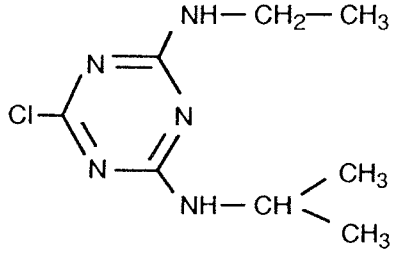
ATRAZINE

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Serv. Reg. No.: 1912-24-9
Replaced CAS Reg. Nos: 11121-31-6, 12040-45-8, 12797-72-7, 39400-72-1, 69771-31-9, 93616-39-8
Chem. Abstr. Name: 6-Chloro-*N*-ethyl-*N'*-(1-methylethyl)-1,3,5-triazine-2,4-diamine
IUPAC Systematic Name: 6-Chloro-N^2-ethyl-N^4-isopropyl-1,3,5-triazine-2,4-diamine
Synonyms: 2-Chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine; 2-chloro-4-(ethylamino)-6-(isopropylamino)triazine; 2-chloro-4-(ethylamino)-6-(isopropylamino)-*s*-triazine



$C_8H_{14}ClN_5$ Mol. wt: 215.69

1.1.2 *Chemical and physical properties*

(*a*) *Description*: Colourless crystals (Royal Society of Chemistry, 1989)

(*b*) *Melting-point*: 175-177°C (Worthing & Walker, 1987)

(*c*) *Spectroscopy data*: Infrared (prism [35712]; grating [13706]) and ultraviolet [16141] spectral data have been reported (Sadtler Research Laboratories, 1980).

(*d*) *Solubility*: Very slightly soluble in water (30 mg/l at 20°C) and hydrocarbon solvents; moderately soluble in ether (1.2%), chloroform (5.2%), methanol (1.8%), ethyl acetate (2.8%), dimethyl sulfoxide (18.3%) and octanol (1%) (Worthing & Walker, 1987; Royal Society of Chemistry, 1989)

(*e*) *Vapour pressure*: 3×10^{-7} mm Hg [0.4×10^{-7} kPa] at 20°C (Royal Society of Chemistry, 1989)

(*f*) *Stability*: Forms salts with acids; stable in slightly acidic or basic media; slowly hydrolysed to inactive hydroxy derivative at 70°C under neutral conditions, more rapidly in alkali or mineral acids (Worthing & Walker, 1987; Royal Society of Chemistry, 1989)

(g) Conversion factor for airborne concentrations[1]: $mg/m^3 = 8.82 \times ppm$

1.1.3 *Trade names, technical products and impurities*

Some common trade names include: A 361; Aatrex; Akticon; Aktikon; Aktinit A; Argezin; Atrataf; Atrazin; ATZ; CET; Chromozin; Cyazin; G 30027; Gesaprim; Herbatoxol; Hungazin; Oleogesaprim; Primatol A; Radazin; Triazine A 1294; Wonuk; Zeapos; Zeazin; Zeazine; Zeopos

In the USA, technical-grade products contain at least 94% atrazine as the sole active ingredient; the percentage of related compounds must also be stated (US Environmental Protection Agency, 1983).

Atrazine is available in the USA as a wettable powder, as water-dispersible granules and in liquid formulations (Anon., 1989a). Formulated atrazine products registered in European countries include, in addition, emulsifiable concentrates, emulsions, suspension concentrates and other granular formulations (Royal Society of Chemistry, 1986).

In the USA, atrazine is also formulated in combination with pendimethalin, metolachlor, cyanazine, *S*-ethyl diisobutylthiocarbamate, *N*,*N*-diallyl-2,2-dichloroacetamide, alachlor, propachlor, bromoxynil octanoate, sodium chlorate, sodium metaborate and the potassium salt of dicamba. Several products contain some ethylene glycol and formaldehyde (see IARC, 1987a) (Anon., 1989a,b).

Combination atrazine products registered in European countries include atrazine with bentazone, bromofenoxim, bromoxynil, butylate, cyanazine, 2,4-D (see IARC, 1987b), dalapon sodium, dicamba, dichlobenil, dichlormid, dichlormidcyanazine, dichlorprop, diuron, *S*-ethyl dipropylthiocarbamate, ethalfluralin, fenteracol, fenuron, linuron, MCPA (see IARC, 1987b), methabenzthiazuron, metolachlor, paraquat dichloride, pendimethalin, petroleum oils, picloram (see monograph, p. 481), prometryne, propachlor, pyridate, simazine (see monograph, p. 495), sodium chlorate, tallow amine ethoxylate, sodium trichloroacetate, terbumeton, terbuthylazine, terbutryn and thiazafluron (Royal Society of Chemistry, 1986).

In the USSR, atrazine is available as a wettable powder, as a paste and in combination with prometryne (Izmerov, 1982).

1.1.4 *Analysis*

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

1.2 Production and use

1.2.1 *Production*

Atrazine was introduced in 1957 (Funari *et al.*, 1988). It is produced through consecutive substitution of ethylamine and isopropylamine on cyanuric chloride in the presence of alkali (Izmerov, 1982).

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[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. Methods for the analysis of atrazine

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection[b]	Reference
Formulation (80% wettable powder)	Dissolve in chloroform; centrifuge	GC/FID	Not reported	Williams (1984)
Drinking-water	Extract in liquid-solid extractor; elute with dichloromethane; concentrate by evaporation	GC/MS	0.1 µg/l (I) 0.3 µg/l (M)	US Environmental Protection Agency (1988)
	Extract with dichloromethane; isolate extract; dry; concentrate with methyl *tert*-butyl ether	GC/NPD	0.13 µg/l (estimated detection limit)	US Environmental Protection Agency (1989a)
	Extract with hexane; inject extract	GC/ECD	2.4 µg/l	US Environmental Protection Agency (1989b)
Forage (all crops)	Extract with chloroform (green forage) or acetonitrile:water (9:1) (dry forage); partition with dichloromethane (dry forage); evaporate to dryness; partition with hexane and acetonitrile; clean-up on alumina column (for all forages)	GC/MCD	0.05-0.1 ppm	US Food and Drug Administration (1989)

[a]Abbreviations: GC/ECD, gas chromatography/electron capture detection; GC/FID, gas chromatography/flame ionization detection; GC/MCD, gas chromatography/microcoulometric detection; GC/MS, gas chromatography/mass spectrometry; GC/NPD, gas chromatography/nitrogen-phosphorous detection
[b]Abbreviations: (I), ion trap mass spectrometer; (M), magnetic sector mass spectrometer

It is produced currently in Argentina, Israel, Mexico, Switzerland and the USA (Meister, 1990). Production in the USA in 1980 was estimated to be 50 000 tonnes, 10 000 tonnes of which were exported (US Environmental Protection Agency, 1980). The major US producer reported production of 40 000-50 000 tonnes per annum between 1981 and 1989.

