ATRAZINE

This substance was considered by a previous working group, in 1990 (IARC, 1991). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 1912-24-9

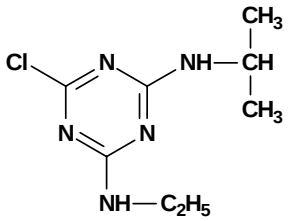
Deleted CAS Reg. Nos: 11121-31-6; 12040-45-8; 12797-72-7; 39400-72-1; 69771-31-9; 93616-39-8

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)triazine; 2-chloro-4-(ethylamino)-6-(isopropylamino)-*s*-triazine; 2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_8H_{14}ClN_5$ Relative molecular mass: 215.69

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless powder (Tomlin, 1994)

(*b*) *Melting-point*: 173°C (Lide, 1997)

(*c*) *Density*: 1.187 g/cm^3 at 20°C (Tomlin, 1994)

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

(*e*) *Solubility*: Slightly soluble in water (33 mg/L at 20°C); soluble in acetone (31 g/L at 25°C), chloroform (35 g/L at 20°C), dichloromethane (28 g/L at 25°C), diethyl

ether (17 g/L at 20°C), ethyl acetate (24 g/L at 25°C), *n*-hexane (0.11 g/L at 25°C), methanol (15 g/L at 25°C), *n*-octanol (10.6 g/L at 25°C) and toluene (6 g/L at 25°C) (Worthing & Walker, 1987; Tomlin, 1994; Budavari, 1996)

(*f*) *Volatility*: Vapour pressure, 0.04 mPa at 20°C (Tomlin, 1994)

(*g*) *Stability*: Forms salts with acids; stable in slightly acidic or basic media; hydrolysed to inactive hydroxy derivative at 70ºC under neutral conditions, more rapidly in alkali or mineral acids (Worthing & Walker, 1987; Tomlin, 1994; Budavari, 1996)

(*h*) *Octanol/water partition coefficient (P)*: log P, 2.61 (Hansch *et al*., 1995)

(*i*) *Conversion factor*: $mg/m^3 = 8.82 \times ppm$

1.1.4 *Technical products and impurities*

Atrazine is commercially available in various forms, including dry flowable, flowable liquid, flowable suspension concentrate, liquid, water-dispersible granular and wettable powder formulations. The purity of technical-grade atrazine ranges from 92 to 97%. The The impurities include dichlorotriazines, tris(alkylamino)triazines and hydroxytriazines (Tomlin, 1994; Oregon State University, 1996; National Registration Authority for Agricultural and Veterinary Chemicals, 1997; Environmental Protection Agency, 1999). The concentration of active ingredient in most atrazine products registered with the United States Environmental Protection Agency is 43, 80 or 90%; the concentration in other atrazine products ranges from 0.58 to 53.5% (Environmental Protection Agency, 1999).

Trade names for atrazine include A 361; Aatrex; Akticon; Aktikon; Aktinit; Argezin; Atranex; Atrataf; Atrazin; Atrazine; ATZ; Azoprim; Cekuzina-T; CET; Chromozin; Cyazin; Fogard; G 30027; Gesaprim; Griffex; Hungazin; Maizina; Mebazine; Oleogesaprim; Oleogesaprim 200; Primatol; Radazin; Triazine A 1294; Vectal; Wonuk; Zeapos; Zeazin; Zeazine (National Toxicology Program, 1991; Tomlin, 1994; Oregon State University, 1996).

Atrazine may be formulated with many other herbicides, including alachlor, acetochlor, ametryn, amitrole, benoxacor, bentazone, bromoxynil, cyanazine, 2,4-D, dicamba potassium salt, dichlobenil, diuron, glyphosate, imazapyr, imazethapyr, metolachlor, pendimethalin, pyridate and simazine. It is also used in mixtures with these and other herbicides for spraying and is also impregnated into fertilizer (Ahrens, 1994; Tomlin, 1994; Novartis, 1999).

1.1.5 *Analysis*

Methods for the analysis of atrazine in various media are presented in Table 1.

1.2 Production and use

1.2.1 *Production*

Cyanuric chloride is reacted with isopropylamine under basic conditions to form 2,4-dichloro-6-isopropylamino-*s*-triazine, which is then reacted with monoethylamine and dilute caustic to form atrazine (Izmerov, 1982).

Table 1. Selected methods for the analysis of atrazine

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Formulations	Dissolve in chloroform; centrifuge	GC/FID	NR	Williams (1984)
Drinking-water	Extract in liquid–solid extractor; elute with ethyl acetate and dichloromethane; concentrate by evaporation	GC/ECD	0.003 µg/L	Environmental Protection Agency (1995a,b) [Methods 508.1 & 525.2]
		GC/MS	0.065 µg/L	
	Extract in liquid–liquid extractor (methyl *tert*-butyl ether or pentane)	GC/ECD	0.082 µg/L (MTBE); 0.099 µg/L (pentane)	Environmental Protection Agency (1995c) [Method 551.1]
	Extract with dichloromethane; isolate; extract; dry; concentrate with methyl *tert*-butyl ether	GC/NPD	0.13 µg/L (estimated)	Environmental Protection Agency (1995d) [Method 507]
	Extract with hexane; inject extract	GC/ECD	2.4 µg/L	Environmental Protection Agency (1995e) [Method 505]
Wastewater	Extract with dichloromethane; dry; exchange to hexane	GC/TBD-N	NR	Spectrum Laboratories (1999) [EPA method 619]
	Extract with dichloromethane (liquid sample); extract with dichloromethane:acetone (1:1) (solid sample); inject directly	GC/NPD	NR	Environmental Protection Agency (1994) [Method 8141A]
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	Food & Drug Administration (1989)

Table 1 (contd)

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Urine	Clean-up sample; wash with water; elute with ethyl acetate; remove water and evaporate to dryness; dissolve in acetone	GC/NPD	0.005 ppm	Cheung (1990)

Abbreviations: GC/ECD, gas chromatography/electron capture detection; GC/FID, gas chromatography/flame ionization detection; GC/FPD, gas chromatography/flame photometric detection; GC/MCD, gas chromatography/microcoulometric detection; GC/MS, gas chromatography/mass spectrometry; GC/NPD, gas chromatography/nitrogen-phosphorous detection; GC/TBD-N, gas chromatography/ thermionic bead detection-nitrogen mode; NR, not reported

Information available in 1995 indicated that atrazine was produced in Brazil, China, Israel, Italy, Romania, South Africa, Switzerland and the United States (Chemical Information Services, 1995). The world production rate is about 70 000 tonnes per year.

1.2.2 *Use*

Atrazine is used in agriculture as a selective pre- and post-emergence herbicide for annual control of grass and broad-leaved weeds. It has been used on asparagus, bananas, citrus groves, coffee, conifer tree crop areas, forestry, fruit orchards, grasslands, grass crops, guavas, macadamia orchards, maize (corn), oil palms, sorghum, sugar cane, pineapples, roses and vines. It has also been used as a soil sterilant for airfields, parking lots and industrial sites and as an algicide in swimming pools. Recently, many of the uses that contribute residues to water have been reduced or eliminated. In the European Union, where a limit of 0.1 μg/L has been set for all pesticide residues in drinking- and groundwater, the use of atrazine-containing herbicides has been limited mainly to agricultural uses on corn and on sorghum (Council of the European Communities, 1980; Worthing & Walker, 1987; Ahrens, 1994; Tomlin, 1994; Novartis, 1999).

In the United States, atrazine has been a staple for weed control in agriculture over the past 35 years. It is used on approximately 67% of all corn acreage, 65% of sorghum acreage and 90% of sugar-cane acreage and is also used on wheat, guavas, macadamia nuts, conifers and turf and for non-selective use along roads (Ahrens, 1994; Ciba-Geigy AG, 1996; Novartis, 1999). The Environmental Protection Agency estimated that 31–35 million kg (active ingredient) of atrazine were used annually in agricultural crop production in the United States in 1987, 1993 and 1995 (Aspelin, 1997).

1.3 Occurrence

1.3.1 *Natural occurrence*

Atrazine is not known to occur naturally.

1.3.2 *Occupational exposure*

According to the 1981–83 United States National Occupational Exposure Survey (National Institute for Occupational Safety and Health, 1998), approximately 1000 chemical industry workers in the United States were potentially exposed to atrazine. No data were available on the number of agricultural workers exposed. Occupational exposure may occur through dermal contact or inhalation during the manufacture, formulation or application of this herbicide (National Institute for Occupational Safety and Health, 1992).

Ikonen *et al.* (1988) determined the ambient air concentrations of atrazine and the urinary excretion of atrazine metabolites (fully *N*-dealkylated atrazine, i.e. 2-chloro-4,6-diamino-*s*-triazine and 2-chloro-4-ethylamino-6-amino-*s*-triazine) in six Finnish railway workers who filled spraying tank wagons. The air concentration in the personal breathing zone over 7–240 min ranged from 0.24 to 0.89 mg/m^3. The sum of the concentration of the two metabolites in urine samples collected after an 8-h work shift ranged from 30 to 110 μmol/L and was correlated with that of atrazine in the ambient air.

Catenacci *et al.* (1990) determined ambient air levels, skin deposition and urinary excretion of free atrazine over several work shifts in four Italian workers exposed to atrazine during its manufacture and packaging in a production plant. The air concentrations (in 8-h time-weighted average [TWA] personal samples) were 0.07–0.53 mg/m^3, and whole-body skin deposition was 4.1–11 mg/h. Urinary excretion of unmodified atrazine correlated with ambient air concentrations. Maximal excretion rates were found during the work shift and varied between 0.1 and 0.3 µg/h.

In another study, Catenacci *et al.* (1993) evaluated the exposure to atrazine of six Italian herbicide manufacturing workers through personal ambient air measurements, skin pad deposition sampling and determinations of urinary metabolites. Total exposure, reported as a dose, varied from 10 to 700 µmol/work shift, being 10 times higher in baggers than in box operators. Cutaneous exposure was twice as high as by the respiratory route for baggers and 10 times as high for box operators. Urinary excretion of metabolites—bis-dealkylated atrazine (80% of total), deisopropylated atrazine (10%), deethylated atrazine (8%) and unmodified atrazine (1–2%)—accounted for only 1–2% of the external dose and was not correlated to it.

The wide discrepancies between external dose and that accounted for by urinary metabolite excretion may be due to low cutaneous absorption of atrazine (Catenacci *et al*., 1995). Dermal absorption of atrazine over a 24-h exposure period in volunteers ranged from 1.2 to 5.6%, depending on the dose (Hui *et al*., 1996). Using these figures and data from the Pesticide Handlers Exposure Database, Breckenridge (1996) estimated the combined occupational exposure to atrazine by inhalation and dermal absorption in a variety of uses, as micrograms of atrazine absorbed per mass of active ingredient used. The estimates range from 0.27 to 158 µg/lb (0.6–350 µg/kg) for 5.6% dermal absorption, depending on the use. The heaviest exposure was that of granular spreaders and handgun operations (27–158 µg/lb active ingredient or 60–350 µg/kg), whereas mixer–loaders (non-handgun), boom applicators, pilots and flaggers had lighter exposure (0.27–4.54 µg/lb active ingredient or 0.6–10 µg/kg).

Information on the use of various atrazine formulations on various crops was combined with the above estimates to yield lifetime average daily doses of atrazine in the treatment of corn, sorghum, sugar-cane and macadamia nuts. These varied from 4×10^{-6} mg/kg bw per day for enclosed-cab ground application on sorghum to 1.6×10^{-3} mg/kg bw per day for some mixer–loader applicators in open cabs on Florida sugar-cane (Lunchick & Selman, 1998).

1.3.3 *Environmental occurrence*

Atrazine and its degradation products occur widely in the global environment as a result of extensive use of atrazine as a pre-and post-emergent herbicide, mainly on maize, sorghum and millet and to a lesser degree on other crops, and as a non-selective herbicide for general weed control. It is found, at generally low levels, in rivers, lakes, estuaries, reservoirs, groundwater and drinking-water. It can also pollute fog and rain when released into the atmosphere during spray application (Thurman *et al*., 1991, 1992;

Goolsby & Battaglin, 1993; Goolsby *et al*., 1993; Huber, 1993; Bintein & Devillers, 1996; Schottler & Eisenreich, 1997; Richards & Baker, 1998; Thurman *et al*., 1998).

(*a*) *Air*

Atmospheric transport and fallout have been implicated in the dispersion of atrazine. Atrazine was detected in ambient air in the region of Paris, France, in 1991 at approximately 0.03 ng/m^3; the maximal concentration in the total atmospheric fallout in rainwater in Paris was 350 ng/L (Chevreuil & Garmouma, 1993). Atrazine was measured at concentrations of < 0.03–2 ng/m^3 in the vapour phase in the Paris area in 1992 and 1993 and at < 5–380 ng/L in fallout in urban and rural sites in the same area. The yearly atmospheric deposition of atrazine was estimated to be 77 µg/m^2 for this area (Chevreuil *et al*., 1996). The concentration of atrazine in rainwater in Switzerland reached 600 ng/L (Buser, 1990). In rainwater samples in Ohio, United States, in 1985, the concentration of atrazine ranged from undetectable (detection limit, 0.05 µg/L) to 1.0 µg/L, according to season (Richards *et al*., 1987).

