OCCUPATIONAL EXPOSURES IN SPRAYING AND APPLICATION OF INSECTICIDES[1]

1. Exposure Data

The public health impact of pesticides, including insecticides, used in agriculture has recently been reviewed (WHO/UNEP, 1990). The overview presented in sections 1.1 and 1.2.1 of this monograph makes extensive reference to that document.

1.1 Historical perspectives

The use of inorganic chemicals to control insects possibly dates back to classical Greece and Rome. Homer mentioned the fumigant value of burning sulfur; Pliny the Elder advocated the insecticidal use of arsenic and referred to the use of soda and olive oil for treating legume seeds. The Chinese were employing moderate amounts of arsenicals as insecticides by the sixteenth century, and, not long afterwards, nicotine was used, in the form of tobacco extracts. By the nineteenth century, both pyrethrum (a natural insecticide obtained by extraction of chrysanthemum flowers) and soap were being used for insect control, as was a combined wash of tobacco, sulfur and lime to combat insects and fungi.

The middle of the nineteenth century marked the first systematic scientific studies into the use of chemicals for crop protection. Work on arsenic compounds led to the introduction in 1867 of Paris green, an impure copper arsenite, used in the USA to check the spread of the Colorado beetle; by 1900, its use was so widespread that probably the first insecticide legislation in the world was enacted to control its use.

In the years between the two World Wars, both the number and the complexity of chemicals for crop protection increased. Tar oils, which include anthracene, creosote and naphtha, were used to control eggs of aphids on dormant trees. During the Second World War, the insecticidal potential of DDT was discovered in Switzerland and insecticidal organophosphorus compounds were developed in Germany. In 1945, the first soil-active carbamate herbicides were discovered by researchers in the United Kingdom, and the organochlorine insecticide chlordane was introduced in the USA and in Germany. Shortly afterwards, the insecticidal carbamates were developed in Switzerland.

During the 1970s and 1980s, many new insecticides were introduced. Typically, these are based on a new understanding of biological and biochemical mechanisms of pest control and

[1]Insecticidal use of arsenicals is not included in this monograph. The carcinogenic activity of arsenic and arsenic compounds was evaluated by previous IARC working groups (IARC, 1980, 1987).

are often effective at lower doses than the older ones. A new, important group of insecticides is the synthetic light-stable pyrethroids, which were developed from naturally occurring pyrethrins. Increasing knowledge of host–pest interactions has led to a new approach to the design of insecticides and new formulations and ways of application.

1.2 Use and exposure

1.2.1 *Trends in worldwide use of insecticides*

A wide range of insecticides, fungicides, molluscicides, bactericides and herbicides, including fumigants, are used, mainly in developed countries but also (and increasingly so) in developing countries. Organochlorine insecticides are still used in the latter but are being replaced gradually by organophosphorus, carbamate and pyrethroid insecticides. Another important use for insecticides is in the control of ectoparasites.

The pests responsible for the greatest losses are locusts, but effective, inexpensive insecticides to control the massive locust infestations that plague some parts of the world have yet to be developed. The crop on which most insecticides are used is cotton.

The most common formulations are emulsifiable concentrates and ultra-low volume concentrates. In urban areas, organochlorine insecticides are now little used; they have been replaced by pyrethrins, pyrethroids and organophosphorus insecticides, such as chlorpyrifos, dichlorvos, fenitrothion, fenthion, malathion and temephos. The worldwide requirements for pesticides in urban public health programmes worldwide are substantial, the annual cost being over US $ 100 million. In 1980, about 50 000 tonnes of pesticides were used in public health programmes in developing countries. It was estimated that such programmes account for about 10% of total pesticide use, the remainder being used mainly in agriculture.

Insecticides are used on a number of crops of different relative importance for world agricultural production (Table 1). Herbicides are used mainly on corn and soya beans, insecticides mainly on cotton and horticultural crops and fungicides mainly on horticultural crops and wheat. Worldwide use of insecticides in 1985 was approximately 29% in Japan and the Far East, 23% in the USA, 12% in western Europe, and 36% in the rest of the world; the corresponding values for herbicides were: 10, 46, 21 and 22%, respectively.

Table 1. The insecticide market by crop in 1985 (million US $ in 1984)[a]

Crop	USA	Western Europe	Japan & Far East	Rest of world	Total
Maize	262	70	28	96	456
Cotton	206	24	149	590	969
Wheat	16	34	23	35	108
Sorghum	20	6	6	24	56
Rice	24	7	498	104	633
Other grains	7	22	5	12	46
Soya beans	30	4	27	67	128
Tobacco	33	8	31	38	108
Peanuts (Groundnuts)	22	1	19	23	65
Sugar beets	8	59	6	24	97
Sugar cane	6	—	9	27	42

Table 1 (contd)

Crop	USA	Western Europe	Japan & Far East	Rest of world	Total
Coffee	—	—	5	39	44
Cocoa	—	—	13	25	38
Tea	—	—	38	19	57
Rubber	—	—	11	8	19
Other field crops	22	43	45	60	170
Alfalfa	18	8	2	4	32
Other hay and forage	2	3	2	6	13
Pasture and rangeland	6	2	2	9	19
Fruit, vegetables and horticultural crops	299	213	329	327	1168
Total	981 (23%)	504 (12%)	1248 (29%)	[1537] (36%)	4268 (100%)

[a]From WHO/UNEP (1990)

1.2.2 *Application principles and techniques*

Methods of application of pesticides, including insecticides, have been reviewed (Haskell, 1985). The aim of insecticide application is to distribute a small amount of active ingredient to the appropriate insect with minimal contamination of non-target organisms. The diversity of possible targets—e.g., insects, plants, soil, walls of dwellings—necessitates a variety of application techniques, which can be summarized in five groups:

(i) release or propulsion through the air to the target either
- in the solid state as dusts or granules, or
- in the liquid state as sprays;

(ii) application directly to or injection into the plant;
(iii) injection into the soil;
(iv) release into irrigation water; or
(v) release into the air with diffusion to the target (fumigation).

Hazards due to drift and inhalation of particles less than 30 μm in diameter have resulted in a decline in the use of dusts, except for treating seeds and small seedlings at the time of transplanting, for which specialized equipment is available. Seed treatment is ideal for protecting young plants with minimal quantities of toxicant, but as phytotoxicity can be a problem the use of granules accurately placed alongside seeds at sowing has increased. Equipment is also available for spot treatment of individual plants, and granules are often broadcast, sometimes by hand; but this requires a higher dose than other application techniques (Matthews, 1985).

Special equipment is needed to meter granules, so the majority of pesticides are applied as sprays. The volume of spray liquid applied varies with the size of target and on whether discrete droplets or a complete film of spray is to be distributed on the target. While 50 to more than 1000 litres/ha may be applied to field crops, bushes and trees, as little as 5 litres/ha

of pesticides may be applied using newer ultra-low volume spray techniques (Matthews, 1985).

Less than 0.1% of the applied dose may reach insect pests in a field crop treated with a foliar spray, whereas up to 30% of an applied herbicide penetrated experimental plants sprayed in a greenhouse (Matthews, 1985). The low efficiency of sprays has been due largely to the wide range of droplet sizes emitted by traditional spraying equipment; control of droplet size is designed to suit the intended target and the method of application (Table 2).

Table 2. Optimal droplet sizes[a]

Target	Droplet size (μm)
Flying insects	10-50
Insects on foliage	30-50
Foliage	40-100
Soil (and avoidance of drift)	250-500
Aerial applications	> 500

[a]Adapted from Matthews (1985)

The five basic classes of ground application equipment include hydraulic sprayers, air sprayers, foggers and aerosol generators, power dusters and hand-held equipment (Anon., 1981). In hydraulic sprayers, the pesticide is delivered under pressure by a pump to one or more nozzles. The type of nozzle regulates droplet size and spray pattern. Hydraulic sprayers are of four basic types:

(i) *Multiple-purpose sprayers* provide versatility for a variety of problems. Spray pressure is adjustable; tank size ranges from 190 to 750 litres; sprayers are skid- or wheel-mounted and powered by auxiliary engines or a power take-off; spray is dispensed through a hand-gun or field boom.