1.2.2 *Use*

Worldwide, atrazine has been one of the most heavily used herbicides over the past 30 years. It is a selective pre- and early post-emergent herbicide (Worthing & Walker, 1987), which acts mainly through root absorption to control many annual broadleaf and grass weeds. The most important use is as a selective herbicide on maize; other crops include sorghum, sugar-cane and pineapple. It is used in heavier doses for non-selective residual control of most annual and many perennial broadleaf and grass weeds in non-crop areas (Royal Society of Chemistry, 1986, 1989). Atrazine is also used on turf for fairways, lawns, sod production and similar areas and on established conifers prior to or after transplanting (Anon., 1989b).

In the USA in 1980, use of atrazine (active ingredient) was as follows (tonnes): maize, 32 000–36 000; sorghum, 4100–5500; sugar-cane, 340–570; sweet maize, 270–360; soya beans, 180–270; wheat, 180–270; cotton, 50–70; and other crops, 90–180 (US Environmental

Protection Agency, 1980). Approximately 34–45 thousand tonnes of atrazine (active ingredient) were used in the USA in 1987 (US Environmental Protection Agency, 1990).

1.3 Occurrence

1.3.1 *Water*

Atrazine has been found in surface water and in groundwater due to its mobility in soil. It is relatively stable in aquatic environments (half-time measured in months) but is degraded by photolysis (US Environmental Protection Agency, 1988).

A monitoring study of Mississippi River water (USA) indicated the presence of atrazine residues at a maximum level of 17 μg/l. Residues were detected throughout the year, with the highest concentrations in June and July (US Environmental Protection Agency, 1988).

Triazine herbicide residues were monitored in central European streams by methods with a limit of detection usually of 0.4 mg/m^3. Residues were found in 80% of samples at below 0.4 mg/m^3, in 14% at 0.4-1 mg/m^3, in 6% at 1-10 mg/m^3 and in 0.3% at levels higher than 10 mg/m^3. Detectable residues consisted mainly of atrazine from downstream sampling sites and mainly peaked during June (Hörmann *et al.*, 1979).

Atrazine was found in 4123 of 10 942 surface water samples in the USA and in 343 of 3208 groundwater samples. The 85th percentile of the residues in the positive samples was 2.3 μg/l in surface water and 1.9 μg/l in groundwater, with maximum concentrations of 2.3 mg/l and 0.7 mg/l, respectively. Atrazine was found in the surface water of 31 states and in groundwater in 13 states in the USA (US Environmental Protection Agency, 1988).

Some 600 000 kg of atrazine are used annually on maize, which is grown extensively in the Lombardy area of Italy. Groundwater from almost 3000 wells was analysed for atrazine residues in 1986: of 2005 public wells, 29 had levels greater than 1.0 μg/l, 281 wells had levels > 0.1-1.0 μg/l, the remaining wells having < 0.1 μg/l. Of the private wells, 61 had levels > 1.0 μg/l, 536 in the range 0.1–1.0 μg/l and the remainder, < 0.1 μg/l. The soil type is thought to play an important role in the contamination of groundwater by atrazine (Funari *et al.*, 1988).

Atrazine residues have also been reported in groundwater in Pennsylvania, Iowa, Nebraska, Wisconsin and Maryland (USA); typical levels ranged from 0.3 to 3 μg/l (Cohen *et al.*, 1986).

1.3.2 *Soil*

Atrazine is degraded in soil by photolysis and microbial processes; the products are dealkylated metabolites, hydroxyatrazine and nonextractable residues. Atrazine and its dealkylated metabolites are relatively mobile, whereas hydroxyatrazine is not.

A study of aerobic soil metabolism in Lakeland sandy loam, Hagerstown silty clay loam and Wehadkee silt loam soils showed conversion of atrazine to hydroxyatrazine after eight weeks to be 38%, 40% and 47%, respectively (Harris, 1967).

The half-time of atrazine in soil ranged from 20 to 101 days. In California, Minnesota and Tennessee (USA) soils, no leaching of atrazine or of metabolites was observed below 15-30.5 cm of soil. The water-holding capacity of a soil is one factor that affects the rate of degradation of atrazine (US Environmental Protection Agency, 1988). For a sandy soil with

4%, 35% and 70% water-holding capacity, the half-times were 151, 37 and 36 days, respectively (Hurle & Kibler, 1976).

In a Mississippi (USA) field study, atrazine in silt loam soil had a half-time of less than 30 days. In loam-to-silt loam soil in Minnesota, phytotoxic atrazine residues persisted for more than one year and were detected in maximum-depth samples (76-107 cm). Phytotoxic residues persisted in Nebraska silty clay and loam soils for 16 months and were found at depths of 30.5-61 cm (US Environmental Protection Agency, 1988).

Atrazine was also found to persist for up to three years on the sides and bottom of irrigation ditches at the maximal depths sampled (67.5-90 cm; Smith *et al.*, 1975).

1.3.3 *Food*

No residue of atrazine was detected in a Canadian national surveillance study in 1984-89 of 1075 samples, which included fruit, vegetables, grain, dairy products and wine (Government of Canada, 1990).

No atrazine residue (< 0.05 ppm [mg/kg]) was reported in a survey of various foods and feeds over the period 1981-86 in 19 851 samples in the USA (Luke *et al.*, 1988).