Measurements from aircraft of the concentrations and flux of agrochemicals over Ottawa, Canada, in June 1993 and July 1994 showed concentrations as high as 4.6 ng/m^3 with fluxes ranging from 1.1 to 2.5 ng/m^2 per s (Zhu *et al*., 1998).

(*b*) *Water*

The concentrations of atrazine in waters receiving runoff from agricultural lands are seasonal, the highest concentrations generally being found during the six weeks to two months after application and lower to undetectable concentrations during the rest of the year. In rivers and streams, the concentrations are highest during runoff after storms in the post-application period (Richards *et al*., 1987; Richards & Baker, 1998). Typically, atrazine is found more frequently and usually at lower concentrations in groundwater than in surface water. The peak concentrations in impounded water bodies, such as reservoirs, are usually lower than those in rivers and streams; they occur at the same time but may persist for longer because of the longer residence time (Tierney *et al*., 1998).

(i) *Surface water*

The heaviest use of atrazine in North America is in the midwestern watershed. The United States Geological Survey involved monitoring of residues of atrazine in 76 midwestern reservoirs in 11 states in 1992–93. Atrazine residues were found in 92% of reservoirs, and the 90th percentile of this distribution between early June and the end of July was about 5 µg/L. The concentrations of atrazine in rivers and streams included in an ecological risk assessment of atrazine in North American surface waters rarely exceeded 20 µg/L (Goolsby & Battaglin, 1993; Goolsby *et al*., 1993; Solomon *et al*., 1996).

Because atrazine is relatively water soluble, it can be transported in surface runoff after application and may reach groundwater as well. Monitoring of surface waters (Thurman *et al*., 1991; Squillace & Thurman, 1992; Thurman *et al*., 1992; Squillace *et al*., 1993; Thurman *et al*., 1994, 1998), including the Mississippi River, United States (Pereira

& Rostad, 1990), has shown the widespread presence of atrazine and its dealkylated degradation products, deethylatrazine and deisopropylatrazine. The same compounds are frequently detected in groundwater (Adams & Thurman, 1991; Squillace & Thurman, 1992). Deethylatrazine and deisopropylatrazine are also common degradation products of three other triazine herbicides: simazine, propazine and cyanazine.

Field studies and a regional study of nine rivers in the midwest corn belt of the United States showed that deethylatrazine and deisopropylatrazine occur frequently in surface water that has received runoff from fields treated with atrazine and cyanazine. The concentrations of deethylatrazine and deisopropylatrazine vary with the hydrological conditions and the timing of runoff, with maximum concentrations reaching 5 µg/L. Atrazine was the source of 98% of the deethylatrazine and 75% of the deisopropylatrazine (Thurman *et al*., 1994).

The concentrations of atrazine in the Minnesota River, United States, exceeded 2000 ng/L, the maximum concentration occurring in mid-June 1990; in 1991, the maximum concentrations in mid-June were 800–900 ng/L. Deethylatrazine was present throughout the year and was detected in 90% of the samples, with maximum concentrations of > 300 ng/L in 1990 and 130 ng/L in 1991. The highest concentration of deisopropylatrazine was 160 ng/L in 1990, and concentrations of 100–200 ng/L were common in June and July 1991 (Schottler *et al*., 1994). The Minnesota River contributes 1–2 tonnes of atrazine to the Mississippi River; larger drainage basins, such as the Ohio and Missouri Rivers, contribute about 40 and 60 tonnes annually, respectively, to the Mississippi River (Goolsby & Battaglin, 1993; Goolsby *et al*., 1991, 1993). The annual transport of atrazine into the Gulf of Mexico via the lower Mississippi River and its tributaries was estimated to be 105 tonnes in 1987 and 429 tonnes in 1989, representing less than 2% of the total atrazine application in the entire Mississippi River Basin (Pereira & Rostad, 1990).

Atrazine has been used intensively in the Great Lakes Basin of North America. It has a long half-life in cold aquatic systems of low productivity, such as oligotrophic lakes and groundwater (Ulrich *et al*., 1994), with an estimated half-life in the Great Lakes exceeding one year (Schottler *et al*., 1994). It has been suggested that the annual input of atrazine ranges from about 1 tonne in Lake Superior to 10–25 tonnes in Lakes Erie and Ontario. While inputs from tributaries and connecting channels accounted for > 75% of the total load to Lakes Erie, Ontario, Huron and Michigan, atmospheric input accounted for 95% of the atrazine in Lake Superior. The internal degradation rates of atrazine are similar throughout the Great Lakes, approximately 5–10% of the total load being lost annually by internal degradation. The ratios of deethylatrazine to atrazine indicate that 1.5, 0.9, 4 and 5% of the total atrazine is converted to deethylatrazine annually in Lakes Michigan, Ontario, Erie and Huron, respectively (Schottler & Eisenreich, 1997).

Atrazine and deethylatrazine were found in 89–100 % (average, 94%) of samples of water from Sydenham River, Ontario, Canada, collected 30–50 times per year between 1981 and 1987 and in 63–100 % (average, 89%) of paired samples of drinking-water from the town of Dresden, Ontario. The annual mean (± SD) levels of atrazine plus deethylatrazine ranged from 1.3 (± 1.3) to 5.1 (± 10) µg/L in the river water and from 1.1

(± 1.1) to 8.3 (± 36) µg/L in the drinking-water samples. The highest level of atrazine plus deethylatrazine, found in Dresden municipal drinking-water, was 210 µg/L in 1987 (Frank *et al*., 1990).

Atrazine was one of the most frequently detected pesticides in surface water and sediment samples collected during 1991–95 in a monitoring network that included 27 stations in South Florida canals in the United States. The highest concentration of atrazine found in surface water was 18 µg/L (number of detections, 274), and the highest concentration in sediment was 50 µg/kg (number of detections, 11) (Miles & Pfeuffer, 1997).

In a 12-month study carried out in 18 Swiss lakes and in rain in 1989, both atrazine and deethylatrazine were detected. The occurrence of atrazine in rain during March to October suggested that atmospheric transport was involved and, although a minor contributor to the larger lakes in the midland region, was likely to be the major source of these compounds in the mountain lakes. The concentration of atrazine was lowest (≤ 1 ng/L) in mountain lakes (altitude, > 800 m) and highest (≤ 460 ng/L) in lakes situated in areas with intensive agricultural use of atrazine. Atrazine was found to be rather stable, and it was removed from lakes mainly via outflowing waters rather than by degradation (Buser, 1990).

In the summer of 1991, atrazine was found to be distributed over the whole area of the German Bight of the North Sea at levels of 1–100 ng/L; the highest concentrations were found in the Elbe estuary, reaching 200 ng/L. The River Elbe is the main source of this polluant in this part of the North Sea (Bester & Hühnerfuss, 1993).

Atrazine was detected in a broad range of Mediterranean estuarial waters in a survey made in 1990–91. The areas studied included the Ebro delta on the eastern coast of Spain, the Rhône delta in the south of France, the River Po, Italy (northern Adriatic Sea), the Thermaïkós and Amvrakikós Gulfs in Greece and the Nile Delta in Egypt. The atrazine concentrations (µg/L; limit of detection, < 0.001 µg/L) were: Ebro drainage canal, 0.058–0.308; Ebro River, 0.017–0.190; Ebro delta lagoons, < 0.001–0.057; Rhône River, 0.040–0.291; Rhône delta, 0.017–0.386; River Po, 0.021–0.118; northern Adriatic, < 0.003–0.018; Axios, Loudhias and Aliakmon Rivers, < 0.05–0.70; Thermaïkós Gulf, < 0.05–0.15; Loúros and Árakthos Rivers, < 0.05–0.26; Amvrakikós Gulf, < 0.05–0.80; and Nile Delta, < 0.001 (Readman *et al*., 1993).

Atrazine was found in 41% of 115 samples at maximum weekly and monthly concentrations of 0.9 and 0.5 µg/L respectively (limit of detection, 0.1 µg/L) at one site in a small agricultural catchment in southern Sweden during 1990–92. At another site in the same general area during 1992–96, atrazine was found in 72% of 95 samples at maximum weekly and monthly concentrations of 3 and 1.5 µg/L, respectively (Kreuger, 1998).

The concentrations (µg/L) and frequency of detection of atrazine in the Arno River in Italy during 1992–95 ranged from a median of 0.06 (maximum, 0.16) (n = 36) with 67% frequency in 1992 to a median of < 0.01 (maximum, 0.07) (n = 51) with a frequency of 4% in 1995 (Griffini *et al*., 1997).

Atrazine, deethylatrazine and deisopropylatrazine were found in surface and groundwater samples from three sampling sites in the Ebro River. While atrazine and deethylatrazine were detected throughout the whole year in the delta waters, deisopropylatrazine was not detected between September and January. Atrazine had the least seasonal variation, remaining at a stable concentration of 0.1 µg/L between March 1992 and March 1993 (Barceló *et al*., 1996).

A review by the Council of Europe of surveys of pesticide residues in surface waters, conducted principally during the period 1985–92 in the Nordic countries, Netherlands and Germany, found that atrazine and other triazine herbicides were detected at a number of sampling sites throughout the year (Lundbergh *et al*., 1995).

(ii) *Groundwater*

In a survey of herbicide residues prevalent in groundwater across Iowa (in which some of the most intense application of herbicides occurs in the United States) in 1995, atrazine and deethylatrazine were detected in 41% and 35% of sample, respectively, at maximum concentrations of 2.1 and 0.59 µg/L, respectively (limit of detection, 0.05 µg/L) (Kolpin *et al*., 1997a).

In 1991, atrazine was detected in 19% of 208 urban wells in nine studies of shallow groundwater that were part of the United States Geological Survey's National Water Quality Assessment Program. The limit of detection was 0.002 µg/L, and the maximum concentration found was 2.3 µg/L (Kolpin *et al*., 1997b).

In a study of triazine herbicides and their degradation products in near-surface aquifiers in midwestern United States in 1991, involving 837 water samples from 303 wells, the median detectable concentration of atrazine (0.15 µg/L, 158 samples) was almost half that of atrazine plus deethylatrazine and deisopropylatrazine (0.26 µg/L; 197 samples) (Kolpin *et al*., 1996).

(iii) *Drinking-water*

In an assessment of atrazine in the drinking-water of residents of Ohio, Illinois and Iowa (United States), only small populations were found to be exposed to average concentrations exceeding the Environmental Protection Agency maximum contaminant level of 3 µg/L, and most were exposed to average concentrations of less than 1 µg/L. Large rivers such as the Ohio and Mississippi and most groundwater sources provide water with relatively low concentrations of atrazine; the highest concentrations were found in a few small, groundwater-based public water supplies and private wells. Only 0.25% of the assessed populations in all three states were exposed to concentrations exceeding the maximum contaminant level, and 94–99% of the populations were exposed to < 1 µg/L. In Ohio, with a population of over 10 million people, the average concentrations were 0.07 µg/L from Lake Erie, 0.84 µg/L from other surface water, 0.025 µg/L from public groundwater and 0.052 µg/L from private groundwater (Richards *et al*., 1995).

In a population-linked assessment of exposure to atrazine in drinking-water supplies in the 21 states of the United States where most atrazine is used, data on community

water systems serving 164 million people were summarized for five consecutive years, 1993–97. A community water system was defined as a facility that provides piped water for human consumption to at least 15 service connections around the year; the source of the raw water may be groundwater, surface water (rivers, lakes and reservoirs) or both (Tierney *et al*., 1998). Atrazine was detected in 7091 (10%) of the samples assessed, with 3% in groundwater (1959 of 57 258 samples), 36% in surface water (4861 of 13 529 samples) and 10% in other water samples (276 of 2776 samples). Of the approximately 125 million people whose exposure to atrazine was measured in this survey, 95 million (75%) had no detectable exposure from the community water systems. When detectable exposures were added to undetectable figures, 112 million (89%) were exposed to mean concentrations of < 0.5 μg/L, and 121 million (97%) were exposed to < 1 μg/L; approximately 3.9 million (3%) were exposed to 1–3 μg/L (Clarkson *et al*., 1998).

Atrazine was found at concentrations of 0.18–1 μg/L in a representative survey in the United States in 1990–91; 50% of the tested wells had concentrations < 0.28 μg/L (Environmental Protection Agency, 1992). In the United States, persons who obtain potable water from private wells represent about 6% of the population. National groundwater studies have shown that over 98% of private wells have concentrations of < 0.02 μg/L atrazine (Tierney *et al*., 1998).

