GENERAL REMARKS

In this fifty-third volume of *IARC Monographs*, the carcinogenic risks to humans from exposure to eight individual insecticides, four fungicides and five herbicides, as well as from occupational exposure in spraying and application of insecticides are reviewed. Eight of the pesticides considered were evaluated previously in the *IARC Monographs* programme; those compounds were re-evaluated in this volume owing to the availability of new data on carcinogenicity in exposed populations and/or in experimental animals. Pesticides and related occupational exposures that were evaluated by previous IARC working groups are listed in Table 1.

Table 1. Pesticides and related occupational exposures that have been evaluated previously in the *IARC Monographs*

Compound	Year	Degree[a] of evidence for carcinogenicity		Overall evaluation of carcinogenicity to humans
		Human	Animal	
Insecticides				
Agents and groups of agents				
Aldrin	1987	I	L	3
Aramite®	1974	ND	S	2B
Arsenic and arsenic compounds	1987	S	L	1[b]
Carbaryl	1976	ND	I	3
Chlordane/heptachlor[c]	1987	I	L	3
Chlordecone	1979	ND	S	2B
Chlordimeform	1983	ND	I	3
Chlorobenzilate	1983	ND	L	3
DDT	1987	I	S	2B
Dichlorvos[c]	1987	ND	I	3
Dicofol	1983	ND	L	3
Dieldrin	1987	I	L	3
Endrin	1974	ND	I	3
Hexachlorocyclohexanes (HCH)	1987	I		2B
Technical-grade HCH			S	
α-HCH			S	
β-HCH			L	
γ-HCH (Lindane)			L	
Malathion	1983	ND	I	3
Methoxychlor	1979	ND	I	3

Table 1 (contd)

Compound	Year	Degree[a] of evidence for carcinogenicity		Overall evaluation of carcinogenicity to humans
		Human	Animal	
Insecticides (contd)				
Agents and groups of agents (contd)				
Methyl parathion	1987	ND	ESL	3
Mirex	1979	ND	S	2B
Parathion	1983	ND	I	3
Piperonyl butoxide	1983	ND	I	3
Tetrachlorvinphos	1983	ND	L	3
Trichlorfon	1983	ND	I	3
Zectran[d]	1976	ND	I	3
Mixtures				
Terpene polychlorinates (Strobane®)	1974	ND	L	3
Toxaphene (polychlorinated camphenes)	1979	ND	S	2B
Fungicides				
Captan	1983	ND	L	3
Chlorophenols	1987	L		2B
Pentachlorophenol[c]			I	
2,4,5-Trichlorophenol[e]			I	
2,4,6-Trichlorophenol[e]			S	
Chlorothalonil	1983	ND	L	3
Copper 8-hydroxyquinoline	1977	ND	I	3
Ferbam	1976	ND	I	3
Hexachlorobenzene	1987	I	S	2B
Maneb	1976	ND	I	3
ortho-Phenylphenol	1983	ND	I	3
Quintozene (Pentachloronitrobenzene)	1974	ND	L	3
Sodium *ortho*-phenylphenate	1987	ND	S	2B
Thiram[c]	1976	ND	I	3
Zineb	1976	ND	I	3
Ziram[c]	1976	ND	I	3
Herbicides				
Amitrole	1987	I	S	2B
Chlorophenoxy herbicides	1987	L		2B
2,4-D			I	
2,4,5-T			I	
MCPA			ND	
Chloropropham	1976	ND	I	3
Diallate	1983	ND	L	3
Fluometuron	1983	ND	I	3

Table 1 (contd)

Compound	Year	Degree[a] of evidence for carcinogenicity		Overall evaluation of carcinogenicity to humans
		Human	Animal	
Herbicides (contd)				
Monuron	1976	ND	L	3
Nitrofen (technical-grade)	1983	ND	S	2B
Propham	1976	ND	I	3
Sulfallate	1983	ND	S	2B
Other				
1,2-Dibromo-3-chloropropane[f]	1987	I	S	2B
Dimethylcarbamoyl chloride[g]	1987	I	S	2A
Ethylene dibromide[h]	1987	I	S	2A
Naphthylthiourea (ANTU)[i]	1987	I	I	3
Sodium diethyldithiocarbamate[h]	1976	ND	I	3