1.3.4 *Occupational exposure*

A study was carried out in the USA to determine the exposure of four men when applying 4 litres of atrazine at 4.5 kg active ingredient/ha by boom sprayer towed by an all-terrain vehicle. Dermal exposure was higher during mixing-loading operations than boom operations, with levels of 272 and 3 μg/kg active ingredient, respectively. Respiratory exposure was similar in both operations at 12 μg/kg active ingredient. The specific area of greatest exposure was the forearm during mixing-loading, which had significantly greater concentrations (686 μg/kg active ingredient) than all other sampling areas (Reed *et al.*, 1990).

Exposure to atrazine during its industrial production was assessed by air monitoring and by measuring free atrazine in the urine of four workers. Ambient air concentrations of atrazine during production and bagging varied from 0.07 to 0.53 mg/m^3 (8-h time-weighted average), and skin deposition (whole body) from 4.11 to 10.66 mg/h. Urinary excretion in exposed workers showed a pattern consistent with exposure, with maximal excretion rates of 0.1-0.3 μg/h during the work shift, which decreased to 0.01-0.04 μg/h 12 h after the workshift (Catenacci *et al.*, 1990).

1.4 Regulations and guidelines

WHO (1987) recommended a drinking-water guideline of 2 μg/l for atrazine. The maximum allowable concentration of atrazine in Canadian drinking-water is 2 μg/l (Health and Welfare Canada, 1990).

An acceptable daily intake of 0.7 μg/kg bw was established by the WHO (1987). National and regional limits for residues of atrazine in foods are given in Table 2.

Occupational exposure limits for atrazine are given in Table 3.

Table 2. National and regional pesticide residue limits for atrazine in foods[a]

Country or region	Residue limit (mg/kg)	Commodities
Argentina	0.25	Maize, sorghum, sweet maize
Australia	0.1[b]	Citrus, grapes, maize, pineapples, sorghum, sugar-cane, sweet maize
	0.02[b]	Lupins
	0.01[b]	Meat, milk, milk products, potatoes
Austria	1.0	Asparagus
	0.5	Maize
	0.1	Other foods of vegetable origin
Belgium	0.1	Fruit, vegetables, maize
	0[c] (0.05)	Other
Brazil	1.0	Conifers, rubber plants, sisal
	0.2	Maize, sorghum, pineapple, sugar-cane, avocados, bananas, mangos, peaches, apples, citrus fruit, nuts, tea, cocoa, coffee
	0.1	Black pepper
Canada	Negligible	Blueberries, maize
European Community	0.1	All products
Finland	0.2	General
France	0.1	Fruit, vegetables
	0.05	Maize
Germany	10	Wild mushrooms
	1.0	Sweet maize
	0.5	Maize
	0.1	Other foods of plant origin
Greece	1.0	Fruit and vegetables
Hungary	0.1	All crops
Ireland	0.1	All products
Israel	15	Maize fodder, sorghum fodder
	10	Wheat fodder and straw
	0.25	Fresh maize, maize grain, sorghum grain
	0.02	Eggs, milk, meat, fat and meat by-products
Italy	0.5	Maize, sorghum
	0.1	Fruit, garden vegetables
Japan	0.02	Oats, etc. and minor cereals; fruit, vegetables, sugar-cane
Kenya	0.25	Maize grain, sorghum grain, sugar-cane, wheat grain
	0.02	Eggs, milk, meat, fat and meat products of cattle, goats, hogs, horses, poultry and sheep

Table 2 (contd)

Country or region	Residue limit (mg/kg)	Commodities
Mexico	15	Maize (forage), sorghum (forage)
	10	Pineapple (forage)
	5	Wheat (straw)
	0.25	Maize (fresh and grain), pineapple, sorghum (grain), sugar-cane, wheat (grain)
Netherlands	0.1	Maize, fruit, vegetables
	0[d] (0.05)	Other
Spain	1.0	Maize and sorghum forage
	0.25	Maize and sorghum grain
	0.1	Other plant products
Switzerland	0.5	Asparagus, grapes
	0.1	All crops except asparagus and grapes
Taiwan	0.5	Field crops, tropical fruits
USA[e]	15	Maize forage or fodder (including field maize, sweet maize, popcorn), sorghum fodder and forage, perennial rye grass
	10	Pineapple fodder and forage
	5	Wheat fodder and straw, millet forage, fodder and straw
	0.25	Fresh maize including sweet maize (kernels plus cobs with husks removed), maize grain, macadamia nuts, pineapples, sorghum grain, sugar-cane, sugar-cane fodder and forage, wheat grain
	0.05	Guava
	0.02	Eggs, milk, meat, fat and meat by-products of cattle, goats, hogs, horses, poultry and sheep (negligible residues)
	15[f]	Orchard grass (hay)
	5.0[c]	Proso millet (fodder, forage, straw)
	4.0[c]	Grass (range)
	0.25[f]	Proso millet, grain
Yugoslavia	0.5	Maize
	0.1	Fruit, vegetables
	0.03	Milk and other dairy products (fat basis)
	0.02	Meat and meat products (fat basis), eggs (shell-free basis)

[a]From Health and Welfare Canada (1990)
[b]Maximum residue limit set 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]Residues shall be absent; the value in parentheses is the highest concentration at which this requirement is still deemed to have been met.
[e]From US Environmental Protection Agency (1989c)
[f]Atrazine and its metabolites

Table 3. Occupational exposure limits for atrazine[a]

Country	Year	Concentration (mg/m^3)	Interpretation[b]
Belgium	1987	10	TWA
Denmark	1987	5	TWA
Finland	1987	10	TWA
		20	STEL
Germany	1989	2	TWA
Mexico	1987	10	TWA
Netherlands	1987	10	TWA
Switzerland	1987	2	TWA
United Kingdom	1987	10	TWA
USA	1989		
OSHA		5	TWA
ACGIH		5	Guideline
USSR	1987	2	MAC

[a]From Cook (1987); American Conference of Governmental Industrial Hygienists (ACGIH) (1989); US Occupational Safety and Health Administration (OSHA) (1989)

[b]TWA, time-weighted average; STEL, short-term exposure limit; MAC, maximum allowable concentration

