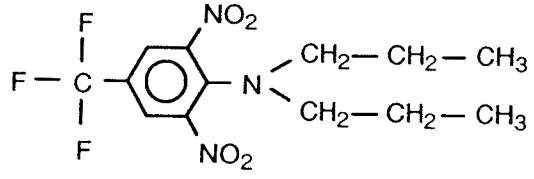
TRIFLURALIN

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Serv. Reg. No.: 1582-09-8
Replaced CAS Reg. Nos: 39300-53-3; 52627-52-8; 61373-95-3; 75635-23-3
Chem. Abstr. Name: 2,6-Dinitro-*N*,*N*-dipropyl-4-(trifluoromethyl)benzenamine
IUPAC Systematic Name: α,α,α-Trifluoro-2,6-dinitro-*N*,*N*-dipropyl-*para*-toluidine; 2,6-dinitro-*N*,*N*-dipropyl-4-trifluoromethylaniline
Synonyms: 4-(Trifluoromethyl)-2,6-dinitro-*N*,*N*-dipropylaniline



$C_{13}H_{16}F_3N_3O_4$ Mol. wt: 335.28

1.1.2 *Chemical and physical properties*

(*a*) *Description*: Yellow-orange crystals (Royal Society of Chemistry, 1989)
(*b*) *Boiling-point*: 139-140°C at 4.2 mm Hg [0.56 kPa] (Budavari, 1989)
(*c*) *Melting-point*: 48.5-49°C (technical-grade, 98% pure) (Worthing & Walker, 1987)
(*d*) *Spectroscopy data*: Infrared spectroscopy data have been reported (US Environmental Protection Agency, 1975).
(*e*) *Solubility*: Slightly soluble in water (< 1 mg/l at 27°C); freely soluble in common organic solvents, such as acetone (400 g/l), Stoddard solvent, xylene (580 g/l) and aromatic naphthas (Worthing & Walker, 1987; Budavari, 1989; Royal Society of Chemistry, 1989; Meister, 1990)
(*f*) *Vapour pressure*: 1.02×10^{-4} mm Hg [0.14×10^{-4} kPa] at 25°C (Royal Society of Chemistry, 1989)
(*g*) *Stability*: Stable to hydrolysis (US Environmental Protection Agency, 1987); decomposed by ultraviolet irradiation under acidic conditions, mainly to 2-amino-6-nitro-α,α,α-trifluoro-*para*-toluidine; at alkaline pH mainly to 2-ethyl-7-nitro-5-fluoromethylbenzimidazole (Leitis & Crosby, 1974)

(*h*) *Conversion factor for airborne concentrations*[1]: $mg/m^3 = 13.71 \times ppm$

1.1.3 *Trade names, technical products and impurities*

Some examples of trade names are: Agreflan; Agriflan 24; Elancolan; L 36352; Lilly 36,352; Nitran; Nitran K; Olitref; Super-Treflan; Synfloran; Trefanocide; Treflan; Trifloran; Trifluraline; Trikepin; Tristar.

In the USA, trifluralin is available as 94.5-98% active ingredient technical product (US Environmental Protection Agency, 1987). It is available as emulsifiable concentrates, granules and liquid formulations (Anon., 1989; Meister, 1990). In Europe, a soluble concentrate is also available (Royal Society of Chemistry, 1986). In the USSR, trifluralin is available as emulsifiable concentrates and in granules (Izmerov, 1985).

Trifluralin is compatible with most other pesticides and may be combined with both dry and liquid fertilizers (Royal Society of Chemistry, 1989). It is formulated in combination with isoproturon, linuron, napropamide, terbutryne, benefin (benfluralin), metribuzin, bromoxynil octanoate, ioxynil octanoate, trietazine, neburon and alachlor with petroleum distillates (Worthing & Walker, 1987; Anon., 1989).

Technical-grade trifluralin may be contaminated with *N*-nitrosodi-*n*-propylamine (Kello, 1989; see IARC, 1978). This compound is present as a result of a side-reaction between nitrosating agents and di-*n*-propylamine during an amination step in the manufacturing process (West & Day, 1979). In the USA, trifluralin may contain no more than 0.5 ppm (mg/kg) total *N*-nitrosamine (US Environmental Protection Agency, 1987) and in Italy, no more than 0.4 ppm (mg/kg) nitrosamines (Anon., 1990). In the specification of FAO (1988), trifluralin may contain no more than 1 mg/kg.

1.1.4 *Analysis*

Selected methods for the analysis of trifluralin in various matrices are given in Table 1.

Table 1. Methods for the analysis of trifluralin[a]

Sample	Sample preparation	Assay procedure	Limit of detection	Reference
Water	Extract with dichloromethane; isolate extract; dry; concentrate with solvent exchange to methyl *tert*-butyl ether	GC/ECD	0.025 µg/l	US Environmental Protection Agency (1989a)
Crops	Extract with methanol; re-extract into dichloromethane; evaporate; dissolve in hexane; clean-up on Florisil column; evaporate to dryness; dissolve in benzene	GC/ECD	0.005-0.01 ppm (mg/kg)	US Food and Drug Administration (1989)

[1]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mm Hg [101.3 kPa])

Table 1 (contd)

Sample	Sample preparation	Assay procedure	Limit of detection	Reference
Specified vegetables (carrots, green beans, *Brassica* vegetables)	Crops containing BHC, ethion and/or zineb require an extra TLC clean-up procedure. Develop TLC plate; scrap trifluralin region; transfer to a micro column; elute with acetone; evaporate eluate to dryness; dissolve residue in benzene	GC/ECD	< 0.01 ppm (mg/kg)	US Food and Drug Administration (1989)
Dry formulation	Extract with acetone in Soxhlet; evaporate; dilute to volume with acetone	GC/FID	Not reported	Williams (1984)
Liquid formulation	Extract with acetone	GC/FID	Not reported	Association of Official Analytical Chemists (1984)

[a]Abbreviations: BHC, benzene hexachloride; GC/ECD, gas chromatograph/electron capture detector; GC/FID, gas chromatograph/flame ionization detector; TLC, thin-layer chromatography

1.2 Production and use

1.2.1 *Production*

Trifluralin was first registered in 1963 (US Environmental Protection Agency, 1987). It is prepared by reacting di-*n*-propylamine with 2,6-dinitro-4-trifluoromethylchlorobenzene (Izmerov, 1985).

