factor was applied. It is therefore considered to provide adequate protection for the bottle-fed infant.

Several methods, including GAC, are capable of reducing atrazine substantially, both in municipal supplies and in individual homes by point-of-entry or point-of-use water treatment systems.

The guideline will remain an IMAC until completion of the full re-evaluation of this compound, currently in progress within the Health Protection Branch of Health Canada.

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