(ii) *Small general-purpose sprayers* are useful for small jobs, for instance in greenhouses, large gardens and golf courses. Tank size ranges up to 100 litres; power is provided by a small engine that furnishes a wide range of pressures (50-500 psi [3.5-35.2 kg/cm^2]); spray is dispensed through a hand-gun or short boom, and the sprayers are usually mounted on a hand-operated cart or attached to a garden tractor.

(iii) *Low-pressure, low-volume sprayers* are commonly used on crops. They can be mounted directly on equipment or are equipped with wheels; tank size ranges up to 950 litres; power is usually provided by a power take-off, but may be supplied by an auxiliary engine; operating pressure is up to 100 psi [7.0 kg/cm^2] and spray is dispensed through a field boom.

(iv) *High-pressure, high-volume sprayers* are used by fruit growers and truck farmers in order to obtain good penetration and coverage in tall growing trees and dense crop growths. These sprayers are essentially the same as multiple purpose sprayers except that larger engines provide up to 1000 psi [70.3 kg/cm^2] and tank size ranges up to 2300 litres (Anon., 1981).

Air sprayers (also known as ultra-low-volume, concentrate blower, airblast and airmist sprayers) are used for spraying orchards, large shade trees and field crops. Pesticides are applied in concentrated form, using relatively small volumes of water, in contrast to hydraulic

sprayers. A low-volume pump delivers the liquid spray under low pressure to the fan, where it is discharged into an air stream in small droplets by a group of nozzles or shear plates. Pump pressures range from 50 to 400 psi [3.5-28.1 kg/cm^2], and fans deliver 5000-25 000 ft^3/mn [2.4-11.8 m^3/s] or air velocities of 100-150 mile/h [160-240 km/h] (Anon., 1981; Joyce, 1985).

Foggers or aerosol generators are designed primarily for control of mosquitoes and flies in large buildings, parks, resorts and communities. These machines disperse fine particles of pesticides into the air, as fogs or mists, where they remain for a considerable time. Fogs and aerosols are produced by either thermal or mechanical methods or a combination. Aerosol equipment is not practical for application of most agricultural pesticides because of its tendency to create drifts (Anon., 1981).

Power dusters are run by engine or power take-offs. Like airblast sprayers, dusters also utilize air streams from a centrifugal fan to carry the pesticide to the target area. They may have single or multiple outlets. Dusters may be impractical for application of some pesticides because of drift hazard (Anon., 1981).

Hand-held equipment is designed primarily for application of pesticides in small areas; this type of equipment includes hand-pump atomizers, aerosol dispensers, compressed air sprayers, knapsack sprayers and dusters. The *hand-pump atomizer* has a hand-operated pump to force an air stream over the tip of a siphon tube; pesticide is sucked from the tube and atomized in the air stream. These sprayers were commonly used to control flying insects in houses but have been almost completely replaced by aerosol dispensers. *Aerosol dispensers* are probably the most common type of applicator for household pest sprays. The pesticide and a propellant, usually freon, are forced, under pressure, through an atomizing nozzle. *Compressed air sprayers* are designed to hold 4-12 litres in the tank. A hand pump is used to pressurize the tank and deliver the pesticide, under pressure, to the nozzle. Spray patterns and droplet size can be regulated by nozzle type. Solutions, emulsions and suspensions of pesticides can be used at pressures of 30-50 psi (2.2-3.5 kg/cm^2]. *Knapsack hand sprayers* are carried on the back and usually have a capacity of 20 litres; a hand-operated piston or diaphragm pump provides the pressure (30-100 psi [2.2-7.0 kg/cm^2]) to expel the pesticide. *Duster hand sprayers* range from small self-contained units to those mounted on wheelbarrows. Air velocity for dispensing the dust is created by a plunger, hand crank or belt attached to a fan or blower (Anon., 1981).

The subject of aerial spray equipment and accessories is complex; however, many aspects of aerial application are similar to ground application. For example, sprayers are basically constructed of the same components. Several classes of aircraft may be used for the application of pesticides, including high-wing monoplanes, low-wing monoplanes, biplanes, multi-engine aircraft (used extensively in forest and rangeland application) and helicopters. Helicopters have some advantages over fixed-wing aircraft: operation at slower speeds; increased safety; improved accuracy of swath, coverage and placement of chemical; and operation without airport facilities. Pesticides are generally released at greater heights than from conventional sprayers (Anon., 1981).

Application equipment can be constructed for dispersing dry or liquid pesticides. Dry chemicals are dispensed from fixed-wing aircraft primarily by ram-air spreaders and spinners. In a ram-air spreader, dry materials are metered from a hopper into the propeller slip stream. The fact that ram-air systems cannot spread materials in a wide swath led to the

development of spinners, which consist of spinning vanes mounted under the hopper that throw material outward in a uniform pattern. The use of spreaders and blowers can nearly double the swath width. In helicopters, two types of dispenser are used: a blower driven by the engine forces dry material from two side tanks and out of short booms, but the material may be spread using spinners instead of the boom; or a single hopper can be suspended on a cable and dry material is dispensed using spinners (Anon., 1981).

Two types of liquid spray systems exist for fixed- and rotary-wing aircraft: the pressure type, in which the spray is applied under specific pressures; and the gravity-feed type, in which the flow of spray solution from the tank dispersion unit relies on gravity. Swath widths of 12-18 m, in the application range of 1.5 to 15 litres/ha, are normal when material is released 1.5-2.5 m above the ground. Booms for fixed- and rotary-wing aircraft, although mounted differently, are basically the same in construction. Boom pipes are round or aerodynamic in cross section. In a fixed-wing aircraft, they are mounted on the trailing edge of the wing and are usually three-quarters the wing length. Atomizers have a nozzle and a variety of spinning screen cages, discs and wire brushes; they are usually driven by fans or electric motors. Atomizers produce droplets of more uniform size and are useful in low-volume spraying, such as for grasshopper and mosquito control (Anon., 1981).

The present trend in pesticide use is to apply highly concentrated material at low rates: ultra-low-volume rates for mosquito control are as low as 0.15 litres/ha. The use of such formulations requires the use of special equipment and application procedures, as the systems must deliver fine droplets to be effective. This can be accomplished by using spinning or flat fan nozzles that discharge 0.15 litres/ha at 40-55 psi [2.8-3.9 kg/cm^2]. For helicopter operations, a single spinning nozzle may provide adequate output at very low rates such as required for mosquito control. Because the ultra-low-volume systems produce fine droplets, the location of the nozzles is important (Anon., 1981).

1.2.3 *Occupational exposures*

Occupational exposures may occur during the manufacture and processing of insecticides as well as during their use. In addition, pesticide residues on plants or fruits may cause significant exposure of farm workers picking or handling the products. Among the more specific occupations with potential exposure are: manufacturers (production workers), formulators, vendors, transporters, mixers, loaders, applicators/operators (farmers or professionals) and pickers and growers.

The relative importance of the routes of occupational exposure is usually in the following order: dermal exposure > respiratory exposure > oral exposure. The occupational groups can have long-term exposure of this type, but very few reports of any effects are available, and further studies are needed to describe better the conditions of chronic exposure that do occur. It is relatively easy to identify people in occupations where exposure to pesticides is common and/or heavier than in the general population, but documentation or measurements of exposure to specific pesticides are seldom available. Furthermore, even if monitoring data or other documentation of exposure are available, it is difficult to evaluate risks associated with specific pesticides because most applicators have contact with a variety of pesticides and because variation in work practices can greatly affect the delivered dose.

Different levels of exposure are encountered depending on the type of application equipment used (Table 3). Furthermore, considerable differences in exposure have been found among the different jobs; most frequently, mixer-loaders have been found to receive the highest exposures, as they work with large quantities of concentrated materials.

Table 3. Estimated exposure of applicators using different application equipment[a]

Type of equipment	Average exposure[b] (range)	No. of observations
Airblast	790 (109-2826)	283
Hand-held hydraulic sprayguns	340 (0.8-2175)	12
Knapsack sprayers	320 (20-11 518)	20
Portable mistblowers	150 (19-546)	6
Hydraulic ground boom sprayers	210 (0.03-3460)	15

[a]From Dover (1985)
[b]Micrograms active ingredient per 100 cm^2 surface area per hour

Selected studies in which occupational exposures in spraying and application of insecticides have actually been measured are presented in Table 4.

