February 1989
(edited March 1992)

Trifluralin

Guideline

The interim maximum acceptable concentration (IMAC) for trifluralin in drinking water is 0.045 mg/L (45 µg/L).

Identity, Use and Sources in the Environment

Trifluralin (treflan) is a dinitroaniline-based herbicide sold in large quantities (over 1 million kilograms active ingredient in 1986) for pre-emergence control of grassy and broadleaf weeds in cereal, grain and vegetable crops.[1]

Trifluralin is almost insoluble in water, with a solubility of 0.2 to 0.4 mg/L at 25°C.[2] It is somewhat volatile, with a vapour pressure of 0.006 Pa at 20°C and a Henry's law constant of 4.0 $Pa \cdot m^3/mol$.[3] It has an evaporation half-life from moist soil surfaces or shallow water of a few to 50 hours.[4] Trifluralin has a moderately high log octanol–water partition coefficient of 3[3] and a bioconcentration factor in aquatic organisms of up to 1000 under conditions of constant exposure.[5]

Photodecomposition, volatilization and microbial degradation are the principal processes responsible for the removal of trifluralin from surface water; each process has a half-life of a few days to a few weeks.[4,6,7] However, trifluralin is moderately persistent in soils for up to a full season after use.[8,9] Although it binds strongly to soils with high organic content,[2,4,10] only up to 10% is adsorbed in sandy soils with low organic content.[11] Because of trifluralin's limited solubility and strong soil adsorption, the U.S. Environmental Protection Agency (EPA) considered it unlikely to leach into groundwater supplies but gave it a higher priority than zero as a candidate for monitoring (category C instead of D), owing to high use.[10]

Exposure

In 1987, trifluralin was detected in several municipal water supplies in Saskatchewan at trace (nanogram per litre) levels.[12] It was not detected in drinking water supplies of 77 municipalities in Manitoba or Alberta (detection limits 0.05 to 0.5 µg/L).[13,14] Trifluralin was detected in one of 91 wells at 41 µg/L in a 1984 survey in southern Ontario.[15] Trifluralin has occasionally been detected at trace levels (below 1 µg/L) in surface waters in Manitoba.[13] Trifluralin was not detected (detection limit 0.1 µg/L) in an eight-week sampling of irrigation water in southern Saskatchewan.[16] Based on a concentration of 0.05 µg/L (or half the usual detection limit of 0.1 µg/L), the estimated median Canadian exposure is 0.08 µg/d, or 1×10^{-6} mg/kg bw per day from drinking water.

In Canada, trifluralin was not detected in a national survey of 120 foods (detection limit 4 ppb).[17] In the United States, trifluralin was not detected in over 27 000 food samples covering 27 crops (detection limit 10 ppb).[2,18] The theoretical maximum dietary intake of trifluralin is estimated to be 0.0271 mg/d, or 0.00039 mg/kg bw per day for an adult, based on the assumption that the maximum permitted residues of 0.1 mg/kg are present in all wheat, peas, beans, tomatoes and turnips consumed.[19,20] Actual residues and intakes are expected to be much lower than this estimate.

Analytical Methods and Treatment Technology

Trifluralin may be monitored in water by extraction with a solvent such as dichloromethane and quantification by gas chromatography with electron capture detection. Confirmatory identification is by gas chromatography–mass spectrometry.[16,21] Using this method, the detection limit was 0.05 µg/L in a Manitoba survey[13] and 0.1 µg/L in a Saskatchewan survey.[16]

The U.S. EPA reported that trifluralin is removed with 100% effectiveness by conventional treatment using alum, sedimentation and filtration. In addition, it may be removed from drinking water by reverse osmosis, granular activated carbon and air stripping.[21]

Health Effects

Absorption of trifluralin from the gastrointestinal tract is dose-dependent, with about 20% absorption in rats given an oral dose of 100 mg/kg bw[22] and almost 90% absorption with an oral dose of 1 mg/kg bw.[23] After

administration of an oral dose of 1 mg/kg bw to rats, 87% was eliminated within 60 hours, 47% via faeces and 40% via urine. Most of the trifluralin was metabolized by several pathways to 17 metabolites, whereas about 10% was eliminated unchanged in the faeces. Only 2.1% remained in rat tissues after 96 hours, with the highest concentration (0.22 ppm) in liver and lower concentrations (0.1 ppm or less) in kidney, fat, lung, spleen, intestine and stomach.[23]

The acute oral toxicity of trifluralin is low. The primary effects of chronic ingestion include reduced body weights, increased liver weights and manifestations of renal toxicity, including glomerulonephritis and renal calculi.

In a 1984 study, four groups of beagle dogs (six per sex per group) were fed 0, 30, 150 or 750 ppm trifluralin in the diet, equivalent to 0, 1, 4.8 and 25 mg/kg bw per day, for one year. Histopathological examination revealed no systemic or organotoxic effects at any dose. Diarrhoea, vomiting, decreases in body weight gain and increases in liver and spleen weights, along with changes in serum chemistry (lipid and protein fractions), were noted at the highest dose.[21,24,25] The no-observed-adverse-effect level (NOAEL) in this study was 4.8 mg/kg bw per day.[24,25]

Trifluralin has been tested in six long-term (two-year) dietary studies, four on rats and two on mice. In the first two bioassays, carried out in the early 1960s on Harlan and on Cox rats, no treatment-related tumorigenic effects were observed. These tests were not adequate by today's standards because of methodological limitations and contamination problems.[2,21] In a National Cancer Institute (NCI) study on Osborne-Mendel rats and on B6C3F_1 mice in which technical trifluralin (later shown to be contaminated with 84 to 86 ppm dipropylnitrosamine [NDPA]) was administered in the diet, there were no tumorigenic effects in rats of either sex or in male mice, but hepatocellular carcinomas and alveolar/bronchiolar adenomas were observed in female mice.[21,26] However, this could have been related to nitrosamine contamination of the trifluralin, as many nitrosamines have been demonstrated to be tumorigenic in mice.[26]