In 1988, atrazine was detected at 1–50 ng/L in a number of new wells that serve as sources of drinking-water in the province of Bergamo in northern Italy (Bagnati *et al*., 1988).

(*c*) *Soil*

Atrazine is degraded in soil by microbial processes and abiotic degradation, yielding deethylatrazine, deisopropylatrazine, hydroxyatrazine and non-extractable residues. Deethylatrazine was the major degradation product from clay-loam and silt-loam plots studied at an experimental field in the Kansas River Valley in the United States in 1989. Deisopropylatrazine was found at significantly lower concentrations than deethylatrazine. Most of the degradation of atrazine occurred in the top metre of soil. The deethylatrazine:atrazine ratio was suggested to be a good indicator of transport of atrazine through the soil (Adams & Thurman, 1991).

Metabolite formation from atrazine and subsequent disappearance were found to be similar in laboratory microcosms and in a field in west Tennessee, United States. The half-life of atrazine was found to be 21 days in the microcosm and 14 days in the field study. Bound residue formation was significant, however, so that the half-life of the chemical may be underestimated (Winkelmann & Klaine, 1991a,b).

In a study of atrazine and its transformation products in surface and subsurface soils from five locations in Iowa, United States, the greatest mobility was seen in sandy and sandy clay–loam subsurface soils, which also had the least organic matter. The mobility relationship of deethylatrazine > atrazine > deisopropylatrazine is consistent with the results of groundwater monitoring (Kruger *et al*., 1996).

An environmental-fate study conducted in a citrus orchard in Valencia, Spain, in 1993 showed a degradation half-life of 11 days for atrazine, the distribution being highest in the upper layer (0–0.05 m) of soil. Of the four pesticides studied (atrazine, simazine, chlorpyrifos and tetrafidon), atrazine was the most soluble in water and the most mobile. The persistence and mobility of residues are closely related to both climatic conditions and agricultural practices (Redondo *et al*., 1997).

In field experiments on various subtropical soils in Taiwan, with various soil temperatures and moisture conditions, the deepest movement of atrazine into the soil was 7 cm (Wang *et al*., 1995, 1996).

In a study in Israel, significant degradation of atrazine (50%) was detected in samples taken from the upper soil (0–25 cm) but none in samples taken from the deepest subsurface soil. Deethylatrazine and deisopropylatrazine were the main degradation products of the upper soil. Inoculation with *Pseudomonas* sp. strain ADP (P.ADP) resulted in 90–100% mineralization of atrazine after 15 days (Shapir & Mandelbaum, 1997).

(*d*) *Food*

No atrazine residue (< 50 µg/kg) was reported in a survey of various food and feeds over the period 1991–92 in 16 428 samples (15 370 surveillance and 1058 compliance) and in the Total Diet Study for 1986–92 in the United States (Food & Drug Administration, 1993). In a further examination of data from the Residue Monitoring Program by the National Food Processors Association, no residues of atrazine, simazine, cyanazine or ametryn were found in 76 973 samples in 1992–94 (Elkins *et al*., 1998).

Field studies on the metabolism of atrazine in corn and sorghum showed that uptake of residues by plants is relatively low and subsequent metabolism is rapid. The metabolism of atrazine in plants is complex and involves at least 15–20 structures. Direct dietary exposure to atrazine residues in treated crops would be expected to be low and to comprise primarily water-soluble metabolites. There is a little propensity for plant metabolites of atrazine to be transferred to meat, milk or eggs (Ballantine & Simoneaux, 1991).

1.4 Regulations and guidelines

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.

WHO (1993) has established an international guideline for atrazine in drinking-water of 0.002 mg/L. The interim maximum acceptable concentration of atrazine in Canadian drinking-water is 0.005 mg/L (United Nations Environment Programme, 1998). The maximum level of atrazine allowed in primary drinking-water in the United States is 0.003 mg/L (Environmental Protection Agency, 1998). Limits on atrazine residues have been set in the Russian Federation in various matrices: ambient air, maximum allowable concentration (MAC), 0.02 mg/m^3; surface water, MAC, 0.5 mg/L; surface water, MAC for fishing, 0.005 mg/L (United Nations Environment Programme, 1998). Owing to its

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

Country or region	Residue limit (mg/kg)	Commodities
Argentina	0.25	Maize, sorghum, sweet corn
Australia	0. l[a]	Edible offal (mammalian), maize, sorghum, sugar-cane, sweet corn
	0.02[a]	Lupins
	0.01[a]	Meat, milk, milk products, potatoes, rape-seed
Austria	0.5	Corn
	0.1	Other foods of vegetable origin
Belgium	0.1	All foodstuffs of vegetable origin
Brazil	1.0	Conifers, rubber plants, sisal
	0.2	Corn, sorghum, pineapple, sugar-cane, avocados, bananas, mangos, peaches, apples, citrus fruit, nuts, tea, cocoa, coffee
	0.1	Black pepper
China (Taiwan)	0.25	Field crops, sugar-cane, tropical fruits
Czech Republic	0.1[a]	All products
European Union	0.1	All products
Finland	0.2	Food products
France	0.1	Fruit, vegetables
	0.05	Corn
Germany	0.1	All products of plant origin
Hungary	0.1	All crops
Iceland	0.1	All crops and foodstuffs
India	0.25	Sugar-cane
	0 (nil)	Maize
Ireland	0.1	All products
Israel[b]	15.0	Maize and sorghum fodder
	0.25	Maize and sorghum grain, sweet corn
	0.02	Meat, milk, eggs
Italy	0.5	Corn, sorghum
	0.1	Fruit, garden vegetables
Japan	0.02	Oats, etc. and minor cereals; fruit, vegetables, sugar-cane
Malaysia	1.0	Asparagus, leafy vegetables
	0.25	Corn, millet, sorghum, wheat, pineapple
	0.1	Raisin, sugar-cane
	0.05	Guava
	0.02	Meat, eggs, milk and milk products
	0.01	Potatoes
Mexico	15	Corn (forage), sorghum (forage)
	10	Pineapple (forage)
	5	Wheat (straw)
	0.25	Corn (fresh and grain), pineapple, sorghum (grain), sugar-cane, wheat (grain)

Table 2 (contd)

Country or region	Residue limit (mg/kg)	Commodities
Netherlands	0.1	Corn, fruit, vegetables
	0 (0.05)[c]	Other
Norway	0.1	All products
Singapore	0.1	Citrus fruit, grapes, maize, pineapples, sorghum, sugar-cane, sweet corn
	0.01	Potatoes
South Africa	0.05	Mealies, sorghum, sugar-cane
Spain	0.1	Citrus fruit, fruit with or without shell, seed fruit, stone fruit, berries and small fruit, other fruit, root and tuber vegetables, bulb vegetables, fruit and pepos, vegetables of the genus *Brassica*, fresh aromatic herbs and leafy vegetables, green legumes (fresh), young stalks, fungi, legumes, oilseeds, potatoes, tea, hops, spices, grains, other products for consumption (tobacco, sugar-beets, sugar-cane, other), hay and forage crops, dried products, other edible seeds, other infusions
Switzerland	0.1	Corn
United Kingdom	0.1	All crops and foodstuffs
United States	15[d]	Corn forage or fodder (including field corn, sweet corn, popcorn), sorghum fodder and forage, perennial rye grass
	10[d]	Pineapple fodder and forage
	5[d]	Wheat fodder and straw
	4.0[d]	Range grasses
	0.25[d]	Fresh corn including sweet corn (kernels plus cobs with husks removed), maize grain, macadamia nuts, pineapples, sorghum grain, sugar-cane, sugar-cane fodder and forage, wheat grain
	0.05[d]	Guava
	0.02[d]	Eggs, milk, meat, fat and meat by-products of cattle, goats, hogs, horses, poultry and sheep (negligible residues)
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)

From Health Canada (1998)

[a] Maximum residue limit set at or about the limit of analytical determination

[b] From State of Israel (1977)

[c] Residues shall be absent; the value in parentheses is the highest concentration at which this requirement is still deemed to have been met.

[d] Atrazine and its metabolites

Table 3. Occupational exposure limits for atrazine

Country	Year	Concentration (mg/m^3)	Interpretation
Australia	1993	5	TWA
Austria	1993	2	TWA
Belgium	1993	5	TWA
Canada	1994	5	TWA
Denmark	1993	2	TWA
Finland	1998	10	TWA
		20	STEL
France	1993	5	TWA
Germany	1998	2 (inhalable fraction of the aerosol)	MAK
Ireland	1997	10	TWA
Netherlands	1997	5	TWA
Russian Federation	1993	2	STEL
Switzerland	1993	2	TWA
United Kingdom	1987	10	TWA
United States			
OSHA (PEL)	1997	5	TWA
NIOSH (REL)	1994	5	TWA
ACGIH[a] (TLV)	1997	5	TWA

From Cook (1987); American Conference of Governmental Industrial Hygienists (ACGIH) (1997; 1998); Deutsches Forschungsgemeinschaft (1998); Occupational Safety and Health Administration (OSHA) (1999)

TWA, time-weighted average; STEL, short-term exposure limit; PEL, permissible exposure limit; REL, recommended exposure limit; TLV, threshold limit value; MAK, maximum workplace concentrations; NIOSH, National Institute for Occupational Safety and Health

[a] The following countries follow the exposure limits suggested by the ACGIH: Bulgaria, Colombia, Jordan, the Republic of Korea, New Zealand, Singapore and Viet Nam

high mobility in soil and its potential to contaminate water, atrazine is banned from use in Italy, Norway and Sweden (National Registration Authority for Agricultural and Veterinary Chemicals, 1997; United Nations Environment Programme, 1998). In 1991, the German government banned all atrazine-containing products (National Registration Authority for Agricultural and Veterinary Chemicals, 1997). In 1993, the United Kingdom banned the use of atrazine in non-agricultural situations, maintaining the agricultural uses on corn (The Pesticide Trust, 1993).

2. Studies of Cancer in Humans

2.1 Cohort studies

On the basis of a retrospective follow-up study of 4388 agricultural chemical production workers in one plant in Alabama, United States, and a study of 1472 workers at a plant in Louisiana, United States, Sathiakumar *et al.* (1996) analysed the mortality pattern among the combined subgroup of 4917 male workers with potential exposure to triazines; 80% were white and 20% were black. The Alabama plant began operation in 1951 and, until the 1980s, manufactured primarily agricultural chemicals, including triazine herbicides and many other pesticides. The Louisiana plant, which started operation in 1970, produced mainly triazine herbicides. The vital status of cohort members was ascertained as of 1 January 1987. Death certificates were used as the source of information on date and cause of death. Periods of employment and associated job title and work area were obtained from company files. By use of a job–exposure matrix constructed by local industrial hygienists, in which job information was converted to information on likelihood of exposure to triazine, cohort members were classified into a group of 2683 (55%) workers who had had definitive or probable exposure and 2234 (45%) who had had possible exposure. Exposure to pesticides other than triazine herbicides was not controlled for in the analysis. The workers were followed-up from the date of starting a triazine-related job up to the date of death, the date of loss to follow-up or 1 January 1987. Overall, 220 deaths were observed, whereas 253 were expected from the mortality rates of the United States male population (standardized mortality ratio [SMR], 0.87; 95% confidence interval [CI], 0.75–0.99). The SMR for all cancer was 1.1 (95% CI, 0.76–1.4) on the basis of 43 observations; five cases were non-Hodgkin lymphomas, with 1.8 expected (SMR, 2.8; 95% CI, 0.91–6.5). Among subjects with definite or probable triazine-related work, 14 cancers were observed (SMR, 0.85; 95% CI, 0.46–1.4), and site-specific cancer analyses yielded no significant findings; three deaths from non-Hodgkin lymphomas were seen when 0.78 were expected (SMR, 3.8; 95% CI, 0.79–11). Two of these three men had had less than one year of employment involving exposure to triazine. Two other cancers of the lymphatic and haematopoietic tissue were seen, when 1.8 were expected. Among men with possible exposure to triazine, 29 cancers were observed (SMR, 1.2; 95% CI, 0.80–1.7), of which two were non-Hodgkin lymphomas when 1.0 was expected. Two cases of soft-tissue sarcoma were also seen among men who had possibly been exposed, with 0.30 expected. Inserting a 10-year latency period into the cancer mortality analysis did not affect the risk estimates substantially. [The Working Group noted that lack of control for exposure to other pesticides reduces the usefulness of this study.]

2.2 Case–control studies

Results of case–control studies of triazines, including atrazine, by cancer site are summarized in Table 4.