Table 4. Occupational exposures in spraying and application of insecticides

Chemical	Population	Levels[a]	Reference
Indoor application			
Malathion	Spraymen treating interior household surfaces for mosquito control in Pakistan	330 mg (average daily dermal exposure)	Baker *et al.* (1978)
Chlorpyrifos	Applicators treating 20 single-family housing units with a paint-on application method (application time per unit was 1.3 h) in Omaha, NE, USA	2.1 μg/cm^2/h (D) 0.01 μg/l/h (R)	Gold *et al.* (1981)
	Applicators treating 20 single-family housing units with a spray application method (application time per unit was 0.81 h) in Omaha, NE, USA	4.1 μg/cm^2/h (D) 0.07 μg/l/h (R)	
Dichlorvos	Commercial pest control applicators treating 20 single-family houses with hand sprayers in NE, USA	Total estimated exposure: 28 μg/kg bw/h (D) 0.4 μg/kg bw/h (R)	Gold & Holcslaw (1985)
Pirimiphosmethyl	Applicators spraying tomato plants in greenhouses in Hungary	424.8 mg/h (D)[b] 44.3 mg/h (D)[c] 165 μg/h (R)[b] 39 μg/h (R)[c]	Adamis *et al.* (1985)
Dimethoate	Applicators spraying tomato plants in greenhouses in Hungary	346.0 mg/h (D)[b] 10.5 mg/h (D)[c] 59 μg/h (R)[b] 1 μg/h (R)[c]	Adamis *et al.* (1985)

Table 4 (contd)

Chemical	Population	Levels[a]	Reference
Indoor application (contd)			
Permethrin	Applicators spraying tomato plants in greenhouses in Hungary	3.9 mg/h (D)[c] 4 μg/h (D)[c]	Adamis *et al.* (1985)
Fenoxycarb	Two technicians treating 20 houses in Omaha, NE, USA, for cockroach infestation	Total exposure: 21.2 mg/h (D) 1.6 mg/h (R)	Ogg & Gold (1988)
Fluvalinate	Tractor driver using boom sprayer to treat ornamental plants at commercial greenhouse in Cortez, FL, USA	265 μg/h (estimated mean total body accumulation rate excluding hands)	Stamper *et al.* (1989)
	Tractor driver using span sprayer to treat ornamental plants at commercial greenhouse in Cortez, FL, USA	3 μg/h (estimated mean total body accumulation rate excluding hands)	
Chlorpyrifos	Tractor driver using boom sprayer to treat ornamental plants at commercial greenhouse in Cortez, FL, USA	3958 μg/h (estimated mean total body accumulation rate excluding hands)	Stamper *et al.* (1989)
	Tractor driver using span sprayer to treat ornamental plants at commercial greenhouse in Cortez, FL, USA	203 μg/h (estimated mean total body accumulation rate excluding hands)	
Lawn, turf and forest application			
Chlorthion	Workers treating pasture land for mosquitoes with aerosol generator in CA, USA		Culver *et al.* (1956)
	14 runs over 2.58 h	9-15 mg (total skin exposure)[d]	
	14 runs over 2.12 h	1-5 mg (total skin exposure)[e]	
Malathion	Workers treating pasture land for mosquitoes with aerosol generator in CA, USA		Culver *et al.* (1956)
	23 runs over 5.23 h	32-86 mg (total skin exposure)[d]	
	23 runs over 5.07 h	6-14 mg (total skin exposure)[e]	
Fenthion	Mosquito control workers using power sprayers (treatment site not stated)	Mean potential exposure: 3.6 mg/h (D) < 16 μg/h (R)	Wolfe *et al.* (1974)
	Mosquito control workers using hand pressure sprayer (treatment site not stated)	Mean potential exposure: 3.6 mg/h (D) < 21 μg/h (R)	

Table 4 (contd)

Chemical	Population	Levels[a]	Reference
Lawn, turf and forest application (contd)			
Fenthion (contd)	Mosquito control workers using hand granular dispersal (treatment site not stated)	Mean potential exposure: 12.3 mg/h (D) 88 µg/h (R)	
Carbaryl 80WP[f]	Two applicators spraying trees (9 times) in NE, USA	Mean total: 128.4 mg/h (D) 0.1 mg/h (R)	Leavitt *et al.* (1982)
	Five applicators spraying trees (once for 25 min) in NE, USA	Total exposure: 59.4 mg/h (D) 0.1 mg/h (R)	
Carbaryl	Five workers using low-pressure garden pump sprayers on a telescoping pole to treat tree boles in Placerville, CA, USA	Mean total body exposure: 62.7 mg	Haverty *et al.* (1983)
	Five workers using high-pressure sprayers to treat tree boles in Placerville, CA, USA	Mean total body exposure: 1.5 mg	
Diazinon	Three sprayers treating lawns (with compressed air sprayers) to duplicate around-the-house use in WA, USA	Mean potential exposure, hands: 5.5 mg/h (D) Mean potential exposure: 1.9 µg/h (R)	Davis *et al.* (1983)
	Three sprayers treating shrubs (with compressed air sprayers) to duplicate around-the-house use in WA, USA	Mean potential exposure, hands: 6.8 mg/h (D) Mean potential exposure: 2.9 µg/h (R)	
	Three sprayers treating lawns (with hose-end sprayers) to duplicate around-the-house use in WA, USA	Mean potential exposure, hands: 25.0 mg/h (D) Mean potential exposure: 7.4 µg/h (R)	
Diazinon	Professional lawn workers using spray guns or rotary spreaders (total work time: 300-400 min) in IN, USA	13-23 ng/m^3 (R) 3.9-130.2 µg/100 cm^2 (D, wrist areas) 30-592 µg/100 cm^2 (D, thigh areas)	Freeborg *et al.* (1985)
Trichlorfon	Professional lawn workers using spray guns (total work time: 456 min) in IN, USA	2 ng/m^3 (R) ND-0.35 µg/100 cm^2 (D, wrist areas)	Freeborg *et al.* (1985)
Chlorpyrifos	Six lawn sprayers monitored for 1 h in MI, USA	Mean calculated exposure: 135 mg/day (D) 22 µg/day (R)	Copley (1987)

Table 4 (contd)

Chemical	Population	Levels[a]	Reference
Agricultural application			
Dimethoate	Eight spraymen using a knapsack sprayer for treatment of crops in Sudan	Total calculated exposure: 175.8 μg/cm^2/day to 8.3 mg/cm^2/day (D); 5.1–19.9 μg/day (R)	Copplestone *et al.* (1976)
Pyrethroid formulation	Seven applicators spraying cotton in the Ivory Coast	Total exposure: 2.8–42.2 mg/h (D); < 100–200 μg/m^3 (R)	Prinsen & Van Sittert (1980)
Carbaryl	Applicator treating apples with a handgun hose-nozzle sprayer in WA, USA	Mean total exposure: 19.6 mg/h (D)	Maitlen *et al.* (1982)
	Applicators treating peas or potatoes with tractor-mounted boom sprayer in WA, USA	Total exposure: 1.6 mg/h (D) (wettable powder); 2.8 mg/h (D) (liquid suspension)	
Parathion	Spray-rig drivers treating citrus trees using an airblast sprayer (from an open tractor) in CA, USA	Mean exposure: 0.33 μg/cm^2/h (D)	Carman *et al.* (1982)
	Spray-rig drivers treating citrus trees using an airblast sprayer (from a cab unit with both side-windows open) in CA, USA	Mean exposure: 0.48 μg/cm^2/h (D)	
	Spray rig drivers treating citrus trees using an airblast sprayer (from a cab unit with windows closed) in CA, USA	Mean exposure: 0.01 μg/cm^2/h (D)	
	Spray rig drivers treating citrus trees using an oscillating boom sprayer (from an open tractor) in CA, USA	Mean exposure: 4.8 μg/cm^2/h (D)	
	Spray rig drivers treating citrus trees using an oscillating boom sprayer (from a cab unit with both side windows open) in CA, USA	Mean exposure: 2.4 μg/cm^2/h (D)	
	Spray rig drivers treating citrus trees using an oscillating boom sprayer (from a cab unit with windows closed) in CA, USA	Mean exposure: 0.03 μg/cm^2/h (D)	
Dimethoate	Spray rig drivers treating citrus trees using an airblast sprayer (from an open tractor) in CA, USA	Mean exposure: 2.5 μg/cm^2/h (D)	Carman *et al.* (1982)
	Spray rig drivers treating citrus trees using an airblast sprayer (from a cab unit with both side windows open) in CA, USA	Mean exposure: 1.5 μg/cm^2/h (D)	
	Spray rig drivers treating citrus trees using an airblast sprayer (from a cab unit with windows closed) in CA, USA	Mean exposure: < 0.01 μg/cm^2/h (D)	

