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Cyanazine

Guideline

The interim maximum acceptable concentration (IMAC) for cyanazine in drinking water is 0.01 mg/L (10 μg/L).

Identity, Use and Sources in the Environment

Cyanazine ($C_9H_{13}ClN_6$) is a triazine herbicide used for pre- and post-emergence weed control for corn, rapeseed and mixed grains. Between 500 000 and 1 000 000 kg are used annually in Canada.[1] The solubility of cyanazine in water is 171 mg/L at 25°C; its vapour pressure at 20°C is 2.1×10^{-7} Pa.[2]

Cyanazine adsorbs to the soil. The degree to which it is adsorbed depends upon soil texture and water and organic matter content.[2] Cyanazine is considered to have strong leaching potential.[3] It is degraded in soil primarily by microbial action, and its half-life in soil is reported to be between two and 10 weeks.[4] Degradation products identified include the amide, two acids and the amine.[4]

Exposure

Cyanazine was detected in nine of 1128 samples of municipal and private water supplies in Quebec (1986), Ontario (1979 to 1986) and Alberta (1978 to 1986) (detection limits ranged from 0.025 to 1 μg/L); concentrations ranged from less than 0.1 μg/L in Quebec water supplies to 4.0 μg/L in Ontario water supplies.[5] Cyanazine was detected in 45 of 440 surface water samples from three Ontario river basins surveyed from 1981 to 1985 (detection limit 0.02 μg/L); total annual use of cyanazine in these areas is more than 175 000 kg, based on records for 1983. The mean detectable concentrations found in each of the three basins were 0.8, 0.1 and 1.5 μg/L.[6]

Based on the residue tolerance limits set by the Food Directorate of the Department of National Health and Welfare,[7] the theoretical maximum daily intake of cyanazine from food is 0.003 mg/d. Actual intake is probably very low, because no residues of cyanazine or its degradation products have been detected in crops following application.[8,9]

Analytical Methods and Treatment Technology

Cyanazine in water may be determined by extraction with chloroform, separation by gas/liquid chromatography and analysis by electrolytic conductivity detector, nitrogen mode (detection limit 0.02 μg/L).[6] Cyanazine in water may also be quantified by extracting with dichloromethane, drying the extract and dissolving it in methanol, separating by high-performance liquid chromatography and measuring by ultraviolet detection (detection limit 6 μg/L).[4]

Cyanazine is reported to be effectively removed from water supplies by granular activated carbon adsorption.[4]

Health Effects

Cyanazine is rapidly absorbed from the gastro-intestinal tract of experimental animals. The major metabolite found in the faeces of treated rats (route and dose unspecified) was 2-hydroxycyanazine; the 4-amino-, N-acetylcysteinyl and corresponding amide and carboxy derivatives were also identified.[10] Between 80 and 88% of doses of radioactively labelled cyanazine are eliminated from the rat and dog within four days, primarily in the urine and faeces.[4]

No information on the toxicity of cyanazine in humans was identified in the literature.

Groups of 20 male and 20 female rats (strain unspecified) were fed daily doses of cyanazine equivalent to 0.075, 0.15, 0.30, 1.25, 2.5 or 5.0 mg/kg bw per day for 13 weeks. The no-observed-adverse-effect level (NOAEL) for reduced kidney weight in males and increased liver weight in females was considered to be 1.25 mg/kg bw per day.[11]

In a limited two-year study in beagle dogs, groups consisting of four males and four females were administered oral doses equivalent to 0.625, 1.25 or 5 mg/kg bw per day of cyanazine (98% active

ingredient, in gelatin capsules). Frequent emesis within one hour of treatment was associated with a reduction in growth rate and serum protein in the high-dose group. The NOAEL was considered to be 1.25 mg/kg bw per day.[12]