Table 4. Case–control studies of triazines, including atrazine, by cancer site

Reference and location	Subjects in the analysis	Exposure contrast	Odds ratio (95% CI)	Comments
Non-Hodgkin lymphoma				
Hoar *et al*. (1986), Kansas, United States	170 white men 948 controls	Ever exposed to triazines versus never worked on a farm	1.9 (0.4–8.0)	Restricted to persons with no use of phenoxyacetic acids
Cantor *et al*. (1992), Iowa–Minnesota, United States	622 white men 1245 controls	Ever used triazines on the farm versus never worked on a farm	1.1 (0.8–1.6)	Adjusted for exposure to other pesticides
		Ever personally handled triazines versus never worked on a farm	1.2 (0.9–1.8)	
Zahm *et al*. (1993a), pooled analysis, United States	993 white men 2918 controls	Ever used atrazine versus never worked on a farm	1.4 (1.1–1.8)	Adjusted for age and state
	636 white male farmers 1901 controls	Ever used atrazine versus never used atrazine	1.2 (0.9–1.7)	Restricted to farming and adjusted for exposure to phenoxyacetic acids and organophosphate insecticides
Zahm *et al*. (1993b), eastern Nebraska, United States	134 white women 707 controls	Ever used triazines versus never worked on a farm	1.2 (0.6–2.6)	
Hodgkin's lymphoma				
Hoar *et al*. (1986), Kansas, United States	121 white men 948 controls	Any herbicide used on a farm versus never worked on a farm	0.9 (0.5–1.6)	Mixed exposure to herbicides
Leukaemia				
Brown *et al*. (1990), Iowa–Minnesota, United States	578 white men 1245 controls	Ever used triazines on a farm versus never worked on a farm	1.1 (0.8–1.5)	Adjusted for exposure to other pesticides

Table 4 (contd)

Reference and location	Subjects in the analysis	Exposure contrast	Odds ratio (95% CI)	Comments
Multiple myeloma				
Brown *et al*. (1993), Iowa, United States	173 white men 650 controls	Any herbicide used on a farm versus never worked on a farm	1.2 (0.8–1.9)	
		Ever having handled atrazine versus never worked on a farm	0.8 (0.4-1.6)	
Soft-tissue sarcoma				
Hoar *et al*. (1986), Kansas, United States	133 white men 948 controls	Any herbicide used on a farm versus never worked on a farm	0.9 (0.5–1.6)	Mixed exposure to herbicides
Ovarian cancer				
Donna *et al*. (1989), Alessandria, Italy	65 women 126 controls	Definite exposure to triazines versus no exposure	2.7 [1.0–6.9]	90% confidence interval; adjusted for reproductive factors but not exposure to other herbicides
		Possible exposure to triazines versus no exposure	1.8 [0.9–3.5]	
Colon cancer				
Hoar *et al.* (1985), Kansas, United States	57 [sex not reported] 948 controls	Exposure to triazines versus never worked on a farm	1.4 (0.2–7.9)	

CI, confidence interval

2.2.1 *Lymphatic and haematopoietic malignancies and soft-tissue sarcoma*

In a case–control study in Kansas, United States, Hoar *et al.* (1986) included 172 histologically confirmed cases of non-Hodgkin lymphoma, 132 of Hodgkin disease and 139 of soft-tissue sarcoma in white men aged 21 years or older during the period 1979–81 (non-Hodgkin lymphoma) and 1976–82 (Hodgkin disease and soft-tissue sarcoma). Cases were identified from the files of a State-wide cancer registry. A total of 1005 control subjects were randomly selected from the background population, with frequency matching by age and vital status. For living cases, controls were selected from a national health care programme (age 65 years or older) or by random-digit dialling (age 64 years or younger); for deceased patients, the controls were selected from Kansas State mortality files. Telephone interviews with subjects or their next-of-kin were completed for 96% of cases and 94% of controls, leaving 170 patients with non-Hodgkin lymphoma, 121 with Hodgkin disease, 133 with soft-tissue sarcoma and 948 control subjects for analysis. The interviews included detailed questions on farming practices, with particular emphasis on use of herbicides and insecticides, including triazines. The main purpose of the study was to test the hypothesis of a link between one or more of the three cancer types under study and exposure to phenoxyacetic acid herbicides on farms. The reference exposure category for calculating the odds ratios was people who had never worked on a farm rather than people never exposed to herbicides on farms. Any use of herbicides was reported for 40 non-Hodgkin lymphoma patients, yielding an odds ratio of 1.6 (95% CI, 0.9–2.6). There was a significant trend in risk with increasing years of herbicide use ($p = 0.02$) and with number of days of exposure per year ($p = 0.0004$). The study showed an association with exposure to triazines, including atrazine (odds ratio, 2.5; 95% CI, 1.2–5.4; 14 exposed cases), and several other herbicides. In the absence of exposure to phenoxyacetic acid, the association with triazines was reduced to 1.9 (95% CI, 0.4–8.0) [or 2.2; 95% CI, 0.4–9.1; conflicting results in table and text]. The odds ratio for non-Hodgkin lymphoma among farmers who did not report use of any herbicides was 1.3 (95% CI, 0.8–2.1). No association was reported between exposure to triazine herbicides and Hodgkin disease or soft-tissue sarcoma. [The Working Group noted that part of the excess risk observed may have been due to the choice of reference category.]

In a subsequent study covering the populations of 66 counties of eastern Nebraska, United States, Zahm *et al*. (1990) included 220 histologically confirmed cases of non-Hodgkin lymphoma diagnosed in white men aged 21 years or older during 1983–86 and 831 white male controls from the general population, frequency matched to cases by age and vital status. Telephone interviews with subjects or their next-of-kin were completed for 201 cases (91%) and 725 control subjects (87%) with collection of information on use of herbicides and insecticides on a farm. Any use of herbicides on a farm [no specification of triazines], in comparison with people who had never lived or worked on a farm, was associated with an increased odds ratio of 1.3 (95% CI, 0.8–2.0) which, in turn, was related mainly to handling phenoxyacetic acids (odds ratio, 1.5; 95% CI, 0.9–2.5).

In another case–control study conducted in Iowa and Minnesota, United States, Cantor *et al.* (1992) studied 780 white men aged 30 years or older, in whom a non-

Hodgkin lymphoma had been newly diagnosed during the period 1980–83. Cases were ascertained from records of the Iowa State Health Registry and a special surveillance of records from Minnesota hospitals and pathology laboratories. In Minnesota, non-Hodgkin lymphoma patients who resided in four large cities at the time of diagnosis were excluded. A control group of white men without a haematopoietic or lymphatic cancer were randomly selected from the same geographic areas and frequency-matched to cases by age, vital status and state of residence, following the same procedures as those described by Hoar *et al*. (1986). Interviews with subjects or their next-of-kin were completed for 694 patients with non-Hodgkin lymphoma (89%) and 1245 controls (approximately 77% response rate); however, only 622 of the cases in interviewed patients were confirmed histologically as non-Hodgkin lymphoma and included in the analysis. Detailed information was sought about socio-demographic variables, life-style factors, occupational history and farming practices, including use of herbicides and insecticides. Farming activities (versus non-farming activities) were associated with a small, but marginally significant increase in risk for non-Hodgkin lymphoma (odds ratio, 1.2; 95% CI, 1.0–1.5), but no trend in risk was seen by first year of work, duration of work or size of the farm. Among those who had worked on a farm, 300 patients (84%) and 603 controls (86%) reported use of at least one herbicide or insecticide, yielding an odds ratio relative to those who had never worked on a farm of 1.2 (95% CI, 0.9–1.4). Any use of triazines, including atrazine, was associated with a slightly increased odds ratio of 1.1 (95% CI, 0.8–1.6), calculated on the basis of 64 exposed cases. [The Working Group noted that part of the excess risk observed may have been due to the choice of reference category.]

To evaluate the relationship between exposure to atrazine in farming and non-Hodgkin lymphoma among white men, Zahm *et al.* (1993a) pooled the data from the three case–control studies conducted in Kansas (Hoar *et al.*, 1986), Iowa–Minnesota (Cantor *et al.*, 1992) and eastern Nebraska (Zahm *et al.*, 1990). In the pooled analysis, data from 993 cases and 2918 controls were included. Overall, 130 patients with non-Hodgkin lymphoma (13%) and 249 controls (9%) had been exposed to atrazine, yielding an odds ratio adjusted for age and state of 1.4 (95% CI, 1.1–1.8). People who had never worked on a farm were used as the unexposed reference category. The age-adjusted odds ratios ranged from a low of 1.2 (95% CI, 0.8–1.8) in Iowa to a high of 2.7 (95% CI, 1.2–5.9) in Kansas. The odds ratio associated with personal handling of atrazine was 1.4 (95% CI, 1.0–1.8; 94 exposed cases). Additional adjustment for any use of phenoxyacetic acid herbicides or organophosphate insecticides, which was restricted to 636 patients with non-Hodgkin lymphoma [64% of all] and 1901 control subjects [65% of all] who reported that they were farmers, reduced the combined odds ratio for non-Hodgkin lymphoma associated with use of atrazine to 1.2 (95% CI, 0.9–1.7). Farmers in Nebraska (the State for which the most detailed information was available on duration and annual frequency of use of atrazine specifically) who had used atrazine for more than 15 years had a twofold risk for non-Hodgkin lymphoma, but the increase disappeared when the analyses were adjusted for use of other herbicides and organophosphate insecticides.

Zahm *et al.* (1993b) studied 206 white women, aged 21 years or older, in 66 counties of eastern Nebraska, United States, in whom histologically confirmed non-Hodgkin lymphoma was diagnosed during the period 1983–86. Cases were identified through the Nebraska Lymphoma Study Group and area hospitals. A total of 824 control subjects were included, frequency-matched on age and vital status, following the same procedures as those described for the study in Kansas (Hoar *et al.*, 1986). Telephone interviews with the women or their next-of-kin were completed for 134 of the initially eligible cases (65%) and 707 of the controls (86%). Detailed information was sought on farming practices, including use of herbicides and insecticides. A total of 119 women [89% of the cases with a completed interview] with non-Hodgkin lymphoma and 471 [67%] controls reported ever having lived or worked on a farm, yielding on odds ratio of 1.0 (95% CI, 0.7–1.4). Any use of triazine herbicides, including atrazine, on the farm was associated with a non-significant risk of 1.2 (95% CI, 0.6–2.6; 12 exposed cases) and personal handling of triazine herbicides with an odds ratio of 2.2 (95% CI, 0.1–32; one exposed case). These estimates were not adjusted for use of other types of herbicide or use of insecticides.

In a case–control study from Iowa and Minnesota, United States, Brown *et al.* (1990) included 669 histologically confirmed cases of leukaemia newly diagnosed among white men aged 30 years or older during 1981–84. Cases were ascertained from records of the Iowa State Health Registry and a special surveillance of records from Minnesota hospitals and pathology laboratories. The control group was the same as that used in the Iowa–Minnesota case–control study of non-Hodgkin lymphoma (Cantor *et al.*, 1992), described above. Personal interviews including detailed questions on farming practices were completed for 578 of the cases (86%) and 1245 controls (77%). Any exposure to triazines, including atrazine, was associated with a slightly increased risk for any type of leukaemia (odds ratio, 1.1; 95% CI, 0.8–1.5; 67 exposed cases). There was a small but significant risk for all types of leukaemia combined (1.2; 95% CI, 1.0–1.5) among persons who lived or worked on a farm; however, the odds ratio for leukaemia among farmers who reported no exposure to pesticides was 1.9 (95% CI, 1.3–2.9).

In a case–control study from Iowa, United States, Brown *et al.* (1993) included 173 white men aged 30 years or older in whom multiple myeloma had been newly diagnosed during 1981–84 and who had been identified from the Iowa Health Registry. The 650 controls included in this study were those used in the case–control studies of non-Hodgkin lymphoma (Cantor *et al.*, 1992) and leukaemia (Brown *et al.*, 1990) in Iowa. The questionnaire was that used in the Iowa–Minnesota study and included detailed questions on occupational history and farming practices. Interviews with subjects or their next-of-kin were completed for 84% of the initially eligible cases and 78% of the controls. Some farming activity was reported by 64% of the patients and 58% of the controls, yielding a non-significantly increased odds ratio of 1.2 (95% CI, 0.8–1.7). The risk for multiple myeloma was not increased among farmers who personally mixed, handled or applied atrazine (odds ratio, 0.8; 95% CI, 0.4–1.6; 12 exposed cases).

2.2.2 *Other sites*

In a hospital-based study in Piedmont, Italy (Donna *et al*., 1984), 60 women in whom a histologically confirmed primary mesothelial ovarian tumour had been diagnosed during 1974–80 were matched to 127 controls in whom another type of cancer had been diagnosed. Personal interviews including questions on occupational history and exposure to herbicides were completed for 91% of the identified cases and 94% of controls. Exposure to herbicides [no information on exposure to any triazines or to triazines as a group] was regarded as 'definite' in eight cases and no controls and as 'probable' in 10 cases and 14 controls. Definite and probable exposure versus no exposure to herbicides was associated with an odds ratio of 4.4 (95% CI, 1.9–16).