Table 4 (contd)

Chemical	Population	Levels[a]	Reference
Agricultural application (contd)			
Chlorobenzilate	Four applicators using airblast sprayers pulled by canopied tractors treating citrus groves in FL, USA	[32.7] mg/h (estimated mean total body exposure)	Nigg & Stamper (1983)
	Two pesticide mixer-loaders at a citrus grove in FL, USA	[8.3] mg/h (estimated mean total body exposure)	
Cypermethrin	Applicators treating crops in the United Republic of Tanzania, the Ivory Coast and Paraguay using an Electrodyn[g] sprayer	3.0–26.9 mg/h (D) (total contamination)	Dover (1985)
	Applicators treating crops in the Republic of Tanzania and the Ivory Coast using a spinning disc sprayer	17.8–369.9 mg/h (D) (total contamination)	
	Applicators treating crops in Paraguay using a knapsack sprayer	29.5 mg/h (D) (total contamination)	
Carbaryl	Applicators treating tall vegetables (maize) in home gardens for 15 min (clothing worn afforded six increasing levels of protection) in PA, USA	0.5–9.9 mg (dust) 0.2–7.7 mg (wettable powder) 0.2–11 mg (aqueous suspension)[h]	Kurtz & Bode (1985)
	Applicators treating low vegetables (green beans) in home gardens for 15 min (clothing worn afforded six increasing levels of protection) in PA, USA	0.5–10.2 mg (dust)[h] 0.2–5.4 mg (wettable powder)[h] 0.2–6.8 mg (aqueous suspension)[h]	
Imidan	Applicators treating fruit trees for 14 h with airblast sprayers (tractors not equipped with spray cabs) in NY, USA	Total exposure: 56.3 μg/cm^2 (D)	Spittler & Bourke (1985)
	Applicators treating fruit trees for 31.3 h with airblast sprayers (tractors equipped with spray cabs) in NY, USA	Total exposure: 40.3 μg/cm^2 (D)	
Terbufos	Eleven Canadian farmers using planter-mounted granular applicators for crop treatment while planting maize	Mean estimated exposure: 72.4 μg/h (D); 11.3 μg/h (R)	Devine *et al.* (1986)
Azinphosmethyl	Orchard sprayers in Ontario, Canada	5.2 mg (D) (mean exposure)	Franklin *et al.* (1986)
	Orchard sprayers in Nova Scotia, Canada	4.3 mg (D) (mean exposure excluding hands) 5.6 mg (D) (mean exposure including hands)	

Table 4 (contd)

Chemical	Population	Levels[a]	Reference
Agricultural application (contd)			
Malathion	Seven mixers for treatment of citrus in CA, USA	762 μg[i] 2161 μg[j]	Fenske (1987)
Aerial application			
Carbaryl	Applicators treating maize from a helicopter with a boom sprayer in WA, USA	Total exposure: 7.4 mg/h (D) (wettable powder); 3.4 mg/h (D) (water-based flowable); 26.5 mg/h (D) (liquid suspension)	Maitlen *et al.* (1982)
Chlordimeform	200 workers including mixers, loaders, applicators, flaggers and cleaners in CA, USA	90 μg/l urine with levels highest in mixer-loaders and lowest in pilots and flaggers	Maddy *et al.* (1986)
Cypermethrin	Pilots using ultra-low-volume spray to treat commercial cotton on farms in MS, USA	0.66 mg/8 h (actual exposure) 1.07 mg/8 h (potential exposure)[k]	Nye (1986)
	Mixer-loaders for ultra-low-volume application to treat commercial cotton on farms in MS, USA	2.43 mg/8 h (actual exposure) 10.5 mg/8 h (potential exposure)[k]	

[a]Abbreviations: bw, body weight; (D), dermal; (R), respiratory
[b]Applicator moved forward and passed through area sprayed
[c]Applicator moved backward
[d]Jeep driver; also did the formulating
[e]During the insecticide application, this man walked behind and along the upwind side of the equipment in order to regulate the machinery and help clock the speed of the jeep; he also did the formulating
[f]80% wettable powder
[g]Glass bottle with built-in nozzle instead of spray tank
[h]Mean estimated exposures to unprotected body areas
[i]Estimated head exposure using fluorescent tracer technique
[j]Estimated head exposure using patch technique
[k]Actual exposure estimates represent the uncovered areas of the head and hands of the workers; potential exposure estimates represent the sum of the residues from the overalls plus the cotton gloves and nylon socks worn by the workers.

In a study of the exposure of agricultural workers to carbaryl, Maitlen *et al.* (1982) found that the mixer-loader operation was not inherently different for ground, aerial or hand-gun applications. Factors that affected the hourly dermal exposure of mixer-loaders included: the formulation used; the use of gloves; and the method (scooping or pouring) of removing powdered insecticide from its container prior to mixing. Powdered formulations resulted in higher total hourly dermal exposures (43.3 mg/h with gloves; 107 mg/h without gloves) than liquid formulations (3.0 mg/h with gloves; 40 mg/h without gloves). An average of 76% of the

total exposure of all mixer-loaders was on the hands. The techniques of scooping and pouring powdered formulations from the container without wearing gloves resulted in total average hourly dermal exposures of 176 and 38 mg/h, respectively.

Dermal exposure to malathion was monitored for mosquito control spray teams treating interior household surfaces in Pakistan. Exposure was found to vary with job category: spraymen experienced the highest exposure to the forehead (mean, 39.3 $\mu g/cm^2$) and chest (mean, 13.6 $\mu g/cm^2$), while mixers had the highest exposure to the arms (mean, 49.6 $\mu g/cm^2$). Supervisors had the lowest exposures to the arms (mean, 2.9 $\mu g/cm^2$). During this study, the authors observed improper work practices which increased dermal exposure to malathion. Spraymen's clothes were wet at the end of the working day, smelled strongly of pesticide, and were worn for several days without washing. Both spraymen and mixers had extensive skin contact with the pesticide while filling and pressurizing the spray tanks. Some mixers mixed the malathion suspension with their hands. Many spray cans leaked pesticide onto the arms, hands and chests of the spraymen. When spray nozzles became clogged, the spraymen sometimes blew through them to unclog them (Baker *et al.*, 1978).

Nye (1986) found that during aerial application of cypermethrin, pilots were exposed primarily *via* contact with the aircraft when entering and leaving, as well as from the cockpit ventilation system. Dermal exposure was predominantly *via* the hands and to a lesser degree, the trunk. For mixer-loaders, exposure was more uniform, but the trunk, gloves and forearms contained most of the cypermethrin residues. Pilots were, on average, exposed to ten times less cypermethrin than mixer-loaders. The author noted that mixer-loaders worked principally with the formulation concentrate, while the pilots were exposed principally to diluted spray.

1.2.4 *Exposure monitoring*

Human exposure can either be measured directly or inferred. Examples of methods for direct measurement are collection of pesticides in breathing-zone air or on pads or clothing worn by workers. These techniques provide a direct, calculable measure of human exposure under actual conditions. Most often, however, direct measurement is not possible; for example, in retrospective studies, exposures may only be inferred from the available information. Coupling biochemical measures with traditional exposure evaluation procedures used in epidemiological studies of cancer offers the best opportunity for improving the assessment of historical pesticide exposures (Moseman & Oswald, 1980; Blair *et al.*, 1989).