Trifluralin is produced currently in Argentina, Brazil, Guatemala, Hungary, Israel, Italy, Mexico, Spain and the USA (Meister, 1990). According to information supplied by current manufacturers, annual worldwide production is approximately 20 000-25 000 tonnes. Production by two companies (in tonnes) was: 1985, ~19 000; 1980, ~28 000; 1975, ~17 600; 1970, ~4100; 1965, ~1500. A third company produced 11 900 tonnes in 1986-89, 9400 tonnes in 1981-85 and 3200 tonnes in 1978-80.

1.2.2 *Use*

Trifluralin is a selective soil herbicide which acts by entering the seedling in the hypocotyl region and disrupting cell division. It also inhibits root development (Royal Society of Chemistry, 1989).

Trifluralin is used for pre-emergence control of many annual grasses and broad-leaved weeds in *Brassicas*, beans, peas, carrots, parsnips, lettuce, capsicums, tomatoes, artichokes, onions, garlic, vines, strawberries, raspberries, citrus fruit, oilseed rape, groundnuts, soya beans, sunflowers, safflowers, ornamental plants, cotton, sugar beets, sugar-cane and in forestry. It is also used with linuron or isoproturon for control of annual grasses and broad-leaved weeds in winter cereals. Trifluralin is normally applied to soil before planting, but it may be applied after planting of some crops (Royal Society of Chemistry, 1989). Trifluralin plus 2,4-D is used as a post-planting herbicide for transplanted rice (Worthing & Walker, 1987).

In the USA in 1980, 90% of yearly usage of trifluralin (active ingredient) was accounted for by three crops: soya beans, 9700 tonnes; cotton, 2900 tonnes; and sunflowers, 1200 tonnes (Weiler, 1980). Approximately 14-16 thousand tonnes of trifluralin (active ingredient) were used in the USA in 1987 (US Environmental Protection Agency, 1990).

1.3 Occurrence

1.3.1 *Water*

Trifluralin was found in 172 of 2047 surface water samples and in one of 507 groundwater samples in the USA. Residues were found in surface water in seven states in the USA at a concentration (85th percentile) of 0.54 μg/litre. Trifluralin has also been detected in finished drinking-water (US Environmental Protection Agency, 1988).

N-Nitroso-di-*n*-propylamine was not detected in water samples from ponds or wells located in or near fields that had been treated with trifluralin at various rates (limit of detection, 0.01 μg/litre) (West & Day, 1979).

1.3.2 *Soil*

In studies carried out anaerobically in the dark at 25°C, trifluralin at 5 ppm (mg/kg) degraded rapidly in a non-sterile silt loam soil, and < 1% of the applied material was detected after 20 days. Autoclaving and flooding of the soil decreased the rate of degradation. Under aerobic conditions, degradation was slower, with 15% of the trifluralin lost after 20 days (Parr & Smith, 1973).

^{14}C-Trifluralin applied at 1.1 kg/ha was relatively immobile in sand, sandy loam, silt, loam and clay loam columns (30 cm) eluted with 60 cm of water. More than 90% of the applied radiolabel remained in the top 0-10 cm segment (US Environmental Protection Agency, 1988).

In the field, ^{14}C-trifluralin (99% pure) applied at a rate of 0.84-6.72 kg/ha dissipated in the top 0-0.5-cm layer of a silt loam soil, with 14, 4 and 1.5% of the amount applied remaining after 1, 2 and 3 years, respectively. Some 30 minor degradation products were identified; none represented more than 2.8% of the amount applied. In a medium loam soil, trifluralin (4 lb/gal [7 kg/litre] emulsifiable concentrate) applied at 0.75 and 1.5 lb/acre [0.85 and 1.7 kg/ha] degraded, with 20 and 32%, respectively, remaining after 120 days. Trifluralin (7 kg/litre emulsifiable concentrate) applied to a sandy loam soil at 1.0 lb active ingredient/acre [1.1 kg/ha] had a half-time of 2-4 months (US Environmental Protection Agency, 1988).

Trifluralin was detected in 12% of soil samples taken from 15 states in the USA at levels ranging from 0.08 to 0.24 ppm (mg/kg). The areas from which the samples were taken were considered to use pesticides regularly according to available records (Stevens *et al.*, 1970). Trifluralin residues were also detected in 3.5% of 1729 agricultural soil samples tested in 1969 in the USA (Wiersma *et al.*, 1972). α,α,α-Trifluorotoluene-3,4,5-triamine, a degradation product of trifluralin, appeared to be a key compound in the formation of soil-bound residues (Golab *et al.*, 1979).

Maximal seasonal losses of trifluralin applied for three consecutive years at 1.4 kg/ha were less than 0.05% in the run-off (water/sediment suspensions) from silty clay loam field

plots planted with cotton or soya beans under a wide range of rainfall (0.3-13 cm) (Willis *et al.*, 1975).

1.3.3 *Food*

As part of the national surveillence programme in Canada, 1344 food samples were analysed for trifluralin in the period 1984-89. Residues were detected in carrots at 0.05-0.3 mg/kg in seven of 138 samples. No residue was detected in fruit, other vegetables or maize (Government of Canada, 1990).

Residues of volatile nitrosamines (*N*-nitrosodimethylamine, *N*-nitrosodi-*n*-propylamine or *N*-butyl-*N*-ethyl-*N*-nitrosamine) were not detected in crops and plants from fields treated with trifluralin at 0.56-2.2 kg/ha (limit of detection 0.2 ppb [μg/kg]) (West & Day, 1979).

1.3.4 *Occupational exposure*

Application of trifluralin containing 3.5-6.4 ppm (mg/kg) *N*-nitroso-di-*n*-propylamine at a rate of 0.69-2 lb/acre [0.78-2.27 kg/ha] resulted in average air concentrations of < 0.001-0.015 μg/m^3 of the nitrosamine and 0.12-37.3 μg/m^3 trifluralin (Day *et al.*, 1982).

1.4 Regulations and guidelines

WHO (1987) recommended a drinking-water guideline level of 170 μg/litre for trifluralin. In the USSR, the maximal allowable concentration in water of open basins is 860 μg/litre and that in basins used for fish-breeding purposes, 0.3 μg/litre (Izmerov, 1985).

The tolerance established in the USA for residues of trifluralin in peppermint oil and spearmint oil is 2 ppm (mg/litre) (US Environmental Protection Agency, 1989c). National pesticide residue limits for trifluralin in foods are presented in Table 2.