2. Studies of Cancer in Humans

2.1 Case-control studies of cancer of the ovary

According to local agricultural experts, triazines are used as herbicides in all maize cultivation in Alessandria province in northern Italy. About 10 times more atrazine than simazine was sold in the province in 1970, according to the National Institute of Statistics (Donna *et al.*, 1989). In a study of herbicide exposure, all 66 incident cases of histologically confirmed primary ovarian tumours diagnosed between 1 January 1974 and 30 June 1980 in the city hospital of Alessandria were considered. Fifty patients still alive in 1981 were interviewed, and information was obtained from next-of-kin for 10 dead cases; the remaining six cases were untraced. Controls were incident cases of cancer at sites other than the ovary from the same hospital, matched by year of diagnosis, age and district of residence: 135 controls were obtained, of whom 127 were interviewed in 1982. Definite herbicide exposure (i.e., self-reported personal herbicide use) was found for eight cases and no control, and probable exposure (i.e., employment as farmer after 1960 and residence in areas of herbicide use) for 10 cases and 14 controls. The relative risk (RR) for ovarian tumours associated with any herbicide exposure was 4.4 (95% confidence interval [CI], 1.9-16.1). The risk was mostly confined to younger subjects; the RR was 9.1 (95% CI, 3.0-28.3) for women under 55 years of age (Donna *et al.*, 1984).

A second study of a different time period in the same area covered women who were at risk of ovarian cancer, aged 20-69 years, and residents in 143 municipalities in the province.

Cases were histologically confirmed primary malignant epithelial tumours of the ovary diagnosed from 1 July 1980 to 30 June 1985. Two controls per case of the same age were selected randomly from the electoral rolls of the study area. Of the 69 eligible cases, 42 were alive and interviewed; relatives were interviewed for 23 of the 27 dead cases. Of the 150 controls selected, 13 could not be interviewed and 11 were excluded because they had undergone a bilateral oophorectomy. In the calculation of odds ratios, adjustment was made for age, number of live births and use of oral contraceptives. Seven cases and seven controls were defined as having been definitely exposed to triazine (preparation or use of triazine herbicides or worked in maize cultivation with reported use of herbicides), giving an odds ratio of 2.7 (90% CI, 1.0-6.9); the numbers of women who had possibly been exposed (acknowledged personal exposure to herbicides or who had worked in some job possibly involving herbicide exposure or who denied personal use of herbicides but worked in maize cultivation after 1964) were 14 cases and 20 controls, giving an odds ratio of 1.8 (0.9-3.5). These odds ratios were slightly higher for women definitely exposed for > 10 years (2.9; 0.9-8.7) than for women exposed for < 10 years (2.3; 0.4-12.3). The same pattern was seen for women who had possibly been exposed. Among subjects definitely exposed to triazine, 4/7 had used triazines and 3/7 had worked in herbicide-treated fields; the equivalent numbers for the controls were 6/7 and 1/7; 5/7 cases and 5/7 controls were also exposed to other herbicides (Donna *et al.*, 1989). [Although risk estimates were not given for exposure to individual triazines, the Working Group noted that the predominant triazine exposure was probably to atrazine; there may also have been exposure to simazine.]

The interpretation of this study was discussed through correspondence (Crosignani *et al.*, 1990; Minder, 1990). In particular, Minder questioned the exposure classification, because 'definitely exposed' included both use of and exposure in the fields to triazines. The authors said that, since triazines are stable chemicals, they had no reason to suppose that preparation and distribution of these herbicides would have led to cumulative exposure greater than that occurring during work carried out in the fields where herbicides were used.

2.2 Case-control studies of lymphatic and haematopoietic malignancies

Parallel population-based case-control interview studies of leukaemia and non-Hodgkin's lymphoma were conducted in Iowa and Minnesota, USA, during 1981-84. In the study of leukaemia (for detailed description, see the monograph on occupational exposures in spraying and application of insecticides, p. 68), 38 cases and 108 controls reported use of atrazine (odds ratio, 1.0; 95% CI, 0.6-1.5) (Brown *et al.*, 1990). In the study of non-Hodgkin's lymphoma, reported in an abstract, small-cell lymphocytic lymphoma was associated with reported use of atrazine (odds ratio, 1.6), as was farming in general (odds ratio, 1.4) [numbers of exposed persons and confidence intervals not given] (Cantor *et al.*, 1985).

In the case-control study undertaken in Kansas, USA, of soft-tissue sarcoma, Hodgkin's disease and non-Hodgkin's lymphoma, described in detail in the monograph on occupational exposures in spraying and application of insecticides (p. 66), 14 cases of non-Hodgkin's lymphoma and 43 controls reported use of triazines (atrazine was one of six triazines mentioned) (odds ratio, 2.5; 95% CI, 1.2-5.4). The odds ratio for non-Hodgkin's lymphoma associated with exposure to triazines was slightly lower in the absence of exposure to phenoxyacetic acid herbicides and uracils (2.2; 95% CI, 0.4-9.1, based on three cases and

11 controls) (Hoar *et al.*, 1986). [The Working Group noted that no information was given about the proportion of triazines represented by atrazine.]

A population-based case-control study was conducted in eastern Nebraska, USA, to evaluate agricultural risk factors for non-Hodgkin's lymphoma (Hoar Zahm *et al.*, 1990). A detailed description of the study design is given in the monograph on occupational exposures in spraying and application of insecticides (p. 66). In an abstract of this study (Hoar Zahm *et al.*, 1988), self-reported use of atrazine was associated with a slightly increased risk (odds ratio, 1.4; 95% CI, 0.8-2.2). Odds ratios by years of atrazine use were 0.9 for 1-5 years, 0.8 for 6-15 years, 2.0 for 16-20 years and 2.0 for 21 or more years. [Although the description is incomplete, the Working Group assumed that these odds ratio were not adjusted for exposures to other chemicals.]

2.3 Case-control study of cancer of the colon

A case-control study from Kansas, USA (reported as a letter to the Editor of *The Lancet*) covered 57 pathologically confirmed cases of colon cancer diagnosed in 1976-82 and 948 population controls selected by random digit dialling, who were interviewed about farming history. Employment on a farm was associated with a slight increase in the incidence of colon cancer (odds ratio, 1.6; 95% CI, 0.8-3.5). The same was true for reported use of triazine (odds ratio, 1.4; 95% CI, 0.2-7.9, based on two exposed cases and 43 exposed controls) (Hoar *et al.*, 1985). [The Working Group noted that apparently the same controls were used as in the study of Hoar *et al.* (1986) and that no information was given about the proportion of triazines represented by atrazine.]