Exposure to pesticides has usually been estimated by monitoring the ambient environment. In some cases, exposure by inhalation has been measured using personal sampler pumps with absorbent filters approximating the breathing zone of the worker (Franklin, 1989). A new technique for estimating exposure by inhalation is to measure the level of the chemical in exhaled breath (Morgan *et al.*, 1989). Exposure by dermal contact is estimated by placing absorbent patches on the worker's body or clothing or by solvent extraction of clothing worn during application. Exposure estimates obtained from ambient monitoring (personal samplers, patches, clothing, tracers) indicate the amount of pesticide that impinges on the surface of the body (contact exposure) and not the absorbed dose (Franklin, 1989).

A number of definitions have been developed for the biological monitoring of exposures in general and for that of insecticides in particular (Foa *et al.*, 1987; Clarkson *et al.*, 1988; Wang *et al.*, 1989). In this monograph, the term 'biological monitoring' is used to cover all those procedures for assessing dose and the biochemical and physiological effects (possibly reversible) in human biological specimens after exposure to insecticides. Industrial hygiene practices and clinical diagnostic procedures are not included in this discussion. Within the limits of this definition, it is obvious that the identification of risks and of groups of subjects at risk is crucial.

Biochemical effects of organophosphorus pesticides can be assessed by measuring the inhibition of certain blood enzymes, as their inhibition usually mirrors that of the corresponding enzyme within the nervous system which represents the molecular target of the organophosphate. Thus, measurement of acetylcholinesterase in red blood cells is widely used to assess cholinergic effects, whereas inhibition of neuropathy target esterase in lymphocytes might be used to assess the delayed neurotoxic effects of some organophosphate insecticides (Hayes *et al.*, 1980; Ames *et al.*, 1989; Lotti, 1989; WHO/UNEP, 1990).

Insecticides can be measured in biological samples by the usual analytical techniques (see the monographs on individual insecticides) or by biological methods. A number of reports are available in which insecticides and/or their metabolites have been measured in body fluids after occupational exposures (Coye *et al.*, 1986; Maroni, 1986; Wang *et al.*, 1989). Examples include the measurement of dialkylphosphates in urine after exposure to organophosphorus insecticides (Coye *et al.*, 1986), of *para*-nitrophenol after exposure to parathion and methylparathion (Wolfe *et al.*, 1970) and of 1-naphthol after exposure to carbaryl (Comer *et al.*, 1975) (e.g., see Coye *et al.*, 1986). Although these procedures are used for quantitative assessments of dose, interpretation of the results is hampered in the absence of pharmacokinetic data in man. Such data are also essential when extrapolating data on toxicity across species.

A somewhat different approach to biological monitoring is the measurement of adducts to proteins (Shugart *et al.*, 1989). Adducts to haemoglobin have been detected with several pesticides (Sabbioni & Neumann, 1990). The advantages of such measurements include the possibility of assessing dose closer to the target, of assessing individual capacity to form electrophiles and of extrapolating data on toxicity more easily across species. When the mechanism of action of a pesticide is understood, more specific markers can be used.

2. Studies of Cancer in Humans

Epidemiological studies on cancer risk following exposure to insecticides can be divided into three types: (a) those referring to specific insecticides with or without mention of insecticides in general; (b) those mentioning only insecticides in general; and (c) those referring to populations exposed to 'pesticides' or 'pesticides/herbicides'. Studies under (a) were considered both in the specific monographs and in the present one. Studies under (b) are reviewed only in the present monograph. As for category (c), in a few cases, the Working Group included studies of populations exposed to 'pesticides' because they provide special information relevant to the evaluation of insecticides.

2.1 Descriptive and ecological studies

2.1.1 *Mortality statistics*

In Central Luzon in the Philippines, the use of organophosphate and organochlorine insecticides increased after adoption of modern rice varieties in the late 1960s. Insecticides were applied by backpack sprayer, usually by men. Protective clothing was not worn. Mortality was studied in three rural municipalities, with a population of 96 000 in 1980 and where more than 80% of the heads of households in typical villages were employed primarily in rice farming. The study covered two periods: 1961-71, with low use of insecticides, and 1972-84, with high use. For men aged 15-54 years, the mean age-standardized mortality rate per 100 000 for cancer (all sites except brain) increased from 21.1 to 25.9. Mortality from leukaemia among men increased from 0.6 to 3.6 per 100 000. Seven of the 11 leukaemia cases recorded since 1961 occurred in 1979-84. The leukaemia rates for women in the same periods were 0.6 and 0.7 per 100 000, respectively (Loevinsohn, 1987).

2.1.2 *Proportionate mortality studies*

Several studies have been undertaken on the basis of death certificates from Wisconsin, USA (Blair & Watts, 1980; Blair & White, 1981; Cantor, 1982; Cantor & Blair, 1984; Saftlas *et al.*, 1987). In the most recent of these, a study population was selected of 35 972 white men, 18 years and older, who resided in 69 of the 70 Wisconsin counties and died in 1968-76 and whose occupation on the death certificate was farm owner, tenant or labourer. Proportionate mortality ratio (PMR) and proportionate cancer mortality ratio (PCMR) values were calculated using mortality of white, non-farming Wisconsin men for comparison. Data from the agricultural censuses in 1949, 1964 and 1969 and from the population census in 1960 were used for constructing indicators of exposures in agriculture in each county. The PMR for all cancers was significantly lower than expected (5634 observed; PMR, 0.92 [95% confidence interval (CI), 0.90-0.94]). This deficit was due in particular to tobacco-related cancers. When the data were analysed after excluding smoking-related causes of death, statistically significant excess risks were found for cancers of the stomach (PCMR, 1.1 [95% CI, 1.0-1.2]), prostate (PCMR, 1.1 [1.1-1.2]) and eye (PCMR, 3.4 [2.2-5.2]) and for all lymphopoietic cancers (PCMR, 1.1 [1.0-1.2]). Analysis by agricultural exposure level revealed a statistically significant excess risk for cancers of other lymphatic tissue (two-thirds were multiple myelomas) in counties with heavy use of insecticides (28 observed; PCMR, 1.6 [1.0-2.2]). The risk was also increased in counties with heavy use of herbicides and fertilizers and a high proportion of maize production.

2.1.3 *Case-control studies with ecological information on exposure*

Several case-control studies employed similar methods to evaluate cancer risks and potential exposure to agricultural insecticides in the USA (Blair & Thomas, 1979; Burmeister *et al.*, 1982, 1983; Cantor & Blair, 1984). Deceased cases were ascertained from death certificates, and controls were deceased residents from the same state, matched to the

cases by date of birth, date of death, race, sex and county of residence. Usual occupation as a farmer was determined from the death certificate. Potential exposure of farmers to insecticides was classified on the basis of their county of residence and insecticide use patterns for that county. Thus, these studies employed both ecological and individual assessments.

Blair and Thomas (1979) found mortality from leukaemia to be elevated among farmers in Nebraska, but the risks were similar among farmers in counties using less insecticides (odds ratio, 1.2; 95% CI, 0.94-1.6) and in counties using more insecticides (odds ratio, 1.3; 1.0-1.7). Similar findings were obtained in Iowa, where the risks for leukaemia among farmers did not appear to be higher among those residing in counties where insecticides were used heavily than in counties where they were used to a lesser extent (Burmeister *et al.*, 1982).

In Iowa, the odds ratio for death due to multiple myeloma for farmers born after 1890 residing in counties in the upper tercile of insecticide use was 2.0 ($p \leq 0.05$) (Burmeister *et al.*, 1983). Cantor and Blair (1984) evaluated risks for multiple myeloma in association with ecological assessments of exposure to insecticides in Wisconsin. Using nonfarmers residing in counties where insecticide use was low as unexposed controls, the odds ratios were 0.9 (95% CI, 0.7-1.3) for nonfarmers residing in counties with high insecticide use, 1.2 (0.9-1.7) for farmers residing in counties with low insecticide use and 1.9 (1.1-3.5) for farmers living in counties with high insecticide use. [These results are based on the same data as those of Saftlas *et al.* (1987).]