Table 2. National pesticide residue limits for trifluralin in foods[a]

Country	Residue limit (mg/kg)	Commodities
Australia	0.5	Carrots
	0.05[b]	Adzuki beans, all other vegetables, cereal grains, chickpeas, cowpeas, eggs, faba beans, fruit, lablab, lupins, meat, milk, milk products, mung beans, oilseeds, peanuts, poultry meat, sugar-cane
Austria	3.0	Cauliflower
	1.0	Carrots
	0.1	Cabbage, oilseeds, sweet red/green peppers, tomatoes
	0.05	Other
Belgium	0.05	Carrots, tomatoes, onions, artichokes, cabbages and related vegetables
	0.01	Grains
	0 (0.01)[c]	Other
Brazil	0.05[d]	Carrots, garlic, onions, citrus fruit, *Brassicas*, eggplant, okra, peppers, tomatoes, field beans, string beans, manioc, oilseeds, coffee beans
Canada	0.5	Carrots
	Negligible	Asparagus, barley, cole crops, crambe, beans, flax, herbs, kale, lentils, mustard seed, peas, peppers, rapeseed (canola oil), rye, safflower (oil), sainfoin forage (meat, milk and eggs), Saskatoon berries, strawberries, soya beans, sunflower, tomatoes, triticale, turnips (rutabagas), wheat

Table 2 (contd)

Country	Residue limit (mg/kg)	Commodities
France	0.05	Carrots, tomatoes, onions, artichokes, cabbage
Germany	3	Cauliflower
	1.0	Carrots
	0.5	Turnips, rutabagas
	0.1	Other vegetable foodstuffs
Hungary	0.1	Crops and food
Italy	0.15	Carrots, oilseeds
	0.05	Citrus fruit, drupes, apples, pears, strawberries, grapes, garden vegetables (except carrots), potatoes, sugar beets, mint
	0.01	Wheat, barley, rye, rice
Japan	0.2	Carrots
	0.01	Rice, oats and other minor cereals, fruit, vegetables (except carrots), potatoes, etc., pulses, tea
Kenya	1.0	Carrots
	0.5	Citrus fruit, cottonseed, cucurbits, fruiting vegetables, grapes, hops, leafy vegetables, nuts, peanuts, root crop vegetables (except carrots), safflower seed, seed and pod vegetables, stone fruits, sugar-cane, sunflower seed, wheat grain
Mexico	1.0	Carrots
	0.2[e]	Alfalfa (hay)
	0.05[e]	Cotton (seed), peanuts, sugar cane, citrus fruit, celery, eggplant, broccoli, wheat, grapes, nuts, squash, safflower seed, chili peppers, cabbage, asparagus, spinach, lettuce, tomato, maize (forage), cucumber, watermelon
Netherlands	0.01[f]	All cereals
	0 (0.01)[g]	Other
Spain	1.0	Carrots
	0.05	Other plant products
Switzerland	0.05	Cereals, rapeseed, tomatoes, cabbages, peas
USA[h]	2	Mung bean sprouts
	1.0	Carrots
	0.2[e]	Alfalfa, hay
	0.1	Peanut (hulls)
	0.05[e]	Asparagus, barley (fodder, forage, hay and straw), citrus fruit, maize grain (excluding popcorn); maize (grain forage and fodder, excluding popcorn), cottonseed, cucurbits, flax seed and straw, grain crops (excluding fresh maize and rice grain), grapes, hops, legume forage, nuts, peanuts, peppermint hay, rape (seed and straw), safflower seed, sorghum (fodder and forage), spearmint hay, stone fruit, sugar-cane, sunflower seeds, upland cress, vegetables (fruiting, leafy, root excluding carrots, seed and pod), wheat (grain and straw)

Table 2 (contd)

Country	Residue limit (mg/kg)	Commodities
USSR[i]	0.05	Vegetables

[a]From Health and Welfare Canada (1990)
[b]At or about the limit of analytical determination
[c]The figure in parentheses is the lower limit for determining residues in the corresponding product according to the standard method of analysis.
[d]Provisional
[e]Tolerance for negligible residues
[f]A pesticide may be used on an eating or drinking ware or raw material without a demonstrable residue remaining. The value listed is considered to be the highest concentration at which this requirement is deemed to have been met.
[g]Residues shall be absent; the value in parentheses is the highest concentration at which this requirement is still deemed to have been met.
[h]From US Environmental Protection Agency (1989b)
[i]From Izmerov (1985)

The USSR has established a maximum allowable concentration in workplace air of 3 mg/m^3 (Cook, 1987).

2. Studies of Cancer in Humans

2.1 Case-control studies of lymphatic and haematopoietic neoplasms

In the population-based case-control study of soft-tissue sarcoma, Hodgkin's disease and non-Hodgkin's lymphoma in Kansas, USA (described in detail in the monograph on occupational exposures in spraying and application of insecticides, p. 66), three cases of non-Hodgkin's lymphoma and two controls reported use of trifluralin (odds ratio, 12.5; 95% confidence interval [CI], 1.6-116.1) (Hoar *et al.*, 1986).

In the population-based case-control study of leukaemia among white male farmers in Iowa and Minnesota, USA (Brown *et al.*, 1990; described in detail in the monograph on occupational exposure in spraying and application of insecticides, p. 68), 32 cases and 87 controls reported use of trifluralin (odds ratio, 1.0; 95% CI, 0.7-1.6).

[Exposure to other pesticides could not be excluded in these studies.]

2.2 Case-control study of cancer of the ovary

In the population-based case-control study of ovarian epithelial cancer in northern Italy (described in detail in the monograph on atrazine, p. 449), one case and three controls were farmers and were judged to have been exposed to trifluralin (alone or with linuron) [crude odds ratio, 0.64; 95% CI, 0.1-6.5]. These subjects were also exposed to triazine herbicides (Donna *et al.*, 1989).