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

Rat: Groups of 53-56 male and 50-55 female Fischer 344/LATI rats, weighing 150-180 g, were fed pelleted diets containing 0 (control), 500 (low dose) or 1000 mg/kg (high dose) atrazine (purity, 98.9%) during the first eight weeks of the study. Because of toxicity, the high dose was reduced to 750 mg/kg of diet and the low dose to 375 mg/kg of diet for life. The experiment was terminated at week 126, when the four surviving males were killed. Six surviving females were killed at week 123. There was no difference in the survival rates in females of all groups; males in the treated groups lived longer than controls. In males of the high-dose group, there was a significantly increased incidence of mammary gland tumours, all but one of which were benign: males—control, 1/48; low-dose, 1/51; and high-dose, 9/53 ($p < 0.05$) (test for trend; $p < 0.01$). In females, a significantly increased incidence of uterine adenocarcinomas was noted: control, 6/45; low-dose, 8/52; and high-dose, 13/45 ($p < 0.05$ trend test). In addition, a few malignant mesenchymal tumours of the uterus were found only in the treated groups: 2/52 low-dose and 1/45 high-dose group. An increased incidence of tumours of the lymphatic and haematopoietic system was noted in females; the numbers of leukaemias and lymphomas combined were 12/44 control, 16/52 low-dose and 22/51 high-dose ($p < 0.05$, trend test) (Pintér *et al.*, 1990).

3.2 Intraperitoneal administration

Mouse: A group of 30 male Swiss mice, four weeks old, received intraperitoneal injections of 'pure' atrazine every third day for 13 injections (total dose, 0.26 mg/kg bw). Two control groups of 50 mice each were treated with saline or were untreated. The experiment was terminated after 375 days, when all surviving animals were killed. The incidence of lymphomas was 6/30 ($p < 0.001$) in the atrazine-treated group and 1/50 in the untreated controls; no tumour was observed in the saline control group (Donna *et al.*, 1986). [The Working Group noted the incomplete reporting of information on survival.]

A group of 25 female Swiss albino mice, seven weeks old, received up to 13 injections of Fogard S (a formulation containing 25% atrazine and 37.5% simazine) at three-day intervals for a total dose of 0.0065 mg of active principle per mouse. One group of 50 saline controls was available. The animals were kept under observation for seven months from the beginning of the treatment. Serial killings took place from one month after the end of treatment to the end of experiment at 15-day intervals. Lymphomas occurred in 2/20 [$p = 0.02$] treated animals; none occurred in the controls (Donna *et al.*, 1981). [The Working Group noted the short duration of treatment and observation, the incomplete reporting of the study and the report of animal losses due to intercurrent disease.]

3.3 Subcutaneous administration

Mouse: A group of 25 female Swiss albino mice, seven weeks old, received 13 subcutaneous injections of Fogard S (a formulation containing 25% atrazine and 37.5% simazine) at three-day intervals for a total dose of 0.0065 mg active principle per mouse. One group of 50 saline controls was also available. All animals were kept under observation for a period of seven months from the beginning of treatment. One animal from each group was sacrificed every 15 days from one month after the end of treatment to the end of the experiment. Lymphomas occurred in 3/24 treated animals compared with none in the controls [$p < 0.01$]. Another mouse had a mesothelioma of the peritoneum (Donna *et al.*, 1981). [The Working Group noted the short duration of treatment and observation, the incomplete reporting of the study and the report of animal losses due to intercurrent disease.]

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Workers occupationally exposed to atrazine excreted some unchanged atrazine in their urine (Catenacci *et al.*, 1990). The majority of an absorbed dose was recoverable in urine as the fully dealkylated metabolite, 2-chloro-4,6-diamino-*s*-triazine, and the monodealkylated metabolite, 2-chloro-4-amino 6-(ethylamino)-*s*-triazine; practically none of the other monodealkylated metabolite, 2-chloro-4-amino-6-(isopropylamino)-*s*-triazine, was found (Ikonen *et al.*, 1988). Neither study identified any of the mercapturate metabolites found in the urine of rats exposed to atrazine.

4.1.2 *Experimental systems*

Atrazine was well absorbed after oral dosing in rats; 72-h urinary recoveries were similar (66%) after administration of either 30 mg/kg bw uniformly labelled ^{14}C-atrazine in corn oil

(Timchalk *et al.*, 1990) or approximately 1.5 mg/kg bw ^{14}C-[ring]-atrazine in ethanol (Bakke *et al.*, 1972). Moderate, inverse dose-dependent absorption (3-8% adults; 3-10% juveniles) through the skin was demonstrated in Fischer F344 rats (Shah *et al.*, 1987).

In rats, less than 0.1% of an oral radioactive dose was detected in expired air. At 72 h after dosing, the retention of radioactivity in the carcass ranged from 4% (Timchalk *et al.*, 1990) to 16% (Bakke *et al.*, 1972). Relative tissue retentions were: liver, kidney, lung > heart, brain > > muscle, fat (Bakke *et al.*, 1972).

A one-compartment model adequately describes the kinetics of atrazine in the plasma of rats. The plasma concentration peaked 8-10 h after dosing, with an apparent absorption half-time of 2.6 h, and there was mono-exponential elimination with a half-time of 10.8 h. Neither the kinetic characteristics nor dose recoveries were affected by concurrent administration of 60 mg/kg bw tridiphane, a herbicidal synergist in plants which blocks glutathione transferase-mediated conjugation (Timchalk *et al.*, 1990).

N-Dealkylation and conjugation with glutathione are the main metabolic pathways in various species *in vivo* and *in vitro* (Böhme & Bär, 1967; Adams *et al.*, 1990; Timchalk *et al.*, 1990). 2-Chloro-4,6-diamino-1,3,5-triazine is the major urinary metabolite (64-67%) in rats, and mercapturates of the mono- and di-dealkylated products are the other major urinary metabolites (13-14% and 9%, respectively) (Timchalk *et al.*, 1990). Minor metabolic pathways in rats may include alkyl side-chain oxidation (Böhme & Bär, 1967). Oxidative dechlorination to 2-hydroxyatrazine, a metabolite formed in plants, did not occur in rat liver homogenates (Dauterman & Muecke, 1974), despite the fact that Bakke *et al.* (1972) claimed to have found some 2-hydroxyatrazine in rat urine and showed that it was metabolized along similar pathways to atrazine.