In another limited study, groups of CD mice (50 per sex) were fed technical cyanazine in the diet at concentrations equivalent to 1.5, 3.75, 7.5, 37.5 or 150 mg/kg bw per day for two years. At the two highest doses, animals had poor appearance and skin sores, increased brain weights, decreased absolute and differential leukocyte values and increased mortality and liver weights in females. Females receiving 150 mg/kg bw per day had anaemia and increased kidney weights. The NOAEL for mice was 7.5 mg/kg bw per day.[13]

Cyanazine was not considered to be carcinogenic based on results of the two-year study in mice,[13] nor was it oncogenic in two two-year studies in rats; how- ever, these studies were judged to be inadequate by the U.S. Environmental Protection Agency.[4] Cyanazine was not mutagenic in the Ames assay,[14] in *in vivo* tests in *Drosophila melanogaster*[15] or in two very limited *in vivo* studies in mice.[4] No significant effects on reproduction were observed in a three-generation study in Long-Evans rats fed dietary doses of 0.15, 0.45, 1.35 or 4.05 mg/kg bw per day.[16]

No foetotoxic or teratogenic effects have been reported in experimental animals following treatment with cyanazine at doses that are not also maternally toxic. Groups of 22 pregnant seven- to 11-month-old New Zealand white rabbits were administered oral doses of cyanazine of 0, 1, 2 or 4 mg/kg bw per day on days 6 through 18 of gestation. Maternal toxic effects such as anorexia, weight loss, death and abortion were observed at the two highest dose levels; these doses also produced alterations in skeletal ossification sites, decreased litter size and increased post-implantation loss. Malformations in the offspring observed at 4 mg/kg bw per day included anophthalmia/ microphthalmia, dilated brain ventricles, domed cranium and thoracoschisis. The NOAEL for toxicity in the mothers and offspring was 1 mg/kg bw per day.[17]

A teratology study was also conducted in groups of 70 pregnant Fischer-344 rats administered doses of cyanazine (98% active ingredient) of 0, 5, 25 or 75 mg/kg bw per day on days 6 through 15 of gestation. Maternal body weight reductions and decreased food intake were observed at all dose levels. Alterations in skeletal ossification sites in the foetus were reported for all treated groups. At 25 and 75 mg/kg bw per day, anophthalmia/microphthalmia, dilated brain ventricles and cleft palate were observed in the foetuses removed by caesarean delivery on day 20 of gestation. Abnormalities of the diaphragm, associated with liver protrusion, were observed at weaning in pups that were delivered by dams from the two highest dose groups. The NOAELs for maternal and foetal toxicity were lower than 5 mg/kg bw per day, whereas the NOAEL for teratogenic effects was considered to be 5 mg/kg bw per day (a maternally toxic dose).[18] However, no maternal or foetal toxicity was observed in Sprague- Dawley rats exposed to cyanazine at dose levels up to 30 mg/kg bw per day.[19]

Rationale

A negligible daily intake (NDI) for cyanazine was established by the Food Directorate of the Department of National Health and Welfare as follows:

$$\text{NDI} = \frac{1.25 \text{ mg/kg bw per day}}{1000} \approx 0.0013 \text{ mg/kg bw per day}^*$$

where:

- 1.25 mg/kg bw per day is considered to be the NOAEL in terms of decreased kidney and increased liver weights in a 13-week study in rats[11]
- 1000 is the uncertainty factor.

The interim maximum acceptable concentration (IMAC) for cyanazine in drinking water is derived from the NDI as follows:

$$\text{IMAC} = \frac{0.0013 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.20}{1.5 \text{ L/d}} \approx 0.01 \text{ mg/L}$$

where:

- 0.0013 mg/kg bw per day is the NDI established by the Food Directorate
- 70 kg is the average body weight of an adult
- 0.20 is the proportion of daily intake of cyanazine allocated to drinking water (the theoretical maximum daily intake from food is about 0.03 times the NDI)
- 1.5 L/d is the average daily consumption of drinking water for an adult.

References

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* The more recent data from the teratology studies[17–19] were not taken into account in the derivation of the NDI. However, the value of the NDI would not differ greatly on the basis of the results of the teratology studies.

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