In a 1980 study undertaken by the registrant, purified trifluralin with NDPA contamination below 0.01 ppm was administered in the diet to F344 rats (60 per sex per group) and B6C3F_1 mice (80 per sex per group). Non-tumorigenic effects in both sexes of rats included reduced kidney, heart, thymus, pancreas and body weights, elevated blood urea nitrogen, hypertrophy of the liver and testes, glomerulonephrosis and formation of renal calculi; the NOAEL was 813 ppm, or approximately 41 mg/kg bw. Effects were similar but less marked in mice. There was no evidence of oncogenicity in female rats or in either sex of mice, in contrast to the results of the NCI study. In male rats, significant dose-related increases in benign and malignant tumours of the urinary transitional epithelium of the kidney and bladder were observed. The combined incidences of benign and malignant tumours in male rats were 0/60, 3/60, 6/60 and 7/60 for doses of 0, 41, 163 and 315 mg/kg bw.[18,21] The registrant claimed that the renal tumours were specific to F344 rats that were subject to chronic renal disease, glomerulonephrosis and renal calculi. In a subsequent 90-day dietary study on males of this strain, minor changes in kidney function, reversible after a six-week recovery period, were demonstrated.[24,25] The World Health Organization (WHO) agreed with the registrant's position that oncogenic effects of trifluralin were not demonstrated in the bioassay.[23]

Trifluralin was not mutagenic with or without metabolic activation in a number of microbial tests on various organisms, including Ames tests on Salmonella typhimurium.[22,27,28] Tests were also negative in a dominant lethal test in *Drosophila*, an *in vitro* mouse lymphoma system[21] and several mammalian *in vivo* tests, including a dominant lethal assay and a chromosomal aberration study in mice (unpublished studies cited in WHO background document prepared for reference 24). An *in vitro* test on human lymphocyte cultures was positive for chromosomal aberrations,[29] as were several *in vivo* mouse bone marrow assays at high but not low concentrations (1/100 of LD_{50}).[30,31] It is not clear whether or not the trifluralin used in these studies was significantly contaminated with nitrosamine.

Trifluralin did not cause teratogenic effects in rats, dogs or rabbits at doses up to 1000 mg/kg bw.[2,21,24] Manifestations of embryotoxicity, including cardiomegaly, wavy ribs, body weight reductions and increases in percentages of runts, occurred at maternally toxic doses above 10 and 20 mg/kg bw in rats and dogs, respectively.[2,21,24] Reproductive effects, including decreased litter size and increases in spontaneous abortions and stillbirths, were observed in rabbits above 225 mg/kg bw by gavage on days 6 to 18 of gestation[21,24] and above 200 ppm in the diet (10 mg/kg bw) in two-, three- and four-generation reproductive studies in rats.[5,11,21,24,25]

Rationale

Based on evaluation by the Food Directorate of the Department of National Health and Welfare, a negligible daily intake (NDI) was established as follows:[25]

$$\text{NDI} = \frac{4.8 \text{ mg/kg bw per day}}{1000} = 0.0048 \text{ mg/kg bw per day}$$

where:

- 4.8 mg/kg bw per day is the NOAEL observed in a one-year feeding study in dogs in which changes in liver and spleen weights and in serum chemistry (lipid and protein fractions) were noted[25]
- 1000 is the uncertainty factor (×10 for interspecies variation; ×10 for intraspecies variation; and ×10 for limitations of the data base).

An interim maximum acceptable concentration (IMAC) was derived from this NDI as follows:

$$\text{IMAC} = \frac{0.0048 \text{ mg/kg bw per day} \times 70 \text{ kg bw} \times 0.20}{1.5 \text{ L/d}} \approx 0.045 \text{ mg/L}$$

where:

- 0.0048 mg/kg bw per day is the NDI, as derived above
- 70 kg bw is the average body weight of an adult
- 0.20 is the proportion of total daily intake arbitrarily considered to be ingested in drinking water (the theoretical maximum residues in Canadian food are at present less than 10% of the NDI; apportionment of 80% of intake to other sources allows for additional intake from food, should tolerances be set in future)
- 1.5 L/d is the average daily consumption of drinking water for an adult.

Because dose-related increases in tumours of the transitional cell epithelium of the kidney and bladder have been observed in one sex of one species of rodent after dietary administration of trifluralin in a single study,[18] and because the structurally similar compound ethylfluralin is considered to be carcinogenic in animals, the potential lifetime cancer risks associated with exposure to trifluralin have been estimated[32] to ensure that the IMAC is protective.

The maximum potential lifetime cancer risk associated with the ingestion of 1 µg/L trifluralin in drinking water has been estimated by the robust linear extrapolation method, employing an interspecies correction for body weights, to be 4.5×10^{-7}, based on the combined incidence of benign and malignant tumours of the kidney and urinary bladder. The lifetime risk from drinking water containing trifluralin at the guideline value of 45 µg/L is therefore estimated to be 2.0×10^{-5}, slightly above a range that is considered to be "essentially negligible."

The IMAC is based on a non-carcinogenic endpoint and will remain an interim value until the results of further carcinogenicity bioassays that clarify the status of trifluralin as a possible tumorigen have been completed and evaluated.

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