N-Nitrosoatrazine is formed from atrazine in acidic aqueous nitrite solutions and by the action of nitrogen oxides at an air:solid interface (Wolfe *et al.*, 1976; Janzowski *et al.*, 1980). *N*-Nitrosoatrazine was hydrolytically stable in aqueous solutions at pH > 4, although it was relatively susceptible to photolysis (Wolfe *et al.*, 1976). While there was virtually no formation of *N*-nitrosoatrazine in acid nitrated soils treated with 2 ppm (mg/kg) atrazine, exogenously added *N*-nitrosoatrazine was found to be relatively immobile in such soil systems and to degrade over a period of several weeks (Kearney *et al.*, 1977).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

The oral LD_{50} of atrazine was reported to be 2000 mg/kg bw in rats (Ben-Dyke *et al.*, 1970) and 672, 737 and 2310 mg/kg bw in adult female, male and weanling male rats, respectively. The dermal LD_{50} was > 2500 mg/kg bw in rats of each sex (Gaines & Linder, 1986).

Administration of atrazine by oral gavage at 100-600 mg/kg bw per day to Wistar rats for seven or 14 days induced both nephrotoxicity and hepatotoxicity (Santa Maria *et al.*, 1986, 1987). Hepatotoxic effects included a dose-related reduction in blood sugar levels and increases in the activity of serum alanine aminotransferase and alkaline phosphatase and in

the level of total serum lipids. Electron micrographs showed degeneration of the smooth endoplasmic reticulum, lipid droplet accumulation and swollen mitochondria (Santa Maria *et al.*, 1987). There was no liver toxicity at the lowest dose tested. Renal toxicity, in the form of a dose-related proteinurea, reduced creatinine clearance and increased urinary electrolyte output, was evident at all dose levels (Santa Maria *et al.*, 1986).

Hormonal imbalances induced by atrazine may be of significance to the interpretation of possible carcinogenic effects in hormonally sensitive tissues. Most work has been directed towards the effects of atrazine on the pituitary–gonadal axis. Steroid hormone metabolism was found to be impaired by atrazine, which inhibits 5-α-steroid reductase in the anterior pituitary of rats (Kniewald *et al.*, 1979). Subsequently, it was shown in male rats that atrazine (at 120 mg/kg bw per day orally for seven days) increased [~ 60-70%] the wet weight of the anterior pituitary and caused hyperaemia and hypertrophy of the chromophobic cells and reductions of 37%, 39% and 46%, respectively, in 5α-steroid reductase, 3α- and 17β-hydroxysteroid dehydrogenase activities *in vivo*. The de-ethylated metabolite was approximately equipotent in reducing 5α-steroid reductase activity after administration *in vivo*. Only 5α-steroid reductase and 17β-hydroxysteroid dehydrogenase were inhibited by either compound in the hypothalamus *in vivo*; deethylatrazine was the more potent inhibitor of these enzymes in the hypothalamus *in vitro* (Babić-Gojmerac *et al.*, 1989). Treatment prenatally with atrazine or de-ethylatrazine (16.6 mg/kg bw subcutaneously) did not alter pituitary metabolism in male rat pups, but atrazine increased 5α-steroid reductase activity in female pups. Treatment pre- and postnatally with atrazine and its metabolite decreased 3α-hydroxysteroid dehydrogenase activity, and atrazine decreased 5α-steroid reductase activity in male pups; both compounds decreased the number of androgen-specific binding sites in the prostate. Neither atrazine nor its metabolite had any effect on female pituitary androgen metabolism (Kniewald *et al.*, 1987). Other studies conducted *in vitro* have demonstrated inhibition of androgen metabolism by atrazine when incubated with rat pituitary homogenates (Kniewald *et al.*, 1979; Babić-Gojmerac *et al.*, 1989).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

In a teratology study, 10, 70 or 700 mg/kg bw technical atrazine were administered by gavage to Charles River rats once a day on gestation days 6-15, and 1, 5 or 75 mg/kg bw was administered by gavage to New Zealand white rabbits on gestation days 7-19. Incomplete ossification of the skeleton increased with the intermediate dose (70 mg/kg bw) and above; other effects on the rat fetus were observed only at maternally toxic doses, in the form of decreased fetal weight (700 mg/kg bw). In rabbits, increased resorption rate, decreased litter size, lowered fetal weight and a higher rate of non-ossification were observed at the high dose (75 mg/kg bw), which was maternally toxic. It was concluded that on a milligram per kilogram basis, pregnant rabbits are more sensitive than pregnant rats and that atrazine is not teratogenic (Infurna *et al.*, 1988).

Embryotoxicity was reported in rats after subcutaneous injection of 1000 or 2000 mg/kg bw atrazine per day on days 3, 6 and 9 of gestation, but not after administration at concentrations of up to 1000 ppm (mg/kg) in the feed from day 1 throughout gestation. Maternal toxicity was not reported (Peters & Cook, 1973).

Application of atrazine to fertile mallard eggs, by immersing them for 30 sec in an aqueous solution, resulted in embryonic death at exposure levels calculated to be more than 67 times that expected after usual application in the field, i.e., more than 400 lb/acre (448 kg/ha) (Hoffman & Albers, 1984).

Perinatal effects on sex steroid metabolism are discussed in section 4.2.2.

4.4 Genetic and related effects (see also Table 4 and Appendices 1 and 2)

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

Atrazine did not induce mutation in bacteriophage, bacteria, *Saccharomyces cerevisiae* or *Nicotiana tabacum*, whereas mutations were induced in *Schizosaccharomyces pombe*, *Aspergillus nidulans* and *Zea mays*; conflicting results were obtained in *Hordeum vulgare*. In *Drosophila melanogaster*, sex-linked recessive lethal mutations were induced in one study but not in another. 6-Thioguanine-resistant mutants were induced in cultured Chinese hamster lung V79 cells, only in the presence of microsomes from potato, and not in the presence of an exogenous metabolic activation system from rat liver.