3. Studies of Cancer in Experimental Animals

3.1 Oral administration[1]

3.1.1 *Mouse*

Groups of 50 male and 50 female B6C3F$_1$ mice, six weeks old, were fed diets containing various levels of technical-grade trifluralin (purity, > 90%; analysis of the compound three years after completion of the bioassay established the presence of 84-88 ppm (mg/kg) *N*-nitrosodi-*n*-propylamine). Initially, males were fed 2000 or 4000 mg/kg of diet; due to toxicity, administration of the high dose was stopped in week 57 of the study for one week, followed by dietary administration for four weeks at the previous concentration. This cyclic administration was continued for 22 weeks. In females, the initial concentrations were 4500 and 9000 mg/kg of diet for 17 weeks; at week 18, the low and high doses were decreased to 2250 mg/kg and 4500 mg/kg, respectively. In week 57, animals in the high-dose group were administered the compound intermittently for 22 weeks (one week on trifluralin-free diet followed by four weeks on trifluralin-treated diet). From week 79, all treated animals were given control diet for a further 12 weeks. The experiment was terminated at week 90. Twenty mice of each sex were used as matched controls, and a pooled control group (60 females and 60 males) was also available. Survival of high-dose males was lower that than in the other groups: 52% of the low-dose and 55% of the control males survived at least 86 weeks compared to only 34% of the high-dose males. In female mice, survival was 95% controls, 92% low-dose and 62% high-dose mice. In females, an increased incidence of hepatocellular carcinomas was noted: control, 0/20; low-dose, 12/47; and high-dose, 21/44 (Fisher exact test, $p < 0.01$; test for trend, $p < 0.001$); in males the incidence was 4/19 controls, 12/47 low-dose and 9/49 high-dose. Hepatocellular adenomas were observed in 3/47 low-dose females and in 2/47 low-dose males. Alveolar/bronchiolar adenomas or carcinomas of the lung were observed predominantly in female treated mice: 0/19 controls, 7/43 low-dose (Fisher exact test, $p = 0.005$ when compared with pooled controls) and 3/30 high-dose (test for trend; $p < 0.026$ when compared with pooled controls). In females, squamous-cell carcinomas of the forestomach occurred in 4/45 low-dose and in 1/44 high-dose animals; no such tumour was observed in controls or treated male mice; however, a squamous-cell papilloma occurred in 1/47 low-dose males (US National Cancer Institute, 1978). [The Working Group noted that contamination of the trifluralin with *N*-nitrosodi-*n*-propylamine was observed three years after the experiment was performed and that no account was made for differential survival.]

Groups of 80 male and 80 female B6C3F$_1$ mice [age unspecified] received trifluralin (technical-grade, containing less than 0.01 μg/g *N*-nitrosodi-*n*-propylamine) in the diet at levels of 563, 2250 or 4500 mg/kg for 24 months. Groups of 120 mice of each sex received a control diet. Survival at the end of the study ranged from 67 to 80% in the various groups. Body weight gains of high-dose mice were reduced by as much as 30% compared to those of

[1]The Working Group was aware of a completed but as yet unpublished study in rats by oral administration (US Environmental Protection Agency, 1988).

controls during the study. There was no increased incidence of neoplasms at any site in treated mice (Francis *et al.*, 1991).

3.1.2 *Rat*

Groups of 50 male and 50 female Osborne-Mendel rats, six weeks old, were initially given 6500 or 13 000 mg/kg of diet technical-grade trifluralin (purity > 90%; analysis of the compound three years after completion of the bioassay established the presence of 84-88 ppm [mg/kg] of *N*-nitrosodi-*n*-propylamine). In week 22 of the study, the low and high concentrations were decreased to 3250 and 6500 mg/kg of diet, respectively. In week 63, administration of trifluralin to the high-dose female rats was stopped for one week and then resumed for four weeks; high-dose males received the same cyclic pattern beginning in week 69. This intermittent feeding pattern was maintained until week 78. All animals were then given control diet until week 111, when the study was terminated. Fifty rats of each sex were used as matched controls. No difference in survival was observed between treated and control groups. The combined incidence of follicular-cell adenomas and carcinomas of the thyroid in female mice was: control, 1/50; low-dose, 7/50 ($p = 0.028$ Fisher exact test); and high-dose, 0/49. Two haemangiosarcomas of the spleen were observed in the 12 low-dose females in which this organ was examined histologically (US National Cancer Institute, 1978). [The Working Group noted the incomplete histological examination of many organs in the treated groups and that contamination of the trifluralin with *N*-nitrosodi-*n*-propylamine was observed three years after the experiment was performed.]

3.2 Administration by injection

Mouse: Groups of 25 female Swiss mice, seven weeks of age, were given 13 intraperitoneal or subcutaneous injections at three-day intervals of 0.25 ml of Treflan® (44.5% trifluralin, 55.5% unspecified), for a total dose of 0.0065 mg trifluralin. Groups of 50 mice received either intraperitoneal or subcutaneous injections of saline. The animals were kept under observation for seven months from the start of treatment; one animal from each group was killed at each 15-day interval beginning one month after the end of treatment. Lymphomas (one was questionable) were reported in 5/25 mice receiving Treflan by subcutaneous injection and in 3/21 mice receiving Treflan by intraperitoneal injection. A mesothelioma was reported in one treated mouse given a subcutaneous injection and in three mice given intraperitoneal injections. No tumour was observed in control mice (Donna *et al.*, 1981). [The Working Group noted the presence of unspecified material in the Treflan mixture and the very early appearence of lymphomas.]

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Few published data are available on the metabolism and disposition of trifluralin. Rats dosed orally with radiolabelled trifluralin ($^{14}CF_3$ or ^{14}C-*N*-propyl-; 100 mg/kg bw) excreted

80% of the dose in the faeces; only 8% was unchanged trifluralin (Emmerson & Anderson, 1966). Incomplete absorption was indicated by the finding that only 11-14% of the radioactivity was recovered from bile. Extensive nitro-reduction to the corresponding amines occurred, probably as a result of metabolism by the gut microflora. Absorbed trifluralin was extensively metabolized, primarily by *N*-dealkylation and nitro-reduction, and then excreted in the urine. The extent of *N*-dealkylation was indicated by the fact that approximately 20% of the dose was recovered from expired air after administration of the ^{14}C-propyl compound. [The Working Group noted that the analytical methods used in this study would have been inadequate to determine the presence of side-chain hydroxylated or benzimidazole metabolites, which have been formed by rat liver microsomes *in vitro* (Nelson *et al.*, 1977).]

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Trifluralin has a relatively low acute toxicity in experimental animals (Worth, 1970; Ben-Dyke *et al.*, 1970; Ladonin *et al.*, 1980; Gaines & Linder, 1986). Acute oral LD_{50} values were 3700-10 000 mg/kg bw in rodents and 2000 mg/kg bw in rabbits, dogs and hens. Trifluralin did not appreciably irritate skin.