In the population of 143 neighbouring municipalities forming the rural districts of Alessandria Province, Italy, Donna *et al.* (1989) studied all women aged 20–69 years in whom a primary malignant epithelial tumour of the ovary had been diagnosed between 1980 and 1985. Cases were identified from all 18 hospitals serving the area; two controls of the same age were randomly selected for each case from the electoral rolls of the municipalities of the study area. Information on reproductive factors, farming activities and occupational exposure to triazines and other herbicides was collected at interviews conducted at the subjects' homes. The response rates were 94% for cases eligible for the study and 84% for controls, leaving 65 cases and 126 controls for analysis. Interviews were conducted with next-of-kin of 35% of cases and none of the controls. The likelihood of exposure to triazines (definitely exposed, possibly exposed and unexposed) was established blindly by two of the authors independently after all of the interviews had been completed. The odds ratios for ovarian cancer, adjusted for age, number of live births and use of contraceptives were 2.7 (90% CI, 1.0–6.9; seven cases) for definitely exposed and 1.8 (90% CI, 0.9–3.5; 14 cases) for possibly exposed. The odds ratios were slightly higher among individuals with at least 10 years of occupational contact with triazines when compared with those with fewer than 10 years of contact. Restricting the analysis to women who reported having worked in agriculture yielded approximately similar risk estimates associated with exposure to triazine herbicides. [The Working Group noted that the odds ratios for exposure to triazines were of borderline significance and were not adjusted for exposure to other herbicides.]

Hoar *et al*. (1985) reported on a case–control study of 57 histologically confirmed cases [sex unspecified] of colon cancer sampled from among all such cases diagnosed in Kansas, United States, in 1976–82. A total of 948 controls were sampled from the general population. Slightly elevated risks were seen for both farmers who had used herbicides (odds ratio, 1.5; 95% CI, 0.6–4.0; 11 cases) and farmers who had not used herbicides (odds ratio, 1.6; 95% CI, 0.8–3.6). Exposure to triazines was associated with an odds ratio of 1.4 (95% CI, 0.2–7.9), on the basis of two exposed cases.

No data were available on exposure to triazines in general or atrazine in particular and the occurrence of breast cancer.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

Mouse: Groups of 60 male and 60 female CD-1 mice [age unspecified] were given atrazine (purity, > 96%) in the diet for at least 91 weeks in two separate studies, at concentrations of 0, 10, 300 or 1000 mg/kg of diet (ppm) in the first study and 0, 10, 300, 1500 or 3000 ppm in the second. The survival of treated males was unaffected, but that of female mice receiving 1000 or 3000 ppm atrazine was significantly decreased. Body-weight gain was reduced in male and female mice given 1500 or 3000 ppm atrazine. There was no treatment-related increase in tumour incidence in male or female mice exposed to atrazine in either study (Stevens *et al.,* 1998).

Atrazine was evaluated for carcinogenicity in (C57BL/6×C3H/Anf)F_1 mice and in (C57BL/6×AKR)F_1 mice fed concentrations of 82 mg/kg of diet (21.5 mg/kg bw) (ppm). Atrazine did not increase the incidence of any benign or malignant tumour in these studies (Innes *et al*., 1969). [The Working Group considered these studies to be inadequate for evaluation since no data were available on the numbers of animals, numbers of dose groups, study duration, observed tumour rates or justification for the low doses used.]

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 of diet (ppm) (high dose) atrazine (purity, 98.9%) during the first eight weeks of the study. Because of toxicity, the high dose was then reduced to 750 ppm and the low dose to 375 ppm. The study was terminated at week 126. The survival of male rats relative to controls was significantly increased at both the high ($p < 0.0001$) and the low ($p = 0.019$) doses. The increased survival of treated female rats was not statistically significant. Female rats had increased incidences of uterine adenocarcinomas (controls, 6/45; low dose, 8/52; high dose, 13/45) and leukaemia and lymphoma (combined) (12/44, 16/52, 22/51), which were significant by the Cochran-Armitage trend test but not by Peto's test for incidental tumours, in which adjustment is made for increased survival observed in treated groups. The overall proportion of animals with benign and malignant uterine tumours was similar in all groups (16/45, 19/52, 17/45). The incidence of primary benign mammary gland tumours was reported to be significantly increased ($p < 0.05$ by Peto's incidental tumour test) in males at the high dose relative to controls (control, 1/48; low dose, 1/51; high dose, 8/53). The mammary gland tumours in males were benign, except for one adenocarcinoma in a male at the high dose (Pintér *et al*., 1990). [The Working Group noted that the statistical methods used to evaluate the mammary gland tumours were inappropriately applied to the total number of tumours/number of animals examined rather than to the number of tumour-bearing animals/number of animals examined.]

In a critique of the study of Pintér *et al*. (1990), Thakur *et al*. (1998) reported that six of the eight mammary gland tumours in males at the high dose occurred after the last control had died at week 111, and that the significant ($p < 0.0001$) difference in survival between the high-dose and control groups had not been properly taken into account in

the evaluation of these tumours. Thakur *et al*. (1998) also noted that the last male at the high dose died at week 136, not week 126, and that Pintér *et al*. (1990) had overlooked a mammary gland fibroma in male controls in their tabulation of tumour rates and subsequent statistical analysis. Thakur *et al*. (1998) concluded that the increase in the incidence of mammary gland tumours in male rats was not significant ($p = 0.8$) when evaluated by a proper statistical analysis with adjustment for survival. [The Working Group concluded that the issue raised by Thakur *et al.* (1998) was valid.]

Atrazine (purity, 97%) was fed to 60 male and 60 female Charles River Fischer Crl:CDF (Fischer 344) rats at concentrations of 10, 70, 200 or 400 mg/kg of diet (ppm) for up to 104 weeks. An additional seven groups of 10 females per dose were treated for and killed at 1, 3, 9, 12, 15, 18 and 24 months. Body-weight gain was reduced in males and females at 400 ppm, but survival was similar in treated and control groups. No significant carcinogenic effects were observed in any group (Wetzel *et al*., 1994; Stevens *et al*., 1998; Thakur *et al*., 1998).

In a similar study, 60 female Sprague-Dawley rats were fed diets containing 0, 70 or 400 ppm atrazine (purity, 97%) for up to 104 weeks, and additional groups of 10 females per dose were treated for and killed at 1, 3, 9, 12, 15, 18 and 24 months. Females at 400 ppm showed a 12% reduction in body-weight gain at 13 weeks and a significant reduction in two-year survival (37%) relative to controls. They also had a statistically significantly ($p < 0.05$) earlier onset of mammary gland tumours relative to controls, although the overall incidences of these neoplasms at the end of the study were similar in the treated and control groups (Wetzel *et al*., 1994; Stevens *et al*., 1998).

Groups of 70–90 male and 70–90 female Sprague-Dawley rats were fed diets containing 0, 10, 70, 500 or 1000 ppm atrazine (purity, 96%) for a maximum of 106 weeks. The body-weight gain of animals at 500 and 1000 ppm was significantly reduced. The survival of males at 1000 ppm was significantly increased, and that of females at this dose was significantly decreased. In females, the incidence of mammary gland fibroadenomas was significantly ($p < 0.01$) increased in animals at 1000 ppm (controls, 29/88; 10 ppm, 29/69; 70 ppm, 36/69; 500 ppm, 39/70; 1000 ppm, 45/89), and the incidence of mammary gland adenocarcinomas was significantly ($p < 0.005$) increased in animals at the three highest doses (15/88, 16/69, 27/69, 27/70 and 43/89). In males, the incidence of interstitial-cell tumour of the testis was statistically signficantly increased ($p < 0.05$) at 1000 ppm (1/90, 3/70, 2/70, 2/70 and 7/90), but the incidence fell within the historical range for controls at that test laboratory (0–12%) and was attributed in part to the significantly better survival of these animals (Stevens *et al*., 1994, 1998).

Groups of 49–54 female Sprague-Dawley rats were fed diets containing 0, 10, 100 or 1000 ppm atrazine (purity, 96%) for life No information on body weight or survival was given. The incidences of mammary gland fibroadenomas were significantly ($p < 0.05$) increased in animals at 10 and 1000 ppm (control, 11/54; 10 ppm, 20/52; 100 ppm, 14/54; 1000 ppm, 22/49), but there was no significant increase in the incidence of malignant mammary gland tumours (11/54, 8/52, 12/54 and 13/49, respectively) (Stevens *et al*., 1994).

Groups of 29–40 female Sprague Dawley rats culled from the F_2 generation of a two-generation study of reproductive toxicity were fed diets containing atrazine (purity, 97.6%) for up to 104 weeks after exposure *in utero* to 0, 10, 50 or 500 ppm atrazine. No information on body weight or survival was given. The incidences of mammary gland tumours were not increased (controls, 11/30; 10 ppm, 10/40; 50 ppm, 13/40; 500 ppm, 11/29) (Stevens *et al*., 1994).

Five groups of 80 female Sprague-Dawley rats, eight weeks old, ovariectomized at seven weeks of age and five groups of 80 intact females were fed diets containing 0, 25, 50, 70 or 400 ppm atrazine (purity, at least 96%) for up to 104 weeks. The body-weight gain of both ovariectomized and intact females receiving 400 ppm atrazine was decreased. The survival of ovariectomized females fed 400 ppm atrazine was unaffected, but that of intact females at this dose was significantly reduced. No mammary tumours were found in any group of treated, ovariectomized females; however, the incidence of mammary gland fibroadenomas in the intact females was significantly ($p < 0.05$) increased at the three highest doses after adjustment for survival (16/80, 25/80, 33/78, 29/80 and 25/80), and the incidence of mammary gland carcinomas was significantly ($p < 0.05$) increased in females at 50 and 400 ppm (12/80, 18/80, 20/78, 14/80 and 27/80) (Stevens *et al*., 1998, 1999).

3.2 Intraperitoneal administration

Mouse: A group of 30 male Swiss mice, four weeks of age, received intraperitoneal injections of 'pure' atrazine in saline 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 in the atrazine-treated group (6/30) was significantly ($p < 0.001$) greater than that in the combined control groups (1/100). The six lymphomas in the treated group comprised two histiocytic lymphomas and four plasma-cell lymphomas; one histiocytic lymphoma was found in the untreated control group (Donna *et al*., 1986). [The Working Group noted that if the histiocytic tumours were sarcomas, they should have been evaluated separately.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

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-1,3,5-triazine and the monodealkylated metabolite 2-chloro-4-amino-6-(ethylamino)-1,3,5-triazine which were

present in equal amounts; practically none of the other monodealkylated metabolite, 2-chloro-4-amino-6-(isopropylamino)-1,3,5-triazine, was found (Ikonen *et al*., 1988).

In a study in which gas chromatography was used to identify deethylated, deisopropylated and di-dealkylated atrazine, as well as atrazine itself, in the urine of atrazine manufacture workers, di-dealkylated atrazine represented 80% of the urinary metabolites (Catenacci *et al*., 1993).

Using a sensitive enzyme-linked immunosorbent assay, Lucas *et al*. (1993) identified a mercapturic acid conjugate of atrazine as the major metabolite in the urine of applicators. Minor metabolites included *N*-dealkylated and *N*-deisopropyl atrazines. No di-dealkylated metabolites were identified, as they would have been expected to degrade during storage, and no hydroxylated conjugates were detected.

4.1.2 *Experimental systems*

Atrazine was well absorbed after oral administration to Fischer 344 rats; the 72-h urinary recoveries were similar (66%) after administration of either 30 mg/kg bw [U-^{14}C]-atrazine in corn oil (Timchalk *et al*., 1990) or approximately 1.5 mg/kg bw [ring-^{14}C]-atrazine in ethanol (Bakke *et al*., 1972). Moderate, inversely dose-dependent absorption (3–8% adults; 3–10% juveniles) through the skin was demonstrated in Fischer 344 rats (Shah *et al*., 1987).

The retention of radiolabel in the carcass of rats ranged from 4% (Timchalk *et al*., 1990) to 16% (Bakke *et al*., 1972) 72 h after dosing with [^{14}C]atrazine. The relative retention in tissues was: liver, kidney, lung > heart, brain >> muscle, fat. Less than 0.1% of an oral radioactive dose was detected in expired air (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 first-order elimination with a half-time of 10.8 h. Neither the kinetic characteristics nor the recovery of the dose 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 pathways of metabolism of atrazine in various species *in vivo* and *in vitro* (Böhme & Bär, 1967; Adams *et al*., 1990; Timchalk *et al*., 1990). The metabolism of atrazine (and three other triazine herbicides, terbuthylazine, ametryne and terbutryne) has been investigated *in vitro* in liver microsomes from rats, pigs and humans. The principal phase-I reactions in all three species were *N*-monodealkylation, hydroxylation of the isopropyl or *tert*-butyl moiety and sulfoxidation of the substrate. Although all species produced the same type of metabolites, there were species-specific differences in the metabolite ratios (Lang *et al*., 1996). Subsequent studies have showed that cytochrome P450 1A2 is the major phase-I enzyme involved in the metabolism of *s*-triazines in human liver microsomes (Lang *et al*., 1997).