Gene conversion was not induced in *S. cerevisiae* or *A. nidulans*. Mitotic recombination was not increased by atrazine in *S. cerevisiae*, while conflicting results were obtained in *A. nidulans*. Aneuploidy was induced in *Neurospora crassa*, *A. nidulans* and *D. melanogaster*.

Dominant lethal effects were induced in *D. melanogaster*. Chromosomal aberrations were induced in the majority of plants studied. In cultured rodent or human cells, atrazine did not induce chromosomal aberrations, sister chromatid exchange or unscheduled DNA synthesis.

Atrazine induced ampicillin-resistant mutations in *Escherichia coli* in a mouse host-mediated assay. In mammals *in vivo*, atrazine induced DNA strand breakage in rat stomach, liver and kidney cells, but not in lung cells, following oral dosing. It induced dominant lethal effects in mouse spermatids but did not induce morphological abnormalities in mouse sperm heads.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Atrazine was introduced in 1957. It is now one of the most extensively used herbicides worldwide, with US production of at least 50 000 tonnes per annum since 1980. It is widely used on maize and to a lesser extent on a variety of other crops.

Atrazine has been formulated as wettable powders, granules and liquid formulations.

Table 4. Genetic and related effects of atrazine

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
BPF, Bacteriophage T4, forward mutation	–	0	20.0000	Andersen *et al.* (1972)
BPR, Bacteriophage, reverse mutation	–	0	1000.0000	Andersen *et al.* (1972)
SAF, *Salmonella typhimurium*, forward mutation	–	–	250.0000	Adler (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	50.0000	Lusby *et al.* (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	–	500.0000	Bartsch *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.0000	Ishidate *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	–[c]	15000.0000	Sumner *et al.* (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	Kappas (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	+[c]	0.0000	Means *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	Mersch-Sundermann *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	Zeiger *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	0	1000.0000	Butler & Hoagland (1989)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	–	500.0000	Mersch-Sundermann *et al.* (1988)
SA3, *Salmonella typhimurium* TA1530, reverse mutation (spot test)	–	0	0.0000	Seiler (1973)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500.0000	Simmon *et al.* (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	50.0000	Lusby *et al.* (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500.0000	Kappas (1988)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500.0000	Zeiger *et al.* (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.0000	Ishidate *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500.0000	Kappas (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500.0000	Zeiger *et al.* (1988)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500.0000	Kappas (1988)

Table 4 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500.0000	Zeiger *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	–	2500.0000	Simmon *et al.* (1977)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	50.0000	Lusby *et al.* (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	–	500.0000	Bartsch *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	0.0000	Ishidate *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500.0000	Kappas (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500.0000	Mersch-Sundermann *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	0	1000.0000	Butler & Hoagland (1989)
SAS, *Salmonella typhimurium*, reverse mutation	–	0	0.0000	Andersen *et al.* (1972)
SAS, *Salmonella typhimurium his* G46, reverse mutation (spot test)	–	0	0.0000	Seiler (1973)
SAS, *Salmonella typhimurium* TA1531, reverse mutation (spot test)	–	0	0.0000	Seiler (1973)
SAS, *Salmonella typhimurium* TA1532, reverse mutation (spot test)	–	0	0.0000	Seiler (1973)
SAS, *Salmonella typhimurium* TA1534, reverse mutation (spot test)	–	0	0.0000	Seiler (1973)
SAS, *Salmonella typhimurium*, reverse mutation	–	–	0.0000	Adler (1980)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	0	1000.0000	Butler & Hoagland (1989)
SAS, *Salmonella typhimurium* TM677, reverse mutation	0	–[c]	1000.0000	Sumner *et al.* (1984)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	500.0000	Kappas (1988)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	500.0000	Mersch-Sundermann *et al.* (1988)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	500.0000	Zeiger *et al.* (1988)
SCG, *Saccharomyces cerevisiae*, gene conversion	–	+[c]	10.0000	Plewa & Gentile (1976)
SCG, *Saccharomyces cerevisiae*, gene conversion	–	–	2000.0000	Adler (1980)
SCG, *Saccharomyces cerevisiae*, gene conversion	–	–	4000.0000	de Bertoldi *et al.* (1980)
SCG, *Saccharomyces cerevisiae*, mitotic recombination	–	0	50.0000	Emnova *et al.* (1987)

Table 4 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ANG, *Aspergillus nidulans*, gene conversion	–	0	8000.0000	de Bertoldi *et al.* (1980)
ANG, *Aspergillus nidulans*, mitotic recombination	–	+	0.0000	Adler (1980)
ANG, *Aspergillus nidulans*, mitotic recombination	–	–	1000.0000	Kappas (1988)
SCF, *Saccharomyces cerevisiae*, forward mutation	–	0	50.0000	Emnova *et al.* (1987)
SZR, *Schizosaccharomyces pombe*, reverse mutation	+	0	17.5000	Mathias (1987)
SZR, *Schizosaccharomyces pombe*, reverse mutation	+	+[c]	70.0000	Mathias *et al.* (1989)
ANF, *Aspergillus nidulans*, forward mutation	–	+	2500.0000	Benigni *et al.* (1979)
ANN, *Aspergillus nidulans*, aneuploidy	–	+	2000.0000	Benigni *et al.* (1979)
NCN, *Neurospora crassa*, aneuploidy	+	0	0.0000	Griffiths (1979)
HSM, *Hordeum vulgare*, mutation	+	0	1000.0000	Wuu & Grant (1966)
HSM, *Hordeum vulgare*, mutation	–	0	200.0000	Stroyev (1968)
PLM, *Zea mays*, mutation	+	0	200.0000	Morgun *et al.* (1982)
PLM, *Zea mays*, mutation	+	0	0.0000	Plewa *et al.* (1984)
PLM, *Nicotiana tabacum*, mutation	–	0	0.0000[d]	Bříza (1989)
TSI, *Tradescantia paludosa*, micronuclei	–	0	200.0000	Ma *et al.* (1984)
HSC, *Hordeum vulgare*, chromosomal aberrations	+	0	500.0000 spray	Wuu & Grant (1967a)
HSC, *Hordeum vulgare*, chromosomal aberrations	–	0	2000.0000	Müller *et al.* (1972)
* *Hordeum vulgare*, decrease in chiasma frequency	+	0	1000.0000	Sharma *et al.* (1982)
VFC, *Vicia faba*, chromosomal aberrations	+	0	400.0000	Wuu & Grant (1967b)
VFC, *Vicia faba*, chromosomal aberrations	–	0	200.0000	Müller *et al.* (1972)
PLC, *Sorghum* sp, chromosomal aberrations	+	0	0.0000[d]	Liang & Liang (1972)
PLC, *Sorghum* sp, chromosomal aberrations	–	0	0.0000	Müller *et al.* (1972)
PLC, *Sorghum* sp, chromosomal aberrations	+	0	0.0000	Lee *et al.* (1974)
PLC, *Nigella damascena*, chromosomal aberrations	–	0	320.0000	Mathias (1987)
PLC, *Nigella damascena*, chromosomal aberrations	+	0	40.0000[d]	Mathias (1987)
PLC, *Zea mays*, chromosomal aberrations	–	0	200.0000	Morgun *et al.* (1982)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+	0	100.0000	Murnik & Nash (1977)