In a carcinogenesis bioassay (see section 3), no remarkable non-neoplastic toxicity was reported in rats or mice, other than reduced growth and a low incidence of forestomach acanthosis and hyperkeratosis in mice (US National Cancer Institute, 1978). [The Working Group noted that the technical-grade trifluralin used was later found to be contaminated with *N*-nitrosodi-*n*-propylamine at 84-88 ppm [mg/kg].] The report of Francis *et al.* (1991) of a study in mice using technical-grade trifluralin that was not contaminated with *N*-nitrosodi-*n*-propylamine confirmed the effects on growth and also revealed progressive glomerulonephritis in female mice. Increases in the blood level of urea nitrogen and the serum level of alkaline phosphatase and decreased erythrocyte and leukocyte counts were reported to be related to treatment in animals of each sex.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Administration of 1 g/kg bw trifluralin per day by gavage to pregnant CD-1 mice on days 6-15 of gestation resulted in a significant reduction in the number of live litters and an increased rate of stillborns and of pups with pathological conditions (runts, haemorrhages on the snount, tail or feet, paralysed hind limbs, defective righting reflex and narrow pelvises). Pups were allowed to be delivered, and 88 different skeletal variants were assessed upon sacrifice at two months of age. In the trifluralin-treated group, 12/88 of these skeletal

variants increased in frequency. The most obvious was the occurrence of 14 ribs, parted frontals, an undoubled foramen ovale and accessory foramina in the cervical vertebrae. These animals appeared normal in physical conformation. Three of the 25 treated mothers died (Beck, 1981).

Application of trifluralin to fertile mallard eggs, by immersing them for 30 sec in an aqueous solution, resulted in embryonic death at exposure levels calculated to be 0.8 times that expected after usual application in the field, i.e., 1.6 lb/acre (1.8 kg/ha). Exposure at this level also reduced growth and increased the rate of bill malformation and of stuntedness in the embryos (Hoffman & Albers, 1984).

4.4 Genetic and related effects (see also Table 3 and Appendices 1 and 2)

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

Trifluralin did not induce mutation in bacteria, in *Drosophila melanogaster* or in cultured mouse lymphoma cells at the *tk* locus. In a single report, chlorophyll mutation was induced in *Zea mays*. Recombination was not induced in *Aspergillus nidulans* or *Saccharomyces cerevisiae*. Aneuploidy was induced in *Neurospora crassa* and *Hordeum vulgare*, but evidence was equivocal in *Sordaria brevicollis* and conflicting in *D. melanogaster*.

DNA repair was not induced in cultured human cells. In a single study, sister chromatid exchange was weakly induced in cultured human lymphocytes.

Chromosomal aberrations were induced by trifluralin in various plant species but not in cultured hamster CHO cells. Equivocal results were obtained in cultured human lymphocytes. In the study in which aberrations were seen, the damage may have been secondary to interference with the mitotic spindle (Donna *et al.*, 1981).

In a single study, sister chromatid exchange was not induced in Chinese hamster bone-marrow cells *in vivo*.

Conflicting evidence was obtained for the induction of aberrations in mouse bone marrow, but consistent reports are available of chromosomal aberration in mouse embryos and male germ-line cells. Dominant lethal mutations were observed in mice. [The Working Group noted that the studies in which effects were seen originated from one laboratory and were performed with a commercial formulation containing 26% trifluralin; other components or impurities were not mentioned.]

Trifluralin metabolites induced chromosomal aberrations in cultured human lymphocytes and in mouse bone-marrow cells *in vivo* (Pilinskaya, 1987).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Trifluralin is a selective pre-emergence herbicide used for the control of annual grasses and certain broadleaf weeds. It was first registered for use in 1963.

Table 3. Genetic and related effects of trifluralin

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
BPF, Bacteriophage, forward mutation	–	0	25.0000	Andersen *et al.* (1972)
BPR, Bacteriophage, reverse mutation	–	0	20.0000	Andersen *et al.* (1972)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	US National Technical Information Service, Environmental Protection Agency (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	250.0000	Benigni *et al.* (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	167.0000	Mortelmans *et al.* (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	400.0000	Garriott *et al.* (1991)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500.0000	US National Technical Information Service, Environmental Protection Agency (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	250.0000	Benigni *et al.* (1982)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	167.0000	Mortelmans *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	400.0000	Garriott *et al.* (1991)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500.0000	US National Technical Information Service, Environmental Protection Agency (1977)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	250.0000	Benigni *et al.* (1982)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	167.0000	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	400.0000	Garriott *et al.* (1991)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500.0000	US National Technical Information Service, Environmental Protection Agency (1977)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	400.0000	Garriott *et al.* (1990)

Table 3 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA9, *Salmonella typhimurium* TA 98, reverse mutation	–	–	250.0000	Benigni *et al.* (1982)
SA9, *Salmonella typhimurium* TA 98, reverse mutation	–	–	167.0000	Mortelmans *et al.* (1986)
SA9, *Salmonella typhimurium* TA 98, reverse mutation	–	–	400.0000	Garriott *et al.* (1990)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	500.0000	US National Technical Information Service, Environmental Protection Agency (1977)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	2500.0000	Moriya *et al.* (1983)
SCH, *Saccharomyces cerevisiae*, D3 homozygosis by recombination	–	–	50000.0000	US National Technical Information Service, Environmental Protection Agency (1977)
ANG, *Aspergillus nidulans*, mitotic recombination	(+)	0	100.0000	Carere & Morpurgo (1981)
ANG, *Aspergillus nidulans*, mitotic recombination	+[c]	0	100.0000	Benigni *et al.* (1982)
ANN, *Aspergillus nidulans*, nondisjunction	–	0	10000.0000	Carere & Morpurgo (1981)
NCN, *Neurospora crassa*, aneuploidy	+	0	1.0000	Griffiths (1979)
SCN, *Saccharomyces cerevisiae*, chromosome loss (aneuploidy)	–	0	250.0000	Whittakeer *et al.* (1990)
*, *Sordaria brevicollis*, aneuploidy	(+)	0	50.0000	Bond & McMillan (1979)
TSI, *Tradescantia paludosa*, micronuclei	?	0	178.0000[d]	Ma *et al.* (1984)
ACC, *Allium cepa*, chromosomal aberrations	+	0	5.0000[d]	Kabarity & Nahas (1979)
HSC, *Hordeum vulgare*, chromosomal aberrations	+	0	40.0000	Oku (1976)
PLC, *Gossypium hirsutum*, chromosomal aberrations	+	0	1.0000	Hess & Bayer
PLC, *Zea meys*, chlorophyll mutations	+	0	0.0000[d]	Lapina *et al.* (1984)
PLC, *Zea meys*, chromosomal aberrations	+	0	0.0000[d]	Grigorenko *et al.* (1986)
VFC, *Vicia faba*, chromosomal aberrations	+	0	90.0000[d]	Wu (1972)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	–	0	100.0000	Murnik (1978) (Abstract)