[a]I, inadequate evidence; S, sufficient evidence; L, limited evidence; ND, no data; ESL, evidence suggesting lack of carcinogenicity
[b]This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group.
[c]Previous evaluation
[d]And molluscicide
[e]Primarily used as chemical intermediate
[f]Soil fumigant/nematicide
[g]Pesticide intermediate
[h]Soil fumigant
[i]Rodenticide

About 1500 chemicals are registered for use in thousands of pesticide formulations; however, fewer than 50 pesticides account for about 75% of those used (Salem & Olajos, 1988).

Crops are affected by different pests and by competition from weeds, with large variations between climatic and agricultural regions. Several insects and other arthropods, fungi, molluscs and bacteria attack crops, resulting in quantitative and qualitative crop losses. The introduction of new plant species and cultivars in plantation and cash crop farming of monocultures can lead to increased problems. The crop losses caused by pests are great in developed as well as developing countries. In North America, Europe and Japan, losses are estimated to be in the range 10-30%, but in developing parts of the world they are substantially higher: Crop losses due to pests and plant diseases of the order of 40% are common in these areas, and losses of as much as 75% have been reported (WHO/UNEP, 1990).

During the last four decades, chemical control of pests and weeds has been dramatically expanded worldwide to minimize such losses. A study by Smith and Gratz (1984) showed that the greatest demand for pesticides in urban vector control was for insecticides. Pesticides are used worldwide, albeit in varying degrees, depending on dominating crops, stage of development, climatic conditions and prevalence of pests. The general development of agropesticide use has been summarized (WHO/UNEP, 1990); this shows the diversified and increasing use of pesticides in agriculture in five stages, from very low to very high. The stages coincide to a certain extent with the general economic development of countries; however, in an individual country, different agricultural stages may occur at the same time in different farming regions. Some countries may also be at different stages for different variables (agropesticide use level, product range, development of local pesticide industry, distribution structure, regulatory infrastructure, area under control and general level of agricultural development).

Worldwide consumption of pesticides in 1985 was estimated at about 3 million tonnes. According to available data, 20% (equivalent to 600 000 tonnes annually) of the whole market is exported to and used in developing countries (WHO/UNEP, 1990). The major applications of pesticides in 1985 were herbicides (46%), insecticides (31%) and fungicides (18.4%) (Anon., 1985). Estimates of world pesticide sales in 1985 are shown in Table 2.

Table 2. Pesticide market value, 1985, by area and product; million US$[a]

Area	Herbicides	Insecticides	Fungicides	Others	Total
USA	3100	1090	330	330	4850
Western Europe	1475	850	1100	400	3825
East Asia	775	1300	785	90	2950
Latin America	485	655	250	60	1450
Eastern Europe	625	450	230	95	1400
Rest of the world	615	655	105	50	1425
World total	7075	5000	2800	1025	15 900
% of total	44.5	31.4	17.6	6.4	

[a]From Wood Mackenzie Agrochemical Service, personal communication, cited in WHO/UNEP (1990)

Overall pesticide use in agriculture, in terms of amounts applied per hectare, has been very much greater in Japan, Europe and the USA (about 75%) than in the rest of the world, although China is also a major user. The fastest growing market, however, is Africa, with a sales increase of 182% between 1980 and 1984. Other rapidly expanding markets are Central and South America (32%), Asia (28%) and the Middle East (26%). Although herbicide sales have been greater than those of insecticides and fungicides in developed countries and some developing countries and are increasing rapidly, this pattern is not being repeated in other developing countries, where by far the greatest proportion of pesticides used are still insecticides. The 15 most widely used pesticides in seven Asian countries (Bangladesh, India, Nepal, Pakistan, Philippines, Republic of Korea and Thailand) are as follows: carbaryl (insecticide), malathion (insecticide), methyl parathion (insecticide), diazinon (insecticide), monocrotophos (insecticide), endosulfan (insecticide), carbofuran (insecticide), mancozeb (fungicide), paraquat (herbicide), aluminium phosphide (insecticide), methyl oxydemeton (insecticide), phosphamidon (insecticide), 2,4-D [(2,4-dichlorophenoxy)acetic acid] (herbicide), 2-*sec*-butylphenyl methylcarbamate (insecticide) and zinc phosphide (insecticide) (WHO/UNEP, 1990).