Proportionate mortality studies and case-control studies with ecological information on exposure are summarized in Table 5.

2.2 Cohort studies

Mortality rates were studied for a cohort of male pesticide applicators in the USA whose exposures included fumigants, carbamates, chlorinated hydrocarbons and organophosphates (Wang & MacMahon, 1979). The cohort was formed of employees from three nationwide pest control companies during the approximately 10 years for which centralized personnel records had been maintained. From a total of 44 083, records were selected for men who had been employed for at least three months between 1 January 1967 and 30 June 1976 by two of the companies and between 1 January 1968 and 30 June 1976 by the other and whose name, social security number, date of birth and dates of employment had been recorded. Examination of a sample of records for 4000 men who had been excluded showed that information was missing for 18%. Individual follow-up was not attempted. In the most recent analysis (MacMahon *et al.*, 1988), the cohort (16 124 men) was linked to Social Security Administration files in 1977 and 1981 and to the National Death Index for 1979-84. A total of 1082 deaths were thus identified, and death certificates were obtained for 994 (92%). The 88 deaths from unknown cause were allocated to causes of death according to the distribution of the deaths of known cause. National mortality rates for US white men were used for comparison, because the majority of the subjects were known to be white. The standardized mortality ratio (SMR) for deaths from all causes was 0.98 (90% CI, 0.93-1.03), and the SMR for all cancers was 1.1 (90% CI, 1.0-1.2]. Analysis by cause of death showed a statistically significant excess risk of lung cancer (SMR, 1.4; 90% CI, 1.1-1.6), which was present throughout the study period; the risk did not increase with duration of employment,

Table 5. Summary of findings for cancers at selected sites from descriptive and ecological studies on use of insecticides in the USA

Reference	Location	Cancer site	Relative risk	95% CI	Comments
Saftlas *et al.* (1987)	Wisconsin	Other lymphatic tissue	1.6	[1.0-2.2]	Farmers in high-use areas
Blair & Thomas (1979)	Nebraska	Leukaemia	1.3	1.0-1.7	Farmers in high-use areas
Burmeister *et al.* (1982)	Iowa	Leukaemia	1.3	0.9-1.9	Farmers in high-use areas (born (1890-1900)
			1.1	0.8-1.7	Farmers in high-use areas (born after 1900)
			1.4	1.1-1.8	Farmers in low-use areas (born 1890-1900)
			1.5	1.2-2.0	Farmers in low-use areas (born after 1900)
Burmeister *et al.* (1983)	Iowa	Multiple myeloma	2.0[a]	NA	Farmers in high-use areas (born (1890-1900)
			2.0[a]	NA	Farmers in high-use areas (born after 1900)
			1.4	NA	Farmers in low-use areas (born 1890-1900)
			1.2	NA	Farmers in low-use areas (born after 1900)
Cantor & Blair (1984)	Wisconsin	Multiple myeloma	1.9	1.1-3.5	Farmers in high-use counties
			1.2	0.9-1.7	Farmers in low-use counties
			0.9	0.7-1.3	Nonfarmers in high-use counties
			1.0	Reference	Nonfarmers in low-use counties

[a] $p \leq 0.05$

the SMRs being 1.4 for 0-4 years of employment, 1.1 for 5-9 years and 0.75 for 10 years or more. The SMRs were 1.3 (90% CI, 0.65-2.2) for skin cancer, 1.2 (0.50-2.5) for cancer of the bladder and 1.0 (0.67-1.4) for lymphatic and haematopoietic cancers. [The Working Group noted that exposure to arsenic was not mentioned but may have occurred.]

A national programme in the USA to monitor the health status of people occupationally exposed to pesticides enlisted 2620 volunteers in 13 states between 1971 and 1973. An effort was made to recontact these subjects in 1977-78, and 70% were successfully traced; 62 deaths were identified, and the cause of death was known for 59. Mortality data were analysed for the 1995 white men, using mortality rates for US white men for comparison. The SMR for neoplastic diseases was 0.39 (10 observed [95% CI, 0.2-0.7]) (Morgan *et al.*, 1980). [The Working Group noted that the study was based on volunteers and that follow-up was incomplete.]

A cohort study of licensed pest control workers in Florida was undertaken (Blair *et al.*, 1983). The authors stated that pest control workers apply a variety of pesticides, including chlorinated hydrocarbons, carbamates, organophosphates, phenoxyacetic acids, phthalimides, coumarins, arsenical insecticides and fungicides. The 4411 workers were identified from licence applications submitted by pest control firms in 1965-66. For each worker, full name, social security number, address, date of birth, primary duty in 1965-66, specific years licensed, and individual and firm certification categories were retrieved from the files. The cohort was followed up until 1 January 1977, and 96% were successfully traced. Death certificates were obtained for 389 of the 428 deceased subjects. Mortality rates for the US national population were used for comparison. The SMR for overall mortality among white male workers was 1.0 (378 observed, 367.5 expected [95% CI, 0.9-1.1]). An excess risk was found for lung cancer (34 observed, 25.1 expected; SMR, 1.4 [0.9-1.9]). Mortality from brain cancer was also elevated (5 observed, 2.5 expected; SMR, 2.0 [0.6-4.7]). The SMRs were [1.3 (0.2-4.8)] for skin cancer, [1.6 (0.3-4.6)] for cancer of the bladder, [2.7 (0.6-8.0)] for laryngeal cancer and [1.3 (0.4-3.4)] for leukaemia. The excess lung cancer risk increased by length of licensure; the SMRs were 1.0 [0.6-1.7] for < 10 years, 1.6 [0.8-2.8] for 10-19 years and 2.9 [1.2-5.6] for > 20 years; this pattern did not change when mortality rates for Florida were used for comparison. The lung cancer mortality was highest for workers employed by firms licensed for controlling rodents and general household pests, but it was elevated in other licensing categories also. [The Working Group noted that potential contact with arsenical insecticides complicates interpretation.]

A proportionate mortality analysis indicated an excess risk for neoplasms of the lymphatic and haematopoietic system and for cancers of the pancreas, lung and prostate among various subgroups of deceased members of the American Federation of Grain Millers' life insurance plan (Alavanja *et al.*, 1987). Following this observation, a cohort study (which included these deaths) was published (Alavanja *et al.*, 1990). Since 1955, which was the year the insurance plan started, 40 247 current or former members had been enrolled. A total of 22 938 white men with complete enrolment records were included in the study. Information on general pesticide use in the grain mills was obtained from interviews with senior employees and managers, from a survey among current union members and from various other sources, but could not be linked to individuals. In the analysis, the cohort was subdivided into workers in flour mills, workers in other grain industries, and workers in

unidentified grain companies. In general, a wider variety of pesticides appeared to be used at the flour mills than at the other facilities. The pesticides most frequently cited as being used in all the flour mills included carbon tetrachloride, ethylene dibromide, malathion, methyl bromide, phosphine and pyrethrum. In a questionnaire survey in 1985-86, 31% of the flour millers reported that they applied pesticides, whereas this proportion was 16% among the other grain millers. The cohort was followed through to 1985. A total of 3668 deaths were identified, and death certificates were found for 3460 (94%). Mortality rates for US white men were used for comparison. The total of 3668 deaths was compared to an expected number of 4125.6 (SMR, 0.89; 95% CI, 0.86-0.92). The SMRs for all causes were 0.85 [0.8-0.9] for flour mills, 1.04 [1.0-1.1] for other grain industries and 0.58 [0.5-0.7] for unidentified grain companies. The SMRs for lung cancer were 0.78 [0.7-0.9] for flour mill workers and 1.1 [0.9-1.4] for workers in other grain industries. Workers in flour mills had slightly elevated risks of developing non-Hodgkin's lymphoma (SMR, 1.5 [0.9-2.3], based on 21 deaths), pancreatic cancer (SMR, 1.3 [0.9-1.9]; 33 deaths) and leukaemia (SMR, 1.4 [0.9-2.0]; 25 deaths); mortality from these causes was not increased among the other grain mill workers. The risk for non-Hodgkin's lymphoma among the flour mill workers increased by time elapsed since first employment, from an SMR of 0.64 for < 5 years, 0.49 for 5-9 years, 1.3 for 10-19 years and 2.3 (95% CI, 1.2-4.0) for > 20 years. A similar pattern was seen for pancreatic cancer (0.87 for < 5 years; 0.30 for 5-9 years; 1.2 for 10-19 years; and 1.9 (1.1-3.0) for ≥ 20 years). No trend by elapsed time was seen for leukaemia. Similar observations were made in a case-control study undertaken within the cohort. A survey showed that the flour mill workers did not differ from the other grain millers in educational level or in smoking habits, but they had a slightly higher consumption of alcohol. The risk for non-Hodgkin's lymphoma is not known to be associated with alcohol consumption, and the excess risk among the flour millers was therefore hypothesized to be associated with use of pesticides in flour mills. The risk for pancreatic cancer could be due to excessive alcohol consumption, but it was noted that mortality from cirrhosis of the liver was not elevated. [The Working Group noted that this cohort is unlikely to have been exposed to arsenic.]