Table 3 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	–[e]	0	30.0000 feeding	Yoon *et al.* (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	–	0	400.0000 injection	Yoon *et al.* (1985)
DMN, *Drosophila melanogaster*, aneuploidy	+	0	100.0000	Murnik (1978) (abstract)
DMN, *Drosophila melanogaster*, aneuploidy	–	0	400.0000	Foureman (1988)
G51, Gene mutation mouse lymphoma, L5178Y	–	–	20.0000	Garriott *et al.* (1990)
CIC, Chromosomal aberrations, Chinese hamster CHO cells *in vitro*	–	–	50.0000	Garriott *et al.* (1990)
UHF, Unscheduled DNA synthesis, human lung fibroblasts WI38 *in vitro*	–	–	335.0000	US National Technical Information Service, Environmental Protection Agency (1977)
UHF, Unscheduled DNA synthesis, EUE cells *in vitro*	–	0	0.0000	Carere & Morpurgo (1981)
UHF, Unscheduled DNA synthesis, EUE cells *in vitro*	–	0	100.0000	Benigni *et al.* (1984)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	(+)	0	0.0000	Ghiazza *et al.* (1984)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	(+)	0	0.0000[d]	Donna *et al.* (1981)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–[e]	0	40.0000	Pilinskaya (1987)
SVA, Sister chromatid exchange, Chinese hamster cells *in vivo*	–	0	500.0000	Garriott *et al.* (1987)
CBA, Chromosomal aberrations, mouse bone marrow *in vivo*	+	0	52.0000 × 1 i.p.[f]	Nehez *et al.* (1979)
CBA, Chromosomal aberrations, mouse bone marrow *in vivo*	–[e]	0	1000.0000	Pilinskaya (1987)
CGC, Chromosomal aberrations, mouse spermatogonia/ spermatocytes	+	0	52.0000 × 1 i.p.[f]	Nehez *et al.* (1980)

Table 3 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CGC, Chromosomal aberrations, mouse spermatogonia/ spermatocytes	+	0	1.6000 × 10 i.p.[f]	Nehez *et al.* (1982)
*Chromosomal aberrations, mouse embryos (males treated *in vivo*)	+	0	52.0000 × 1 i.p.[f]	Nehez *et al.* (1980)
DLM, Dominant lethal test, mouse	+	0	52.0000 × 1 i.p.[f]	Nehez *et al.* (1980)

*Not displayed on profile

[a] +, positive; (+), weakly positive; –, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)

[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

[c] Technical grade, +; pure, sample, –

[d] Treflan (44.5% trifluralin) tested; dose represents concentration of trifluralin

[e] The metabolites 2,6-dinitro-4-(trifluoro)aniline and 2,6-diamino-4-(trifluoro)aniline gave positive results

[f] Olitref (26% trifluralin) tested; dose represents concentration of trifluralin

Trifluralin has been formulated as emulsifiable concentrates, granules and liquids.

Exposure to trifluralin may occur during its production and application and, at much lower levels, from consumption of residues in food and water.

N-Nitrosodi-*n*-propylamine has been detected in technical trifluralin, and levels of nitrosamines in trifluralin have been restricted in some countries.

5.2 Carcinogenicity in humans

Use of trifluralin was associated with an increased risk for non-Hodgkin's lymphoma in a study in the USA. A study of ovarian cancer in Italy did not suggest an association with exposure to trifluralin. Both results were based on small numbers of exposed subjects. A larger US study showed no association with the occurrence of leukaemia.

5.3 Carcinogenicity in experimental animals

One technical grade of trifluralin (possibly contaminated with *N*-nitrosodi-*n*-propylamine) was tested for carcinogenicity in mice and rats by administration in the diet. In female mice, it induced an increased incidence of hepatocellular carcinomas; in the same study, an increase in the incidence of lung adenomas or carcinomas was observed in females. An increased incidence of squamous-cell carcinomas of the forestomach was noted in female mice at the lower but not at the higher dose. In rats, an increase in the combined incidence of follicular-cell adenomas and carcinomas of the thyroid was noted at the lower but not at the higher dose in females.

Another preparation of trifluralin was tested for carcinogenicity in mice by administration in the diet. No increase in tumour incidence was observed.

5.4 Other relevant data

In a single study, trifluralin was embryolethal and increased the incidence of skeletal variants in mice at doses that caused some maternal toxicity.

No data were available on the genetic and related effects of trifluralin in humans.

A commercial trifluralin formulation induced chromosomal aberrations in bone-marrow, embryonal cells and the male germ line in mice. Chromosomal aberrations were also induced in plants. Aneuploidy was induced in several lower eukaryotes. There was little evidence for the induction of gene mutation in any test system.

5.5. Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of trifluralin.

There is *limited evidence* in experimental animals for the carcinogenicity of technical-grade trifluralin.

Overall evaluation

Trifluralin *is not classifiable as to its carcinogenicity to humans (Group 3).*

---

[1]For definition of the italicized terms, see Preamble, pp. 26-28.

6. References

Andersen, K.J., Leighty, E.G. & Takahashi, M.K. (1972) Evaluation of herbicides for possible mutagenic properties. *J. agric. Food Chem., 20*, 649-656

Anon. (1989) *Crop Protection Chemicals Reference*, 5th ed., New York, Chemical and Pharmaceutical Press, pp. 1081-1130, 1617-1632

Anon. (1990) Trifluralin. *Gazzetta Ufficiale della Republica Italiana*, Serie Generale no. 78, *24 March*, Art. 4

Beck, S.L. (1981) Assessment of adult skeletons to detect prenatal exposure to 2,4,5-T or trifluralin in mice. *Teratology, 23*, 33-55

Ben-Dyke, R., Sanderson, D.M. & Noakes, D.N. (1970) Acute toxicity data for pesticides (1970) *World Rev. Pest Control, 9*, 119-127

Benigni, R., Bignami, M., Conti, L., Crebelli, R., Dogliotti, E., Falcone, E. & Carere, A. (1982) In vitro mutational studies with trifluralin and trifluorotoluene derivatives. *Ann. Ist. super. Sanità, 18*, 123-126

Bond, D.J. & McMillan, L. (1979) Meiotic aneuploidy: its origins and induction following chemical treatment in *Sordaria brevicollis*. *Environ. Health Perspect., 31*, 67-74

Brown, L.M., Blair, A., Gibson, R., Everett, G.D., Cantor, K.P., Schuman, L.M., Burmeister, L.F., Van Lier, S.F. & Dick, F. (1990) Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. *Cancer Res., 50*, 6585-6591

Budavari, S., ed. (1989) *The Merck Index*, 11th ed., Rahway, NJ, Merck & Co., p. 1523

Carere, A. & Morpurgo, G. (1981) Comparison of the mutagenic activity of pesticides *in vitro* in various short-term assays. *Progr. Mutat. Res., 2*, 87-104