Another factor of importance for assessing the potential public health impact of pesticides is the seasonality of their use. Each pest is of importance only during a limited part of the growing season, and human exposures are therefore likely to be limited to the same seasons, when pesticide use occurs. For example, in some parts of West Africa, herbicides and fungicides tend to be used early in the growing season, whereas insecticides are used at a later stage (WHO/UNEP, 1990).

The future use of pesticides depends on several factors. The need for pest control using the available products is important. Other factors are marketing regulations, environmental concerns and the availability of alternative methods. About 25% of all pesticides is presently used in developing countries, mainly on cash crops. Depending on the stage of development of a country, the type and amounts of pesticides will change from a low level of organochlorines on a few crops to a wide range and higher total dosage of insecticides, fungicides and herbicides on a large variety of crops. The present trend is that many crops are submitted to pesticide treatment as soon as land-use is intensified. Public health programmes for control of vector-borne diseases are the other important pesticide application, and the amounts used may currently, in some developing countries, far exceed the amounts used for the control of agricultural pests and diseases (WHO/UNEP, 1990).

Reliable global estimates of morbidity and mortality due to acute exposures to pesticides are not available. In some countries, however, when data are available, they indicate that the problem varies greatly from place to place. For instance, a comparison of mortality due to pesticides in the USA for 1973 and 1974 with the rates of the previous years indicates a decline in pesticide-related fatalities from 152 to 52 between 1956 and 1974. An average of 35 pesticide-related deaths per annum was recorded throughout the 1970s; the majority of these deaths involved either gross safety violations or incompetence. The numbers of deaths due to occupational exposure to pesticides were reported as five in 1973 and seven in 1974 (Hayes & Vaugh, 1977).

In Sri Lanka, on the contrary, yearly pesticide-related deaths in 1975-80 were about 1000 out of 13 000 hospital admissions; of these deaths, about 10-15% were related to occupational exposures. Similar findings were obtained in Indonesia, Malaysia and Thailand (Jeyaratnam *et al.*, 1982, 1987). Educational and safety programmes have been developed by international organizations, such as WHO, UNEP and FAO, to prevent acute poisoning.

The monograph on **occupational exposures in spraying and application of insecticides** specifically covers studies of workers exposed during the use of insecticides; the few studies on workers exposed during the manufacture of insecticides were not included in the monograph. Many epidemiological studies of cancer refer to 'agricultural workers' or to exposures to pesticides generally rather than to insecticides specifically, and these studies were also not evaluated. Surprisingly few epidemiological studies are available on occupational exposures in spraying and application of insecticides, given that many of these compounds have been in common use since 1950. For several chemicals considered in this volume, the available epidemiological studies concerned populations with multiple exposures to different pesticides, and the information often did not allow the Working Group to disentangle their separate effects. Groups recorded as exposed to insecticides specifically may be exposed to one or a number of the insecticides considered in this volume, to other specified insecticides or, as is more usually the case, to unspecified insecticides. All such studies were taken into account in evaluating the carcinogenic risk of occupational exposure in the spraying and application of insecticides.

Of the insecticides reviewed in this volume, **aldicarb** is used only for agricultural purposes; **dichlorvos** is used to protect stored grain, in veterinary medicine and in the control of insects in houses and other buildings; **chlordane** and **heptachlor** are also used for insect control (notably termites) in buildings. The synthetic pyrethroids, **permethrin, deltamethrin** and **fenvalerate**, are used in agriculture as well as in houses and gardens and for the protection of stored products. **DDT** has been used in crop protection but has also been used extensively for the control of insect-borne diseases.