The dealkylation product 2-chloro-4,6-diamino-1,3,5-triazine is the major urinary metabolite (64–67%) in rats, others being mercapturates of the mono- and di-dealkylated products (13–14% and 9%, respectively) (Timchalk *et al*., 1990). Minor metabolic path-

ways in rats may include alkyl side-chain oxidation (Böhme & Bar, 1967). Oxidative dechlorination to 2-hydroxyatrazine, a metabolite formed in plants (Shimabukuro *et al*., 1971), did not occur in rat liver homogenates (Dauterman & Muecke, 1974), although Bakke *et al*. (1972) claimed to have found some 2-hydroxyatrazine in rat urine and showed that it was metabolized along pathways similar to those of atrazine.

As there appear to be no remarkable qualitative differences in metabolism among species, the metabolic data do not readily explain the apparent strain-specific development of mammary gland tumours in atrazine-treated Sprague-Dawley rats.

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 [strain not specified] (Ben-Dyke *et al*., 1970) and 670, 740 and 2300 mg/kg bw in adult female and male, and weanling male Sherman rats, respectively, while the dermal LD_{50} was > 2500 mg/kg bw in Sherman rats of each sex (Gaines & Linder, 1986).

Administration of atrazine by oral gavage at 100–600 mg/kg bw per day to adult male Wistar rats for 7 or 14 days induced both nephrotoxicity and hepatotoxicity (Santa Maria *et al*., 1986, 1987). The hepatotoxic effects included a dose-related reduction in blood sugar concentration and increases in the activity of serum alanine aminotransferase and alkaline phosphatase and in total serum lipids. Electron micrographs showed degeneration of the smooth endoplasmic reticulum, lipid droplet accumulation and swollen mitochondria. The lowest dose was not toxic to the liver (Santa Maria *et al*., 1987). Renal toxicity, including dose-related proteinurea, reduced creatinine clearance and increased urinary electrolyte output, was seen at all doses (Santa Maria *et al*., 1986).

Hormonal imbalances induced by atrazine appears to be significant in the interpretation of possible carcinogenic effects on the mammary gland. Most of the work has been directed towards the effects of atrazine on the hypothalamus–pituitary–gonadal axis. Steroid hormone metabolism was found to be impaired by atrazine, which inhibits 5α-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 the wet weight of the anterior pituitary by 60–70%, caused hyperaemia and hypertrophy of the chromophobic cells and reductions of 37, 39 and 46%, respectively, in the activities of 5α-steroid reductase and 3α- and 17β-hydroxysteroid dehydrogenase *in vivo*. The deethylated 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* (Babic-Gojmerac *et al*., 1989).

Subcutaneous administration to Fischer rats of atrazine at 16.6 mg/kg bw from the first day of gestation was reported to increase the conversion of testosterone to 5α-dihydrotestosterone in the anterior hypothalamus of 28-day-old female, but not male, offspring. When 21-day-old offspring were examined after exposure during gestation and lactation, males had a decreased capacity to convert testosterone to either 5α-androstane-3α,17β-diol or 5α-dihydrotestosterone, while no effects were seen in females. In contrast, the number of 5α-dihydrotestosterone receptors in the prostate was enhanced in 21-day-old males exposed during gestation and lactation but not in 28-day-old males exposed only during gestation (Kniewald *et al.*, 1987). Studies *in vitro* have demonstrated inhibition of androgen metabolism by atrazine when incubated with rat pituitary homogenates (Kniewald *et al*., 1979; Babic-Gojmerac *et al*., 1989).

Under equilibrium conditions, atrazine was unable to compete with oestradiol for binding to rat uterine oestrogen receptors. Weak competition was noted when the cytosol was preincubated at 25°C prior to incubation with the tracer (Tennant *et al*., 1994a).

Treatment of adult, ovariectomized Sprague-Dawley rats with up to 300 mg/kg bw atrazine by oral gavage for three days did not increase uterine weight or uterine progesterone concentrations, suggesting lack of oestrogenic potential. When 2 μg/kg bw oestradiol were given by subcutaneous injection in conjunction with an oral dose of 300 mg/kg bw, there was significant inhibition (~25%) of the uterotrophic response (Tennant *et al*., 1994b). In a similar study, immature female Sprague-Dawley rats were dosed with 0, 50, 150 or 300 mg/kg bw atrazine by gavage for three days. Uterine weight was not increased, but there were significant decreases in uterine progesterone receptor binding activity and peroxidase activity. When atrazine was combined with oestradiol, however, it had no anti-oestrogenic effect on the uterus, but decreases were still observed in uterine progesterone receptor binding and peroxidase activity (Connor *et al*., 1996). In the same study, atrazine did not affect basal or oestradiol-induced MCF-7 cell proliferation *in vitro* or affect oestradiol-induced luciferase activity in MCF-7 cells transfected with a Gal4-regulated human oestrogen receptor chimaera.

Female Long Evans and Sprague-Dawley rats which had been determined to have regular four-day oestrous cycles received 0, 75, 150 or 300 mg/kg bw per day atrazine by gavage in a suspension of 1% carboxymethylcellulose for 21 days. Atrazine disrupted the regular oestrous cycles in both strains, at all doses in the Long Evans rats but only at 150 or 300 mg/kg per day for a longer period of time in Sprague-Dawley rats. The increased time spent in vaginal dioestrous was associated with elevated serum progesterone and low oestradiol concentrations, indicative of a repetitive pseudopregnancy condition. This hormonal perturbation was not considered to be conducive to the development of mammary tumours, although there was some indication of prolonged oestrous at the lowest dose tested (Cooper *et al*., 1996).

Sprague-Dawley and Fischer 344 rats were fed atrazine at 0, 10, 70, 200 or 400 mg/kg of diet (ppm), the highest dose being the maximum tolerated dose (resulting in a 10–15% reduction in body-weight gain), for 24 months. Atrazine at 400 ppm lengthened the oestrus cycle of the Sprague-Dawley rats and increased the percentage of days in oestrus (i.e. days

under the influence of increased endogenous oestrogen) earlier in life than in controls. This effect was associated with an increased incidence and earlier age of onset of mammary 'tumours' [type not specified] in this sensitive rat strain. Feeding of atrazine at 70 ppm had no effect on these parameters when compared with vehicle-treated controls. The response of Fischer 344 rats to atrazine was clearly different from that of Sprague-Dawley rats, as atrazine at similar doses did not affect circulating oestrogen and prolactin levels, the percentage of days spent in oestrus or the incidence or time of onset of mammary gland neoplasms (Wetzel *et al*., 1994).

The effects of atrazine on the luteinizing hormone (LH) surge was investigated in female Sprague-Dawley rats. After ovariectomy, the animals received an implanted sustained-release capsule containing oestradiol-17β (4 mg/mL sesame seed oil) and were then given atrazine by gavage at a daily dose of 300 mg/kg bw for three days. The time-course of the LH surge was monitored from 11.00 h on the third day. Control animals had peaks at 18.00 h, whereas treated animals had only a slight increase in LH at 22.00 h. After exposure to 0, 2.5, 5, 40 or 200 mg/kg atrazine for 30 days (the last three days after ovariectomy), the LH surge was delayed and attenuated at the highest dose (Simpkins *et al*., 1998).

Groups of 80 eight-week-old intact or ovariectomized female Sprague-Dawley rats received atrazine in the diet at concentrations of 0, 25, 50, 70 or 400 ppm. Twenty rats per group were necropsied after 52 weeks of treatment, and the remainder were examined at 104 weeks. No mammary tumours were found in ovariectomized females, whereas the incidence of mammary carcinomas was increased in intact rats at 50 and 400 ppm, and the incidence of fibroadenomas was significantly greater than that in controls at 50, 70 and 400 ppm (Stevens *et al*., 1998, 1999).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

Data on Ontario farm families from the 1986 Canadian Census of Agriculture were used to assess the effect of exposure of men to pesticides on pregnancy outcome. Use of a number of pesticides and chemicals, including atrazine, in the three-month period preceding a pregnancy was assessed from a questionnaire completed by 1898 couples who conceived during the study period. The use of atrazine itself was not associated with increased odds ratios for miscarriage, pre-term delivery or babies who were small for gestational age, although combinations of activities involving exposure to a variety of chemicals including atrazine generated odds ratios of 2 or greater in some instances (Savitz *et al*., 1997).

4.3.2 *Experimental systems*

Atrazine was tested for teratogenicity in both natural and buffered waters in the FETAX (frog embryo teratogenicity assay-*Xenopus*). The LD_{50} values for embryos were 100 mg/L in buffered water and 126 mg/L in natural water samples, with corresponding effective concentrations (EC_{50}) for malformations of 33 mg/L and < 8 mg/L, indicating

that atrazine is more teratogenic than embryo-lethal in this system. The lowest effective concentrations of atrazine were 11 mg/L in buffered samples and 1.1 mg/L in natural waters (Morgan *et al*., 1996). [The Working Group noted that the embryotoxic effects occurred only at high concentrations of atrazine approaching its maximal water solubility.] Atrazine was included in a group of pesticides characterized as only slightly toxic after application to developing mallard embryos (Hoffman & Albers, 1984).

It was reported in an abstract that subcutaneous injections of atrazine to neonatal rats on days 4–7 after birth prolonged the period of vaginal opening (Zeljenkova & Vargova, 1996). Daily exposure of adult Fischer rats to 0 or 120 mg/kg bw atrazine by oral gavage in a suspension in paraffin oil for seven days reduced the body weights of both males and females. Fewer treated females had normal oestrous cycles, and the number of days in dioestrous was significantly increased. When both males and females were exposed or when exposed females were mated with unexposed males, fertility was reduced during the first week after exposure, but pregnancy outcome was not affected in those females that became inseminated. No similar effects were observed when only the males were exposed, but atrazine did cause a significant increase in the relative weights of the pituitary and prostate (Šimic *et al*., 1994).

Groups of 10 adult female Fischer 344 rats received 0 or 120 mg/kg bw per day atrazine by oral gavage six times at two-day intervals, and the oestrous cycle was evaluated during and for 12 days after the treatment period. Two weeks later, they were mated to untreated males, and their offspring were evaluated for spontaneous motor activity at 70 days of age and avoidance conditioning at 72 and 73 days of age. The body weights of the dams were reduced during the treatment period, but no effects were noted on the oestrous cycle, conception or litter size. Female offspring showed increased motor activity, while males had shorter latency times and increased shock avoidance (Peruzovic *et al*., 1995).

In an evaluation of potential developmental toxicity, groups of 27 CD rats were given atrazine (technical-grade, purity unspecified) at doses of 0, 10, 70 or 700 mg/kg bw per day by gavage on gestation days 6-15. The vehicle was 3% aqueous starch containing 0.5% Tween 80. The dams were necropsied on day 20 of gestation and the fetuses examined for viability, growth and malformations. The incidence of mortality during treatment of dams at the highest dose was 78%; surviving females had reduced body and liver weights at term, but there was no effect on relative liver weight. The rate of post-implantation loss was more than twice that of the controls, and the fetuses of dams that survived this dose showed marked growth retardation. The feed consumption of animals at this dose was significantly reduced throughout the treatment and post-treatment periods. The feed consumption of dams at 70 mg/kg bw per day was slightly but statistically significantly decreased on days 6 and 7, and their body-weight gain was significantly reduced on days 6–10, but all survived to day 20. There were no treatment-related effects on fetal viability, growth or the incidence of external malformations at the low or intermediate doses, although the incidence of several minor skeletal variations was increased in fetuses at the intermediate dose (Infurna *et al*., 1988).

Groups of 19 New Zealand white rabbits were given doses of 0, 1, 5 or 75 mg/kg bw per day atrazine (technical-grade, purity unspecified) by gavage on gestation days 7–19. The vehicle was 3% aqueous starch containing 0.5% Tween 80. The does were necropsied on day 29 of gestation and the fetuses were examined for viability, growth and malformations. Spontaneous abortions were observed in two does at the high dose and in one doe each at the intermediate and low doses. Does at the high dose had severely reduced feed consumption, reduced body-weight gain, reduced absolute but not relative liver weights, an increased incidence of fetal resorptions and post-implantation loss and decreased fetal body weights of the offspring; in addition, skeletal ossification was noted in this group. There were no dose-related increases in the incidence of malformations (Infurna *et al*., 1988).