Cook, W.A., ed. (1987) *Occupational Exposure Limits—Worldwide*, Washington DC, American Industrial Hygiene Association, p. 222

Day, E.W., Jr, Saunders, D.G., Mosier, J.W., McKinney, E.M., Powers, F.L., Griggs, R.D. & Frank, R. (1982) Estimation of inhalation exposure to *N*-nitrosodipropylamine during the application and incorporation of the herbicide trifluralin. *Environ. Sci. Technol., 16*, 131-136

Donna, A., Betta, P.G., Gagliardi, F., Ghiazza, G.F., Gallareto, M. & Gabutto, V. (1981) Preliminary experimental contribution to the study of possible carcinogenic activity of two herbicides containing atrazine-simazine and trifluralin as active principles. *Pathologica, 73*, 707-721

Donna, A., Crosignani, P., Robutti, F., Betta, P.G., Bocca, R., Mariani, N., Ferrario, F., Fissi, R. & Berrino, F. (1989) Triazine herbicides and ovarian epithelial neoplasms. *Scand. J. Work Environ. Health, 15*, 47-53

Emmerson, J.L. & Anderson, R.C. (1966) Metabolism of trifluralin in the rat and dog. *Toxicol. appl. Pharmacol., 9*, 84-97

FAO (1988) *FAO Specifications for Plant Protection Products, Trifluralin*, (AGP-CP/235), Rome

Foureman, P.A. (1988) The TX;Y test for the detection of nondisjunction and chromosome breakage in *Drosophila melanogaster*. II. Results of female exposures. *Mutat. Res., 203*, 309-316

Francis, P.C., Emmerson, J.L., Adams, E.R. & Owen, N.V. (1991) Oncogenicity study of trifluralin in $B6C3F_1$ mice. *Food chem. Toxicol., 29*, 549-555

Gaines, T.B. & Linder, R.E. (1986) Acute toxicity of pesticides in adult and weanling rats. *Fundam. appl. Toxicol., 7*, 299-308

Garriott, M.L., Adams, E.R., Probst, G.S., Emmerson, J.L., Oberly, T.J., Kindig, D.E.F., Neal, S.B., Bewsey, B.J. & Rexroat, M.A. (1991) Genotoxicity studies on the preemergence herbicide trifluralin. *Mutat. Res., 260*, 187-193

Ghiazza, G., Zavarise, G., Lanero, M. & Ferraro, G. (1984) SCE (sister chromatid exchange) induced in chromosomes of human lymphocytes by trifluralin, atrazine and simazine (Ital.). *Boll. Soc. It. Biol. sper., 60*, 2149-2153

Golab, T., Althaus, W.A. & Wooten, H.L. (1979) Fate of [^{14}C] trifluralin in soil. *Agric. Food Chem., 27*, 163-179

Government of Canada (1990) *Report on National Surveillance Data from 1984/85 to 1988/89*, Ottawa

Griffiths, A.J.F. (1979) Neurospora prototroph selection system for studying aneuploid production. *Environ. Health Perspect., 31*, 75-80

Grigorenko, N.V., Fasilchenko, V.F., Merezhinski, Y.G., Morgun, V.V., Logvinenko, V.F. & Sharmankin, S.V. (1986) Cytogenetic activity of a herbicide treflan, and its metabolites as applied to maize (Russ.). *Tsitol. Genet., 20*, 294-298

Health and Welfare Canada (1990) *National Pesticide Residue Limits in Food*, Ottawa, Bureau of Chemical Safety, Food Directorate, Health Protection Branch

Hess, D. & Bayer, D. (1974) The effect of trifluralin on the ultrastructure of dividing cells of the root meristem of cotton (*Gossypium hirsutum* L. 'Acala 4-42'). *J. Cell Sci., 15*, 429-441

Hoar, S.K., Blair, A., Holmes, F.F., Boysen, C.D., Robel, R.J., Hoover, R. & Fraumeni, J.F., Jr (1986) Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *J. Am. med. Assoc., 256*, 1141-1147

Hoffman, D.J. & Albers, P.H. (1984) Evaluation of potential embryotoxicity and teratogenicity of 42 herbicides, insecticides, and petroleum contaminants to mallard eggs. *Arch. environ. Contam. Toxicol., 13*, 15-27

IARC (1978) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 17, *Some* N-*Nitroso Compounds*, Lyon, pp. 177-189

Izmerov, N.F., ed. (1985) *International Register of Potentially Toxic Chemicals. Scientific Reviews of Soviet Literature on Toxicity and Hazards of Chemicals: Trifluralin* (Issue 80), Moscow, Centre of International Projects, United Nations Environment Programme

Kabarity, A. & Nahas, A. (1979) Induction of polyploidy and C-tumours after treating *Allium cepa* root tips with the herbicide 'Treflan'. *Biol. plant., 21*, 253-258

Kello, D. (1989) WHO drinking water quality guidelines for selected herbicides. *Food Addit. Contam., 6* (*Suppl. 1*), S79-S85

Ladonin, V.F., Hassan, A. & Winteringham, F.P.W. (1980) Dinitroaniline herbicides. *Chemosphere, 9*, 67-69

Lapina, T.V., Grigorenko, N.V., Morgun, V.V., Logvinenko, V.F. & Merezhinski, M.G. (1984) Study of mutagenic effect of herbicides Treflan, Ramrod and Banvell-D on a maize (Russ.). *Tsitol. Genet., 18*, 119-122

Leitis, E. & Crosby, D.G. (1974) Photodecomposition of trifluralin. *J. agric. Food Chem., 22*, 842-848

Ma, T.-H., Harris, M.M., Anderson, V.A., Ahmed, I., Mohammad, K., Bare, J.L. & Lin, G. (1984) Tradescantia-micronucleus (Trad-MCN) tests on 140 health-related agents. *Mutat. Res., 138*, 157-167

Meister, R.T., ed. (1990) *Farm Chemicals Handbook '90*, Willoughby, OH, Meister Publishing Company, p. C294

Moriya, M., Ohta, T., Watanabe, K., Miyazawa, T., Kato, K. & Shirazu, Y. (1983) Further mutagenicity studies on pesticides in bacterial reversion assay systems. *Mutat. Res., 116*, 185-216

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B. & Zeiger, E. (1986) *Salmonella* mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ. Mutagenesis, 8* (Suppl. 7), 1-119

Murnik, M.R. (1978) Mutagenicity of the herbicide trifluralin in *Drosophila melanogaster* (Abstract no. 149). *Mutat. Res., 53*, 235-236