Captafol is a non-systemic, protective and curative fungicide that has been used on plants and for seed treatment; it has also been used as a wood preservative. **Ziram** and **thiram** are both foliar fungicides; thiram is also used in seed treatment, and both are used as curing agents in the rubber industry. **Pentachlorophenol** is used principally as a wood preservative; it is used to protect against wood-boring insects and as a herbicide. Pentachlorophenol is also a widespread environmental pollutant; residues are found in all media and in humans. The US National Human Monitoring Program for Pesticides found in a three-year study with the collaboration of the US Public Health Service that pentachlorophenol occurred in 85% of urine samples from the general population of the USA (Kutz *et al.*, 1978).

Of the herbicides, **monuron** is used for total weed control in non-crop areas; **trifluralin** is a selective herbicide used for pre-emergence control of grasses and broad-leafed weeds; and **picloram** and the triazines, **atrazine** and **simazine**, are used in crop and non-crop areas against broad-leafed weeds and/or grasses. Simazine is also used as an aquatic herbicide and algicide.

Some pesticides reviewed in this volume, e.g., chlordane, DDT, captafol, aldicarb, monuron, trifluralin, picloram and pentachlorophenol, now have restricted use in some countries. Use of the organochlorine insecticides DDT and chlordane in agriculture reached a maximum in the 1960s but has declined since, and they have been banned in several countries. There continues, however, to be widespread general exposure to persistent organochlorine pesticides in developing countries. These compounds are known to bioaccumulate in the environment and in food chains. Exposure of humans to pesticide residues in food has been reported in only two 'market basket' surveys from North America; the lack of such data from developing countries makes it difficult to estimate exposure or potential exposure and bioaccumulation for these regions.

Several quantitative and qualitative difficulties are encountered in evaluating the precise exposures of people working with pesticides:

(i) Workers involved in the production of pesticides are exposed both to technical products, which generally contain about 95% pure material, as well as to formulated products, which contain from 10 to 50% of the active ingredient.

(ii) Formulations contain 'inert' non-pesticidal ingredients, some of which are known carcinogens and mutagens, although efforts have been made to remove them (US

Environmental Protection Agency, 1987, 1989). Such substances are added to pesticide products as solvents, emulsifiers and aerosol propellants and may, at some dose, have toxicological effects; however, the toxicity of these chemicals has generally not been tested.

(iii) Public health and agricultural use of pesticides involves handling formulated products, mixing them for spraying, spraying, eventually disposing of excess material and cleaning spray equipment. Formulations are generally prepared for application by the applicators themselves, and technical products and application patterns differ in various parts of the world. Workers in developing countries may have high occupational exposures to pesticides owing to inadequate working conditions (lack of protective clothing, unsafe pesticide spraying and storage practices) or to deficient sociocultural conditions (illiteracy, bad housing, inefficient garbage disposal and sewage systems, etc.). Residues in food and water are another potential source of exposure. In this case, the levels of pesticides involved are several orders of magnitude lower than those associated with production and application.

(iv) Nitroso derivatives of pesticides may occur as impurities in technical products; these include *N*-nitrosodi-*n*-propylamine in trifluralin and *N*-nitrosodiethylamine and *N*-nitrosodiisopropylamine in picloram. In both situations, the amount of nitrosamines permissible in technical material has been regulated. Where possible, the Working Group took note of the likely effect of these and other impurities when evaluating the reported studies. Since the interaction of nitrite with chemicals is considered to be a general phenomenon, however, not specifically related to the use of pesticides, and has been dealt with in other *IARC Monographs*, such studies are not included in the evaluations in these monographs.

Biologically active impurities are known to arise from synthesis, formulation and storage of pesticides. Regulatory bodies require the specification of technical material in order to identify impurities present at levels higher than 0.1-1% (WHO, 1985). Furthermore, in some cases, data on toxicity are required for impurities present at levels higher than 1%.

Impurities may also be formed owing to interaction with coformulants and to storage under inappropriate conditions (WHO, 1986), but little information is available. There are indications that the resulting impurities might be much more acutely toxic than the original compound (WHO/UNEP, 1990), but the Working Group was not aware of any study showing increased long-term toxicity due to contamination. Dioxins and other impurities found in technical products, such as pentachlorophenol and 2,4,5-T, have been discussed in detail elsewhere (IARC, 1977).