Cancer incidence was studied in a cohort of 25 945 male farmers licensed for use of pesticides in 1970-74 in the Piedmont region of Italy. The pesticides were mainly in toxicological classes I and II according to Italian law. The cohort was matched to the Piedmont Hospital Discharge File for the period 1976-83, and 631 cancer cases were found. The number of person-years accumulated by the cohort members in 1976-83 was estimated. Cancer incidence rates for non-licensed men were used for comparison, estimated by subtracting cases and person-years for licensed men from those of the total population. The total of 631 cancer cases observed in the licensed group was compared with 877.8 expected cases. The standardized incidence ratios (SIR) were 0.7 (95% CI, 0.6-0.8) for all cancers, 1.4 (1.0-1.8) for malignant neoplasms of the skin, 1.4 (1.0-1.9) for malignant lymphoma, 1.0 (0.6-1.4) for malignancies of the nervous system and 1.1 (0.8-1.5) for leukaemia and multiple myeloma. Other cancer sites were not included in the analysis. The risk for malignant lymphomas was higher in residents of villages with a high proportion of arable land (SIR, 1.8; 95% CI, 1.2-2.5) (Corrao *et al.*, 1989).

A study of 316 pesticide-exposed workers in Neubrandenburg in eastern Germany indicated an excess risk for lung cancer (Barthel, 1976). A subsequent study was therefore

undertaken of 1658 men who had worked as agricultural plant protection workers or plant protection agronomists for at least five years in the 14 districts of the eastern part of Germany (excluding Berlin) during 1948-72 (Barthel, 1981a,b). About 70% of the potential study population was identified and included in the study. Respiratory protective equipment was rarely used. Before 1960, the pesticides included the insecticides calcium arsenate (banned since 1955), DDT, hexachlorocyclohexanes, methyl parathion and toxaphene, the fungicide cupral and the herbicides 4,6-dinitro-*ortho*-cresol, (2,4-dichlorophenoxy)acetic acid (2,4-D) and 4-chloro-2-methylphenoxyacetic acid (MCPA). A variety of pesticides was gradually introduced after 1960, of which zineb, maneb, simazine and chloral hydrate were used to a large extent. The cohort was followed up for cancer incidence and mortality through to 1978, and 169 malignant neoplasms were observed. Tumour incidence rates for the eastern part of Germany in 1973 were used to calculate expected numbers of tumour cases for the years 1970-78. Fifty bronchial carcinomas were observed in this period, where 27.5 cases were expected (SIR, 1.8 [95% CI, 1.4-2.4]). The lung cancer risk increased with length of exposure: SIR for < 10 years, 1.2 [0.5-2.5]; 10-19 years, 1.7 [1.1-2.4]; and > 19 years, 3.0 [1.7-4.7]. There was, however, no difference for workers first exposed in 1948-60 (SIR, 1.8 [1.3-2.5]) or those first exposed in 1961-72 (SIR, 1.7 [0.5-3.9]). A questionnaire survey among 163 randomly selected pesticide workers and an equivalent number of population controls showed no difference in smoking habits.

Cancer incidence was studied in a cohort of 20 245 licensed pesticide applicators in Sweden (Wiklund *et al.*, 1986, 1987, 1989). Since 1965, a licence has been mandatory for using the most acutely toxic pesticides. The workers in the study had been issued a licence between 1965 and 1976 and were followed up for cancer incidence to 31 December 1982. A survey on a random sample of 268 workers showed that 15% had used insecticides in the 1950s, 34% in the 1960s and 46% in the 1970s. During the 1950s and 1960s, DDT was the insecticide used most frequently, and in the 1970s, fenitrothion; 72% of the workers had been exposed to phenoxyacetic acid herbicides, and exposure to other herbicides and fungicides was also reported. Cancer incidence rates for the Swedish population were used for comparison. A total of 558 cancer cases were observed in the cohort (SIR, 0.86; 95% CI, 0.79-0.93). Excess risks were observed for lip cancer (14 observed; 1.8; 0.96-2.9), testicular cancer (18 observed; 1.6; 0.92-2.5) and Hodgkin's disease (11 observed; 1.2; 0.60-2.2) but not for lung cancer (38 observed, 0.50; 0.35-0.68), non-Hodgkin's lymphoma (21 observed; 1.0; 0.63-1.5) or cancer at any other site. The SIR for testicular cancer increased with time since licensure (0-4 years, 0.94; 5-9 years, 1.4; ≥ 10 years, 2.5; based on four, six and eight cases, respectively). The SIR for lung cancer increased with years since first employment from 0.31 (0-4 years) to 0.49 (5-9 years) to 0.56 (≥ 10 years). The authors provided data showing that smoking was less prevalent among pesticide applicators than among other occupational categories in Sweden, strongly suggesting that the observed deficit of lung cancer was due to lower cigarette consumption. A follow-up from date of licensure until 31 December 1984 indicated no excess risk for soft-tissue sarcomas (seven cases observed; SIR, 0.9; 95% CI, 0.4-1.9) (Wiklund *et al.*, 1988).

Cohort studies are summarized in Table 6.

Table 6. Summary of findings in cohort studies on spraying and application of insecticides

Reference	Location	Occupation	Cancer site	SMR	95% CI	Comments
MacMahon *et al.* (1988)	USA	Pest control workers	Lung	1.4	1.1–1.6	No trend for lung cancer with duration of employment; 90% confidence interval
			Skin	1.3	0.65–2.2	
			Bladder	1.2	0.50–2.5	
			Lymphatic & haematopoietic	1.0	0.67–1.4	
Blair *et al.* (1983)	USA	Licensed pest control workers	Larynx	[2.7]	[0.6–8.0]	Trend for lung cancer with duration of licensure
			Lung	1.4	[0.9–1.9]	
			Skin	[1.3]	[0.2–4.8]	
			Bladder	[1.6]	[0.3–4.6]	
			Leukaemia	[1.3]	[0.4–3.4]	
			Brain	2.0	[0.6–4.7]	
Alavanja *et al.* (1990)	USA	Flour millers	Lung	0.78	[0.7–0.9]	Trend for lymphomas and pancreas with time since first employment
			Leukaemia	1.4	[0.9–2.0]	
			Non-Hodgkin's lymphoma	1.5	[0.9–2.3]	
			Pancreas	1.3	[0.9–1.9]	
Corrao *et al.* (1989)	Italy	Farmers licensed for use of pesticides (Tox. class I + II)	Skin	1.4	1.0–1.8	SIR
			Lymphomas	1.4	1.0–1.9	
			Haematopoietic	1.1	0.8–1.5	
			Nervous system	1.0	0.6–1.4	
Barthel (1981a,b)	Germany	Plant protection workers and agronomists	Lung	1.8	[1.4–2.4]	SIR; trend with length of exposure
Wiklund *et al.* (1989)	Sweden	Licensed pesticide applicators	Lung	0.50	0.35–0.68	SIR; trend for testicular and lung cancer with time
			Non-Hodgkin's lymphoma	1.0	0.63–1.5	
			Hodgkin's disease	1.2	0.60–2.2	
			Lip	1.8	0.96–2.9	
			Testis	1.6	0.92–2.5	