Nehéz, M., Páldy, A., Selypes, A., Körösfalvi, M., Lörinczi, I. & Berensci, G. (1979) The mutagenic effect of trifluralin-containing herbicide on mouse bone marrow *in vivo*. *Ecotoxicol. environ. Saf., 3*, 454-457

Nehéz, M., Páldy, A., Selypes, A., Körösfalvi, M., Lörinczi, I. & Berensci, G. (1980) The mutagenic effect of trifluralin-containing herbicide on mouse germ cells *in vivo*. *Ecotoxicol. environ. Saf., 4*, 263-266

Nehéz, M., Selypes, A., Páldy, A., Mazzag, E., Berensci, G. & Jármay, K. (1982) The effects of five weeks treatment with dinitro-o-cresol or trifluralin-containing pesticides in the germ cells of male mice. *J. appl. Toxicol., 2*, 179-180

Nelson, J.O., Kearney, P.C., Plimmer, J.R. & Menzer, R.E. (1977) Metabolism of trifluralin, profluralin and fluchloralin by rat liver microsomes. *Pestic. Biochem. Physiol., 7*, 73-82

Oku, K. (1976) Effect of some herbicides on somatic division in barley (Jpn.). *Kromosomo, II*, 63-68

Parr, J.F. & Smith, S. (1973) Degradation of trifluralin under laboratory conditions and soil anaerobiosis. *Soil Sci., 115*, 55-63

Pilinskaya, M.S.A. (1987) Evaluation of the cytogenetic effect of the herbicide treflan and of a number of its metabolites on mammalian somatic cells (Russ.). *Tsitol. Genet., 21*, 131-135

Royal Society of Chemistry (1986) *European Directory of Agrochemical Products*, Vol. 2, *Herbicides*, Cambridge, pp. 580-586

Royal Society of Chemistry (1989) *The Agrochemicals Handbook* [Dialog Information Services (File 306)], Cambridge

Stevens, L., Collier, C.W. & Woodham, D.W. (1970) Monitoring pesticides in soils from areas of regular, limited and no pesticide use. *Pestic. Monit. J., 4*, 145-166

US Environmental Protection Agency (1975) Infrared spectra of pesticides. In: *Manual of Chemical Methods for Pesticides and Devices*, Arlington, VA, Association of Official Analytical Chemists

US Environmental Protection Agency (1987) *Guidance for the Reregistration of Pesticide Products Containing Trifluralin as the Active Ingredient*, Washington DC

US Environmental Protection Agency (1988) *Trifluralin*, Washington DC, Office of Drinking Water

US Environmental Protection Agency (1989a) Method 508. Revision 3.0. Determination of chlorinated pesticides in water by gas chromatography with an electron capture detector. In: *Methods for the Determination of Organic Compounds in Drinking Water* (EPA Report No. EPA-600/4-88/039; US NTIS PB89-220461), Cincinnati, OH, Environmental Monitoring Systems Laboratory, pp. 171-198

US Environmental Protection Agency (1989b) Trifluralin; tolerances for residues. Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities. *US Code fed. Regul., Title 40*, Part 180.207

US Environmental Protection Agency (1989c) Trifluralin. Tolerances for pesticides in food. *US Code fed. Regul., Title 40*, Part 185.5900

US Environmental Protection Agency (1990) *Pesticides Industry Sales and Usage: 1988 Market Estimates*, Washington DC, Office of Pesticide Programs

US Food and Drug Administration (1989) Trifluralin. In: *Pesticide Analytical Manual*, Vol. II, *Methods Which Detect Multiple Residues*, Washington DC, US Department of Health and Human Services, pp. 1-15

US National Cancer Institute (1978) *Bioassay of Trifluralin for Possible Carcinogenicity* (Technical Report Series No. 34; DHEW Publ. No. (NIH) 78-834), Bethesda, MD

US National Technical Information Service, Environmental Protection Agency (1977) *Evaluation of Selected Pesticides as Chemical Mutagens:* in vitro *and* in vivo *Studies* (EPA-600/1-77-028), Washington DC

US National Technical Information Service, Environmental Protection Agency (1984) In Vitro *and* In Vivo *Mutagenicity Studies of Environmental Chemicals* (EPA-600/1-84-003), Washington DC

Weiler, E. (1980) *Preliminary Quantitative Usage Analysis of Trifluralin*, Washington DC, US Environmental Protection Agency

West, S.D. & Day, E.W., Jr (1979) Determination of volatile nitrosamines in crops and soils treated with dinitroaniline herbicides. *Agric. Food Chem., 27*, 1075-1080

Whittaker, S.G., Zimmermann, F.K., Dicus, B., Piegorsch, W.W., Resnick, M.A. & Fogel, S. (1990) Detection of induced mitotic chromosome loss in *Saccharomyces cerevisiae*—an interlaboratory assessment of 12 chemicals. *Mutat. Res., 241*, 225-242

WHO (1987) *Drinking-water Quality: Guidelines for Selected Herbicides* (Environmental Health Criteria 27), Copenhagen, p. 8

Wiersma, G.B., Tai, H. & Sand, P.F. (1972) Pesticide residue levels in soils FY 1969—National Soils Monitoring Program. *Pestic. Monit. J., 6*, 194-201

Williams, S., ed. (1984) *Official Methods of Analysis of the Association of Official Analytical Chemists*, 14th ed., Washington DC, Association of Official Analytical Chemists, pp. 108-109,

Willis, G.H., Rogers, R.L. & Southwick, L.M. (1975) Losses of diuron, linuron, fenac and trifluralin in surface drainage water. *J. environ. Qual., 4*, 399-402

Worth, H.M. (1970) The toxicological evaluation of benefin and trifluralin. In: Deichmann, W.B., Peñalver, R.A. & Radomski, J.L., eds, *Pesticides Symposia. Inter-American Conferences on Toxicology and Occupational Medicine*, Miami, FL, Halos and Associates, Inc., pp. 263-267

Worthing, C.R. & Walker, S.B., eds (1987) *The Pesticide Manual: A World Compendium*, 8th ed., Thornton Heath, British Crop Protection Council, pp. 832-833

Wu, T.-P. (1972) Some cytological effects of treflan and mitomycin C on root tips of *Vicia faba* L. *Taiwania, 17*, 248-254

Yoon, J.S., Mason, J.M., Valencia, R., Woodruff, R.C. & Zimmering, S. (1985) Chemical mutagenesis testing in *Drosophila*. IV. Results of 45 coded compounds tested for the National Toxicology Program. *Environ. Mutagenesis, 7*, 349-367