Atrazine was a component of two mixtures designed to mimic the contaminants of groundwater due to agricultural practices that were evaluated for developmental and reproductive toxicity. The mixture contained several other pesticides, fertilizers and other organic substances commonly found in groundwater at two sites in the United States. CD-1 mice were evaluated in a continuous breeding protocol, and a standard study of developmental toxicity was conducted in Sprague-Dawley rats exposed on days 6–20 of gestation. The animals received drinking-water containing the mixtures, in which the concentrations of atrazine were 0, 0.5, 5 and 50 ng/mL (equivalent to 1, 10 and 100 times the median concentration of atrazine at the two sites). In mice, no effects were noted on the reproductive performance of F_0 or F_1 individuals or on spermatogenesis, epididymal sperm concentration, per cent motile sperm, per cent abnormal sperm or the histological appearance of the testis. No evidence of developmental toxicity was observed in rats (Heindel *et al*., 1994).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 5 for references)

Atrazine did not induce mutation in bacteriophage, bacteria, *Saccharomyces cerevisiae* or *Nicotiana tabacum*, whereas mutations were induced in *Schizosaccharomyces pombe*, *Aspergillus nidulans*, *Zea mays* and *Drosophila melanogaster*; conflicting results were obtained with *Hordeum vulgare*. In *Drosophila melanogaster*, sex-linked recessive lethal mutations were induced in two studies but not in a third. 6-Thioguanine-resistant mutants were induced in cultured Chinese hamster lung V79 cells, but 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 *A. nidulans*; conflicting results were obtained with *S. cerevisiae*. Mitotic recombination was not increased by atrazine in *S. cerevisiae*, while conflicting results were obtained with *A. nidulans*. Aneuploidy was induced in *Neurospora crassa, A. nidulans* and *D. melanogaster*. An assay for micronucleus induction in *Tradescantia* gave negative results.

Table 5. Genetic and related effects of atrazine

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Escherichia coli PQ37, SOS repair	–	–	1000 µg/plate	Ruiz & Marzin (1997)
Bacteriophage T4, forward mutation	–	NT	20 µg/plate	Andersen *et al.* (1972)
Bacteriophage, reverse mutation	–	NT	1000 µg/plate	Andersen *et al.* (1972)
Salmonella typhimurium, forward mutation, $8AG^R$	–	–	250	Adler (1980)
Salmonella typhimurium TA100, TA98, TA1535, TA1537, TA1538, reverse mutation	NT	–	5000 µg/plate	Simmon *et al.* (1977)
Salmonella typhimurium TA100, TA98, TA1535, reverse mutation	–	–	100 µg/plate	Lusby *et al.* (1979)
Salmonella typhimurium TA100, TA98, reverse mutation	NT	–	1100 µg/plate	Bartsch *et al.* (1980)
Salmonella typhimurium TA100, TM677, reverse mutation	NT	–[c]	30 000 µg/plate	Sumner *et al.* (1984)
Salmonella typhimurium TA100, TA98, TA97, TA1535, TA1537, TA1538, reverse mutation	–	–	1000 µg/plate	Kappas (1988)
Salmonella typhimurium TA100, reverse mutation	NT	+[c]	NR	Means *et al.* (1988)
Salmonella typhimurium TA100, TA98, TA97, TA102, reverse mutation	–	–	1000 µg/plate	Mersch-Sundermann *et al.* (1988)
Salmonella typhimurium TA100, TA98, TA97, TA1535, TA1537, TA1538, reverse mutation	–	–	1000 µg/plate	Zeiger *et al.* (1988)
Salmonella typhimurium TA100, TA98, TA97, reverse mutation	–	NT	2000 µg/plate	Butler & Hoagland (1989)
Salmonella typhimurium TA100, TA98, TA102, TA1535, TA1537, reverse mutation	–	–	1000 µg/plate	Ruiz & Marzin (1997)
Salmonella typhimurium TA100, TA98, reverse mutation	–	–	1000 µg/plate	Morichetti *et al.* (1992)
Salmonella typhimurium TA1530, TA1531, TA1532, TA1534, *his* G45, reverse mutation (spot test)	–	NT	NR	Seiler (1973)
Salmonella typhimurium (eight unidentified strains), reverse mutation	–	NT	NR	Andersen *et al.* (1972)
Salmonella typhimurium (strains not identified), reverse mutation	–	–	NR	Adler (1980)
Escherichia coli, forward mutation, Amp^R	–	–	430 µg/plate	Adler (1980)

Table 5 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Saccharomyces cerevisiae, gene conversion	–	+[c]	10	Plewa & Gentile (1976)
Saccharomyces cerevisiae, gene conversion	–	–	2000	Adler (1980)
Saccharomyces cerevisiae, gene conversion	–	–	4000	de Bertoldi *et al.* (1980)
Saccharomyces cerevisiae, mitotic recombination	–	NT	50	Emnova *et al.* (1987)
Saccharomyces cerevisiae, gene conversion (stationary phase cells)	+	NT	64 800	Morichetti *et al.* (1992)
Saccharomyces cerevisiae, gene conversion (logarithmic phase cells)	+	NT	540	Morichetti *et al.* (1992)
Saccharomyces cerevisiae, reverse mutation (stationary phase cells)	–	NT	75 600	Morichetti *et al.* (1992)
Saccharomyces cerevisiae, reverse mutation (logarithmic phase cells)	(+)	NT	2160	Morichetti *et al.* (1992)
Aspergillus nidulans, gene conversion	–	NT	8000	de Bertoldi *et al.* (1980)
Aspergillus nidulans, mitotic recombination	–	+	NR	Adler (1980)
Aspergillus nidulans, mitotic recombination	–	–	1000	Kappas (1988)
Saccharomyces cerevisiae, forward mutation	–	NT	50	Emnova *et al.* (1987)
Schizosaccharomyces pombe, reverse mutation	+	NT	17.5	Mathias (1987)
Schizosaccharomyces pombe, reverse mutation	+	+[c]	70	Mathias (1987)
Aspergillus nidulans, forward mutation	–	+	2500	Benigni *et al.* (1979)
Aspergillus nidulans, aneuploidy	–	+	2000	Benigni *et al.* (1979)
Neurospora crassa, aneuploidy	+	NT	NR	Griffiths (1979)
Hordeum vulgare, mutation	+	NT	1000	Wuu & Grant (1966)
Hordeum vulgare, mutation	–	NT	200	Stroev (1968)
Zea mays, mutation	+	NT	200	Morgun *et al.* (1982)
Zea mays, mutation	+	NT	NR	Plewa (1985)
Nicotiana tabacum, mutation	–	NT	NR[d]	Briza (1989)
Tradescantia paludosa, micronucleus formation	–	NT	200	Ma *et al.* (1984)
Hordeum vulgare, chromosomal aberrations	+	NT	500 (spray)	Wuu & Grant (1967a)
Hordeum vulgare, chromosomal aberrations	–	NT	2000	Müller *et al.* (1972)

Table 5 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Vicia faba, chromosomal aberrations	+	NT	400	Wuu & Grant (1967b)
Vicia faba, chromosomal aberrations	–	NT	200	Khudoley *et al.* (1987)
Sorghum sp., chromosomal aberrations	+	NT	NR[d]	Liang & Liang (1972)
Sorghum sp., chromosomal aberrations	–	NT	NR	Müller *et al.* (1972)
Sorghum sp., chromosomal aberrations	+	NT	NR	Lee *et al.* (1974)
Nigella damascena, chromosomal aberrations	–	NT	320	Mathias (1987)
Nigella damascena, chromosomal aberrations	+	NT	40[d]	Mathias (1987)
Zea mays, chromosomal aberrations	–	NT	200	Morgun *et al.* (1982)
Drosophila melanogaster, somatic mutation	+		1000 µg/g feed	Torres *et al.* (1992)
Drosophila melanogaster, somatic mutation	+		200 µg/g feed	Tripathy *et al.* (1993)
Drosophila melanogaster, sex-linked recessive lethal mutation	+		100 µg/g feed	Murnik & Nash (1977)
Drosophila melanogaster, sex-linked recessive lethal mutation	–		2000 µg/g feed	Adler (1980)
Drosophila melanogaster, sex-linked recessive lethal mutation	+		200 µg/g feed	Tripathy *et al.* (1993)
Drosophila melanogaster, dominant lethal mutation	+		100 µg/g feed	Murnik & Nash (1977)
Drosophila melanogaster, aneuploidy	+		100 µg/g feed	Murnik & Nash (1977)
Gene mutation, Chinese hamster lung V79 cells *in vitro*, *hprt* locus	–	–[e]	2000	Adler (1980)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	–	2000	Adler (1980)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	–	2000	Adler (1980)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	NT	250	Ishidate (1988)
DNA damage, human lymphocytes *in vitro*	+	–	100	Ribas *et al.* (1995)
DNA repair exclusive of unscheduled DNA synthesis, human lymphocytes *in vitro*	–	NT	25	Surrallés *et al.* (1995)
Unscheduled DNA synthesis, human EUE cells *in vitro*	–	–[e]	650	Adler (1980)
Sister chromatid exchange, human lymphocytes *in vitro*	–	NT	NR	Ghiazza *et al.* (1984)
Sister chromatid exchange, human lymphocytes *in vitro*	–	–	10	Dunkelberg *et al.* (1994)

Table 5 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	0.1	Meisner *et al.* (1992)
Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	1	Meisner *et al.* (1993)
Host-mediated assay, *Escherichia coli* Amp^R in mouse	+		100 po × 1	Adler (1980)
DNA strand breaks, rat stomach, liver and kidney *in vivo*	+		875 po × 1	Pino *et al.* (1988)
DNA strand breaks, rat stomach, liver and kidney *in vivo*	+		350 po × 15	Pino *et al.* (1988)
DNA strand breaks, rat lung *in vivo*	–		875 po × 1	Pino *et al.* (1988)
DNA strand breaks, rat lung *in vivo*	–		350 po × 15	Pino *et al.* (1988)
Rana catesbeiana tadpoles, DNA damage	+		4 µg/mL	Clements *et al.* (1997)
Micronucleus formation, NMRI female mouse bone-marrow cells *in vivo*	+		1400 po × 1	Gebel *et al.* (1997)
Micronucleus formation, NMRI male mouse bone-marrow cells *in vivo*	–		1750 po × 1	Gebel *et al.* (1997)
Chromosome aberrations, mouse bone-marrow cells *in vivo*	–		20 ppm drinking-water × 90 d	Meisner *et al.* (1992)
Dominant lethal effects, mouse spermatids	(+)		1500 po × 1	Adler (1980)
Sperm morphology, mouse	–		600 ip × 4	Osterloh *et al.* (1983)

[a] +, positive; (+), weakly positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; unless untherwise stated, in-vitro test, µg/mL; in-vivo test, mg/kg bw per day; NR, not reported; po, oral; d, days; ip, intraperitoneal

[c] Extracts of atrazine-treated *Zea mays*

[d] Commercial pesticide

[e] Positive with potato microsomes at doses up to 3 mmol/L

Dominant lethal effects were induced in *D. melanogaster*. Chromosomal aberrations were induced in the majority of plants studied and in human lymphocytes *in vitro,* but not in cultured rodent cells. Atrazine did not induce sister chromatid exchange or unscheduled DNA synthesis in cultured rodent or human cells. In a single study, it gave rise to DNA damage in human lymphocytes *in vitro*.

Atrazine induced ampicillin-resistant mutations in *Escherichia coli* in a mouse host-mediated assay. In mammals *in vivo*, atrazine induced DNA damage in tadpoles and DNA strand breakage in rat stomach, liver and kidney cells, but not in lung cells, after oral dosing. It weakly induced dominant lethal effects in mouse spermatids but did not induce morphological abnormalities in mouse sperm heads. It did not induce chromosomal aberrations in bone-marrow cells of mice treated *in vivo*, but induced micronuclei in the bone marrow of female mice, but not male mice, treated *in vivo* in one experiment.

4.5 Mechanistic considerations

Several reports on the mode of action of atrazine-induced mammary tumour development in the Sprague-Dawley rat have been published since the last IARC (1991) review (Eldridge *et al.*, 1994a,b; Stevens *et al.*, 1994; Wetzel *et al.*, 1994; Chapin *et al.*, 1996; Connor *et al.*, 1996, 1998; Eldridge *et al.*, 1998; Simpkins *et al.*, 1998; Thakur *et al.*, 1998). Atrazine at high doses in the diet is associated with an increased incidence and/or an earlier onset of mammary gland tumours in female Sprague-Dawley rats; however, it is not tumorigenic in Fischer 344 rats or in CD-1 mice of either sex.