Table 4 (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	–	0	2000.0000	Adler (1980)
DML, *Drosophila melanogaster*, dominant lethal mutation	+	0	100.0000	Murnik & Nash (1977)
DMN, *Drosophila melanogaster*, aneuploidy	+	0	100.0000	Murnik & Nash (1977)
G9H, Gene mutation, Chinese hamster lung V79 cells *in vitro*, *hprt* locus	–	–[e]	2000.0000	Adler (1980)
SIC, Sister chromatid exchange, Chinese hamster CHO cells *in vitro*	–	–	2000.0000	Adler (1980)
CIC, Chromosomal aberrations, Chinese hamster CHO cells *in vitro*	–	–	2000.0000	Adler (1980)
CIC, Chromosomal aberrations, Chinese hamster cells *in vitro*	–	0	250.0000	Ishidate (1988)
UHF, Unscheduled DNA synthesis, human EUE cells *in vitro*	–	–[e]	650.0000	Adler (1980)
SHL, Sister chromatid exchanges, human lymphocytes *in vitro*	–	0	0.0000	Ghiazza *et al.* (1984)
HMM, Host-mediated assay, *Escherichia coli* ampr in mouse	+	0	100.0000 × 1 p.o.	Adler (1980)
DVA, DNA strand breaks, rat stomach, liver and kidney *in vivo*	+	0	875.0000 × 1 p.o.	Pino *et al.* (1988)
DVA, DNA strand breaks, rat stomach, liver and kidney *in vivo*	+	0	350.0000 × 15 p.o.	Pino *et al.* (1988)
DVA, DNA strand breaks, rat lung *in vivo*	–	0	875.0000 × 1 p.o.	Pino *et al.* (1988)
DVA, DNA strand breaks, rat lung *in vivo*	–	0	350.0000 × 15 p.o.	Pino *et al.* (1988)
DLM, Dominant lethal mutation, mouse spermatids	(+)	0	1500.0000 × 1 p.o.	Adler (1980)
SPM, Sperm morphology, mouse	–	0	600.0000	Osterloh *et al.* (1983)

*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] Tested with extracts of atrazine-treated *Zea mays*

[d] Commercial pesticide

[e] Positive with potato microsomes at doses up to 3 mM

Exposure can occur during production and application of atrazine and *via* contaminated ground- and surface water. Exposure could also occur from consumption of foods containing residues. Atrazine residues were not detected in large-scale surveys of foods products in Canada and the USA.

5.2 Carcinogenicity in humans

One population-based case-control study in northern Italy found an elevated risk for ovarian cancer in women considered to have been exposed to triazine herbicides. A hospital-based case-control study in the same area found an elevated risk for ovarian tumours among women exposed to herbicides, including triazine herbicides.

A case-control study from Kansas, USA, indicated an association between self-reported use of triazine herbicides and risk for non-Hodgkin's lymphoma. A nonsignificant doubling of the risk was found in the absence of exposure to phenoxyacetic acid herbicides and uracils. In another study in Kansas, USA, in which apparently the same controls were used, self-reported use of triazine herbicides was associated with a slight excess risk of colon cancer, as was employment on a farm in general.

In two case-control studies from Iowa and Minnesota, USA, there was no association between self-reported use of atrazine and leukaemia, whereas a slightly increased risk was suggested for a subgroup of lymphomas.

In a case-control study in Nebraska, USA, a nonsignificant elevation in risk for non-Hodgkin's lymphoma was associated with self-reported use of atrazine. Risks were greater among men with 16 or more years of use than among those with a shorter duration.

These seven studies were considered to provide some evidence for the carcinogenicity of exposure to triazine herbicides. Complex exposures and insufficient reporting made it difficult to evaluate the carcinogenicity of individual triazine herbicides, including atrazine.

5.3 Carcinogenicity in experimental animals

Atrazine was tested for carcinogenicity in one experiment by oral administration to rats, producing increased incidences of mammary tumours (mainly benign) in males and of uterine adenocarcinomas and tumours of the haematopoietic system in females. It was also tested by intraperitoneal administration to mice; it was stated in a preliminary report to have produced an increase in the incidence of lymphomas.

5.4 Other relevant data

Atrazine was embryotoxic and embryolethal but not teratogenic in rats and rabbits when administered at maternally toxic doses.

Atrazine and its de-ethylated metabolite have been shown to alter the activity of some testosterone-metabolizing enzymes in the rat pituitary and hypothalamus, and to decrease hormone-receptor binding in the prostate.

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

Atrazine induced DNA strand breaks in stomach, liver and kidney cells but not lung cells of rats treated orally. Chromosomal aberrations were induced in plants and insects, but not in cultured rodent cells. Aneuploidy was induced in *Drosophila melanogaster* and fungi. Atrazine induced gene mutation in plants, but not in bacteria or cultured rodent cells.

5.5 Evaluation[1]

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

There is *limited evidence* in experimental animals for the carcinogenicity of atrazine.

In making the overall evaluation, the Working Group took into consideration the following supporting evidence. The increased risks for tumours that are known to be associated with hormonal factors, which were observed in studies of both animals and human beings, are consistent with the known effects of atrazine on the hypothalamic–pituitary–gonadal axis.

Overall evaluation

Atrazine *is possibly carcinogenic to humans (Group 2B).*

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

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