For several of the chemicals that are considered in this volume, occupational cohorts were studied but no information was available on smoking habits. Since smoking is a well-known cause of several cancers, including those of the lung, larynx, oesophagus and bladder, the possibility must be entertained that any association found between occupational exposure and tobacco-related cancer sites is due in fact to smoking. In making such an evaluation, the following points are usually considered:

(i) The occurrence of only *one* tobacco-related cancer in association with the exposure under consideration makes tobacco use an unlikely explanation; in particular, the incidence of or mortality from non-neoplastic diseases related to tobacco should be taken into consideration.

(ii) When exposure-response patterns are observed, it is unlikely that tobacco use is an explanation, because use of tobacco rarely parallels an exposure pattern (Siemiatycki *et al.*, 1988).

(iii) Comparison between crude and smoking-adjusted odds ratios for lung cancer across different occupations showed no systematic difference between the two (Blair *et al.*, 1985). Analysis of smoking habits among occupational categories in large populations also suggests that differences are not likely to exert a strong confounding effect (Brackbill *et al.*, 1988; Stellman *et al.*, 1988; Levin *et al.*, 1990).

(iv) Since the relative risks for cancers caused by tobacco are known quite precisely, it is possible to calculate the magnitude of a smoking differential that must occur in order to explain differences in many observed cancer rates. It can be shown arithmetically that in order to distort risk estimates appreciably, the distribution of smoking habits in an occupational cohort must be quite different from that of the comparison population.

(v) Tobacco use complicates evaluation of tobacco-related cancers among farmers, since data from around the world indicate that they have a lower prevalence of smoking than the general population. This is especially relevant for the monograph on occupational exposures in spraying and application of insecticides. Farmers in several countries, however, have increased risks for soft-tissue sarcomas and for cancers of the lymphohaematopoietic system, brain, prostate, stomach and lip (Pearce & Reif, 1990).

In general, the published studies on carcinogenicity and toxicity in experimental systems were carried out using pesticidally active material (nonetheless, sometimes of unspecified purity) rather than using a formulated product; human exposure, in contrast, is often to a number of formulated products. Extrapolation from experimental data based on pure compounds to the human situation in which technical products are used is therefore not straightforward.

In several studies of the carcinogenicity of DDT in mice (see pp. 202 *et seq.*), an inverse relationship was observed between the incidence of liver neoplasia and lymphoma; more specifically, increases in the incidence of liver tumours appeared to be related to decreases in that of lymphoma. In some studies, this phenomenon may be explained by a reduction in survival due to toxicity or other factors in high-dose groups—those groups that have often shown increased incidences of liver tumours; however, this explanation does not apply to all cases in which the phenomenon has been observed. The Working Group reported the incidence of lymphomas in those studies in which it differed in treated groups from that in controls. It was the position of the Working Group that the observation of decreases in the incidences of certain tumours is generally not relevant to an evaluation of carcinogenicity as defined by the IARC: 'an increase in the incidence of malignant neoplasms; the induction of benign neoplasms may in some circumstances contribute to the judgement that (an) exposure is carcinogenic'.

Pesticides hold a somewhat unique position among man-made chemicals. Because of their high biological activities, numerous studies have been performed on their toxicology. Unfortunately, for a number of reasons, such data have rarely been published and therefore cannot be evaluated here, even though they are summarized in other WHO publications. Mention is made whenever information was derived from such publications.

WHO (1985) has established specifications for many pesticides used in public health. These include a description of the material and its ingredients, its chemical and physical properties and methods for determining those properties. Specifications have been set for both technical-grade products and common formulations. FAO (1987) has similar specifications for plant protection products. These also include specifications for the technical material and common formulations.

Codex maximum residue limits are applied to pesticide residues present in raw agricultural products treated with a pesticide according to good agricultural practice. They are usually at the parts per million level. For commodities entering international trade, maximum residue limits are applicable at the point of entry into a country. In addition, each country has its own national maximum residue limits or tolerances, which may differ from that of the Codex Alimentarius (FAO, 1978; Codex Committee on Pesticide Residues, 1990).

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