Short- and longer-term studies performed with Sprague-Dawley and Fischer 344 rats have shown that the mammary tumours induced in Sprague-Dawley rats given high doses of atrazine in the diet are likely to be the result of an accelerating effect on normal, age-related perturbations of the oestrous cycle, with a resultant increase in exposure to endogenous oestrogen and prolactin (Eldridge *et al.*, 1994a; Wetzel *et al.*, 1994; Connor *et al.*, 1998; Eldridge *et al.*, 1998; Hauswirth & Wetzel, 1998; Simpkins *et al.*, 1998; O'Connor *et al*., 1999). Increased exposure to endogenous oestrogen and prolactin most likely leads to the promotion of earlier development of mammary gland tumours (Cutts, 1964; Cutts & Noble, 1964; Manni *et al.*, 1977; Chapin *et al*., 1996). The lack of effect of atrazine on the incidence of mammary tumours and other evidence of proliferative activity in ovariectomized Sprague-Dawley rats fed the highest dose tested (400 ppm) suggest a non-genotoxic mechanism of action associated with hormonal imbalance. The absence of mutagenicity further supports a non-genotoxic mechanism.

Reproductive senescence in untreated, ageing female Sprague-Dawley rats occurs before mid-life, at which time there is a gradual transition from normal four- to five-day oestrous cycles to extended periods of continuous oestrus (Huang *et al.*, 1978; Lu *et al.*, 1979; Simpkins *et al.*, 1998). The basis for this change appears to involve loss of the capacity of the hypothalamus to mediate the release of sufficient LH from the pituitary gland to induce ovulation (Meites *et al.*, 1977; Wise, 1982, 1984). The early appearance and high spontaneous incidence of mammary gland tumours in untreated, ageing female Sprague-Dawley rats have been attributed to this ageing process (Haseman *et al.,* 1984; McMartin

et al., 1992; Simpkins *et al.*, 1998; Stevens *et al.*, 1998). Several studies have demonstrated that administration of atrazine to female Sprague-Dawley rats results in an attenuated LH surge (Simpkins *et al.*, 1998), an increase in the number of days in oestrus (Eldridge *et al.*, 1994a; Wetzel *et al.*, 1994; Eldridge *et al.*, 1998) and histological changes characteristic of extended exposure to endogenous oestrogen (Eldridge *et al.*, 1994a, 1998). Therefore, the mechanism of action appears to involve disruption of the neuroendocrine pathways responsible for the LH surge (Eldridge *et al.*, 1998; Simpkins *et al.*, 1998). The results of studies of carcinogenicity and mode of action indicate that the dose at which this effect occurs in female Sprague-Dawley rats is 70–400 ppm in the diet, whereas dietary exposure of Fischer 344 rats to concentrations as high as 400 ppm has no effect on the incidence of mammary gland neoplasia.

While the details of the disruption of the neuroendocrine pathways that regulate ovulation in Sprague-Dawley rats have not been elucidated, the mechanism probaby does not involve a direct oestrogenic action of atrazine or binding of atrazine and/or its metabolites to the oestrogen receptor. Atrazine did not induce changes in oestrogen-responsive tissues (e.g. increased uterine weight, uterine peroxidase activity or binding to uterine progesterone receptors) in either ovariectomized Sprague-Dawley rats or intact Fischer 344 rats or mice (Tennant *et al.*, 1994b; Connor *et al.*, 1998), and atrazine and its metabolites had no effect on oestrogen receptor binding *in vitro* (Tennant *et al.*, 1994a; Connor *et al.*, 1996, 1998). In fact, atrazine may have weak antioestrogenic activity (Tennant *et al.*, 1994a,b).

The strain difference in the premature onset of mammary tumours (insensitive Fischer 344 rats and sensitive Sprague-Dawley rats) has been attributed to differences in the normal ageing of the reproductive tract in these strains (Eldridge *et al*., 1994b; Stevens *et al.*, 1994; summarized by Chapin *et al*., 1996; Eldridge *et al*., 1998; Thakur *et al*., 1998). Reproductive cycling begins to decline in female Sprague-Dawley rats of less than one year of age, presumably due to loss of sensitivity of the adrenergic neurons in the hypothalamus that control production of gonadotropin-releasing hormone. This loss of stimulation reduces the release of follicle-stimulating hormone and LH and ultimately delays ovulation. The delayed ovulation, in turn, allows prolonged exposure to oestrogens, with an effect seen as persistent vaginal cornification. In contrast, the adrenergic neurons of female Fischer 344 rats do not lose their sensitivity to oestrogen stimulation, and regular cycling is maintained for a much longer time (Lu *et al*., 1979; Estes & Simpkins, 1984). Reproductive ageing in this strain of rat is believed to be due to inability to control daily prolactin surges, prolonged activity of the corpora lutea and greater progesterone release. Fischer 344 rats have been reported to have not only lower exposure to endogenous oestrogen and/or prolactin but also a lower spontaneous incidence of mammary gland tumours than Sprague-Dawley rats (van Zwieten *et al.*, 1994; Eldridge *et al.*, 1998). The endocrine milieu of ageing Sprague-Dawley rats thus favours the development of mammary tumours, resulting in the difference in the incidence of spontaneous tumours in ageing females of these two strains.

In women, reproductive senescence is characterized by ovarian depletion, declining oestrogen levels and, eventually, dioestrus (Chapin *et al.*, 1996; Simpkins *et al.,* 1998). While the pattern of reproductive senescence in female Fischer 344 rats is not identical to that of women, Fischer 344 rats share the following features with women, in contrast to female Sprague-Dawley rats: later onset of senescence, low oestrogen concentrations during late life and an ability to control LH secretion during reproductive senescence (Simpkins *et al.*, 1998). The difference in the pattern of reproductive senescence between women (reduced serum oestrogen) and female Sprague-Dawley rats (prolonged elevated serum oestrogen) suggests that the mechanism of action proposed for atrazine-associated mammary tumours in rats would not be operative in humans. The ageing female Sprague-Dawley rat is thus not an appropriate model for the assessment of mammary tumour development in women (Table 6; Chapin *et al.*, 1996).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Atrazine is a triazine herbicide widely used on a variety of crops, notably maize, sorghum and sugar-cane, for the pre- and post-emergent control of broad-leaved weeds. Occupational exposure may occur through both inhalation and dermal absorption during its manufacture, its formulation and its application by spraying. It is found widely, together with its dealkylated degradation products, in rivers, lakes, estuaries, ground-water and reservoirs. In drinking-water, the levels rarely exceed 1 μg/L. Surveys of various foods and feeds have generally indicated no detectable atrazine residue.

5.2 Human carcinogenicity data

A combined analysis of the results of two cohort studies of agricultural chemical production workers in the United States showed decreased mortality from cancers at all sites combined among the subset of workers who had had definite or probable exposure to triazine. Site-specific analyses in this subset of workers yielded no significant findings; a non-significant increase in the number of deaths from non-Hodgkin lymphoma was seen, but was based on very few observed cases.

A pooled analysis of the results of three population-based case–control studies of men in Kansas, eastern Nebraska and Iowa–Minnesota, United States, in which the risk for non-Hodgkin lymphoma in relation to exposure to atrazine and other herbicides on farms was evaluated, showed a significant association; however, the association was weaker when adjustment was made for reported use of phenoxyacetic acid herbicides or organophosphate insecticides. A sub-analysis of results for farmers in Nebraska, the State in which the most detailed information on atrazine use was available, showed no excess risk for non-Hodgkin lymphoma among farmers who had used atrazine for at least 15 years, after adjustment for use of other pesticides. In a case–control study of non-Hodgkin lymphoma among women in eastern Nebraska, a slight, nonsignificant increase

Table 6. Comparison of reproductive senescence in female rodent strains and women

Parameter	Sprague-Dawley rat	Fischer 344 rat	Women
Start of senescence (% of normal lifespan)	30–40	60–70	60–70
Principal cause of senescence	Hypothalamic failure to stimulate LH/FSH	Hypothalamic failure to control prolactin surges	Depletion of ovarian oocyte content
LH surge capability	Lost	Maintained	Maintained
Predominant cycle pattern	Persistent oestrus	Pseudopregnancy episodes	Menopause (dioestrus)
Oestrogen secretion	Elevated, prolonged	Reduced	Reduced
Oestrogen:progesterone ratio	Elevated	Reduced	Reduced
Prolactin secretion	Persistently elevated	Episodically elevated	Reduced
Spontaneous mammary tumour incidence (lifetime) (%)	30–40	2–5	8–10
Principal known factors that increase mammary tumour risk	Prolactin, oestrogen, chemical mutagens	Prolactin, oestrogen, chemical mutagens	Family history, parity, diet, body weight
Prolactin dependence	High	Median	None

From Chapin *et al*. (1996)
LH, luteinizing hormone; FSH, follicle-stimulating hormone

in risk was seen. In all these studies, farmers tended to have an increased risk for non-Hodgkin lymphoma, but the excess could not be attributed to atrazine.

Less information was available to evaluate the association between exposure to atrazine and other cancers of the lymphatic and haematopoietic tissues. One study of Hodgkin disease in Kansas, one study of leukaemia in Iowa–Minnesota and one study of multiple myeloma from Iowa gave no indication of excess risk among persons handling triazine herbicides.

In a population-based study in Italy, definite exposure to triazines was associated with a two- to threefold increase of borderline significance in the risk for ovarian cancer. The study was small, and potential confounding by exposure to other herbicides was not controlled for in the analysis.

5.3 Animal carcinogenicity data

Atrazine was tested for carcinogenicity in one study in mice by oral administration in the diet. No increase in tumour incidence was observed. It was also tested by oral

administration in two studies in Fischer rats and in five studies in Sprague-Dawley rats, including a comparison of intact and ovariectomized females of the latter strain. In Fischer rats, no increase in tumour incidence was observed in one adequate study. The incidence of mammary tumours was increased in intact Sprague-Dawley females in four studies, but no increase was seen in ovariectomized Sprague-Dawley females. Atrazine was also tested by intraperitoneal injection in one study in mice; an increased incidence of lymphomas was reported.

5.4 Other relevant data

N-Dealkylation and conjugation with glutathione are the main metabolic pathways for atrazine in various species *in vivo*. There do not appear to be qualitative differences in the metabolism of atrazine between the strains and species studied that would explain the fact that mammary gland tumours develop in Sprague-Dawley rats but not in Fischer 344 rats or CD-1 mice.

Atrazine has been tested for developmental toxicity in rats and rabbits. No teratogenic effects have been observed. Fetal loss and reduced fetal body weights were seen in rabbits; the incidences of some minor skeletal variants were elevated in exposed fetal rats. No developmental effects were seen in a study of mice and rats exposed to groundwater contaminants that included atrazine.

The evidence from biological assays (e.g. uterine weight, stromal cell proliferation, epithelial cell height) and from in-vitro assays of oestrogen receptors indicates that atrazine does not have intrinsic oestrogenic activity.

Long-term administration of atrazine enhances the onset of reproductive senescence in female Sprague-Dawley (but not Fischer 344) rats, resulting in an earlier onset of persistent oestrus and tissue changes characteristic of long-term exposure to elevated oestrogen levels. Atrazine appears to disrupt neuroendocrine pathways in the hypothalamus by as yet undetermined mechanisms, resulting in attenuation of the luteinizing hormone surge that normally results in ovulation. These hormonal imbalances seen after atrazine administration were associated with an increased incidence and earlier onset of mammary tumours in some but not all studies of carcinogenicity in Sprague-Dawley rats, and not in Fischer 344 rats or CD-1 mice. Ovariectomized Sprague-Dawley rats exposed for two years to the highest dose of atrazine used in the bioassay in which ovariectomized and intact animals were compared did not develop either tumours or other proliferative lesions in the mammary gland.

In contrast to the hormonal changes in Sprague-Dawley rats, reproductive senescence in women is characterized by depletion of the ovarian oocyte content and reduced oestrogen secretion.

No data were available on the genetic and related effects of atrazine in humans. There is weak evidence for genotoxic effects in mammalian cells *in vivo* and *in vitro*. Atrazine was mutagenic in *Drosophila*, yeast and plant cells but was not mutagenic to bacteria. Overall, the results of genotoxicity testing would not appear to bear directly on the strain-specific tumour induction in female Sprague-Dawley rats.

5.5 Evaluation

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

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

Overall evaluation

In making its overall evaluation, the Working Group concluded that the mammary tumours associated with exposure to atrazine involve a non-DNA-reactive, hormonally mediated mechanism. In reaching the conclusion, the following evidence was considered:

(a) Atrazine produces mammary tumours (fibroadenomas, adenocarcinomas) only in intact female Sprague-Dawley rats (not in Fischer 344 rats, CD-1 mice or ovariectomized Sprague-Dawley rats) and does not increase the incidences of other tumour types.
(b) Atrazine affects neuroendocrine pathways of the hypothalamus to accelerate the onset of reproductive senescence in female Sprague-Dawley but not Fischer 344 rats.
(c) Atrazine does not have intrinsic oestrogenic activity.
(d) There are critical interspecies differences in the hormonal changes associated with reproductive senescence.

Therefore, there is strong evidence that the mechanism by which atrazine increases the incidence of mammary gland tumours in Sprague-Dawley rats is not relevant to humans.

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

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