2.3 Case-control interview studies

2.3.1 *Lymphatic and haematopoietic systems and soft-tissue sarcoma*

Hoar *et al.* (1986) conducted a population-based case-control study of white male residents of Kansas, USA, 21 years or older. Information was collected on 139 histologically confirmed cases of soft-tissue sarcoma and 132 of Hodgkin's disease diagnosed in 1976-82 and on a random sample of 172 cases of non-Hodgkin's lymphoma diagnosed in 1979-81. Three population controls were matched to each case on age and vital status: living controls up to 64 years of age were selected by random digit dialling; older subjects were selected from Medicare files; and deceased controls were selected from state mortality files, after excluding index neoplasms, a malignancy at an ill-defined site, homicide and suicide. After exclusions, a total of 1005 controls were selected. Patients and controls, or their next of kin, were interviewed by telephone about farming practices. Interviews were obtained for 96% of patients and 94% of controls. Information on herbicide and insecticide use provided by a sample of farmers among enrolled subjects was validated by interviewing their pesticide suppliers. A small excess of non-Hodgkin's lymphoma (odds ratio, 1.5; 95% CI, 0.9-2.4) was found among patients reporting use of any insecticides. Odds ratios by year of first use of insecticides among farmers were 1.7 for use prior to 1946, 1.5 for 1946-55, 0.7 for 1956-65 and 1.5 for 1966 or later. No association was observed with number of hectares treated. Adjustment for days per year of herbicide use reduced the odds ratio for insecticide use to 1.1 (95% CI, 0.6-2.2). Risks for non-Hodgkin's lymphoma increased slightly, however, with days per year of insecticide use, even after adjusting for exposure to herbicides (odds ratio, 1.2 (95% CI, 0.5-2.8) for one to two days of insecticide use; and 1.4 (0.6-3.1) for more than two days of insecticide use). A further analysis of these data was undertaken by Hoar Zahm *et al.* (1988). A small excess risk for soft-tissue sarcoma was seen among farmers using insecticides on animals (odds ratio, 1.6; 95% CI, 0.9-2.5) but not among those using insecticides on crops (0.8; 0.4-1.6). Relative risks for use on animals rose with time since first use to 4.9 (0.6-64.1) among farmers who first used them in 1945 or earlier. Potentially greater exposure might be expected during treatment of animals because higher concentrations are sprayed in confined spaces, such as barns. Excess risks were associated with most of the major classes of insecticides. No association was observed between the risk for Hodgkin's disease and use of insecticides.

In a study of similar design to the study in Kansas, all non-Hodgkin's lymphomas occurring among white men 21 years or older between 1983 and 1986 in 66 counties in eastern Nebraska were ascertained through local hospitals (Hoar Zahm *et al.*, 1990). Population-based controls were frequency matched to cases on race, age and vital status. A total of 227 cases of non-Hodgkin's lymphoma and 831 controls were selected. Telephone interviews were conducted to obtain detailed information on specific agricultural chemicals used, and responses were obtained from 201 cases (91%) and 725 controls (87%). There was little evidence of an association between non-Hodgkin's lymphoma among farmers and use of insecticides overall (odds ratio, 1.1; 95% CI, 0.7-1.6); but non-Hodgkin's lymphoma was associated with use of organophosphorus insecticides (odds ratio, 2.4, adjusted for use of 2,4-D). Risks rose with days per year of use of organophosphorus compounds (odds ratios,

1.7 for 1-5 days/year, 1.8 for 6-20 days/year and 3.1 for 21 or more days/year). [Numbers of exposed subjects and confidence intervals were not provided.]

A population-based case-control study was conducted in Washington State (USA) to investigate the relationship between soft-tissue sarcoma and non-Hodgkin's lymphoma and past exposure to phenoxyacetic acid herbicides and chlorinated phenols (Woods *et al.*, 1987). Between 1981 and 1984, 206 soft-tissue sarcomas and 746 non-Hodgkin's lymphomas were diagnosed in men aged 20-79 years. Of these cases, 13% were excluded due to physicians' refusal; 91% of the remaining patients (or their proxies) were interviewed and information was derived about pesticide exposures. Of the remaining 163 soft-tissue sarcoma cases, 33 were excluded on the basis of a pathology review, and two were excluded for other reasons, leaving 128 soft-tissue sarcoma cases to be included in the analysis. Of the remaining 586 non-Hodgkin's lymphoma cases, 10 were excluded for various reasons, leaving 576 cases to be included in the analysis. Controls for living cases were selected by random-digit telephone dialling (for those aged 20-64 years) and from Health Case Financing Administration files (for those aged 65-79 years); deceased controls were obtained from death certificates and matched on five-year age group. Interviews were obtained for 694 of the 910 controls (76%). Odds ratios for potential exposure to chlordane were 1.6 (95% CI, 0.7-3.8) for non-Hodgkin's lymphoma and 0.96 (0.2-4.8) for soft-tissue sarcoma. Potential exposure to DDT yielded odds ratios of 1.8 (1.0-3.2) for non-Hodgkin's lymphoma and 1.1 (0.4-3.2) for soft-tissue sarcoma. Adjustment for exposure to some other pesticides did not substantially change these risk estimates. Another evaluation of the data from this study restricted analyses to farmers (Woods & Polissar, 1989). The relative risks for non-Hodgkin's lymphoma among farmers potentially exposed were 1.6 (0.5-5.1) for chlordane and 1.7 (0.9-3.3) for DDT.

A population-based, multicentre case-control study of multiple myeloma in people under 80 years of age was carried out between 1977 and 1981 in four US areas covered by cancer registries (Morris *et al.*, 1986). Interviews were obtained with 698 cases (89% of eligible subjects) and 1683 controls (83%); 32% of case interviews and 1% of those for controls were with next-of-kin. Controls were obtained by household sampling in one area and by random digit dialling in the remaining three areas; they were matched to cases on age, sex and race. Self-reported exposures to chemicals were grouped into 20 categories, some of which were further subdivided. The odds ratio for exposure to pesticides was 2.6 (95% CI, 1.5-4.6); an odds ratio of similar magnitude was obtained when reports from surrogate respondents were excluded (2.9; 1.5-5.5). The numbers of cases and controls who reported exposure to various classes of insecticides were two cases and five controls for organophosphorus compounds [odds ratio, 1.0; 0.2-5.1], nine cases and eight controls for organochlorines [2.8; 1.1-7.0] and three cases and five controls for arsenicals [1.5; 0.4-6.2]. [Subjects exposed to other pesticides were excluded when calculating these odds ratios.]

A case-control study on multiple myeloma was conducted within a prospective study of 1.2 million American Cancer Society volunteers who in 1982 filled in a self-administered questionnaire on diseases and several cancer risk factors, including occupation and exposure to pesticides and herbicides. They were followed for mortality up to 1984 or 1986, and 282 deceased subjects with mention of multiple myeloma on their death certificate were identified. Prevalent cases of multiple myeloma and subjects with related symptoms

identified at the time of entry into the cohort were excluded, leaving 128 incident cases, who were matched on sex, age, residence and race to four randomly selected controls. A logistic regression analysis adjusting for potential confounders was presented. The odds ratio for occupation as a farmer was 2.7 (95% CI, 1.3-5.7; based on 16 cases and 28 controls exposed); the odds ratio for exposure to pesticides and herbicides was 1.6 (0.7-3.7; 12 cases and 25 controls). When these variables were combined, nonfarmers exposed to pesticides and herbicides experienced no excess risk (crude odds ratio, 1.0; 95% CI, 0.3-3.1), whereas exposed farmers had an elevated risk (crude odds ratio, 4.3; 95% CI, 1.7-10.9), which was greater than that of unexposed farmers (crude odds ratio, 1.7; 95% CI, 0.8-4.0) (Boffetta *et al.*, 1989).

A population-based case-control study of leukaemia among white men aged 30 years or older in Iowa (1981-83) and in Minnesota (1980-82) covered a total of 669 eligible cases (Brown *et al.*, 1990). Living controls were selected by random digit dialling (< 65 years) and from Medicare records (> 65 years); deceased controls were selected from death certificates. Interviews were completed with 86% of the cases or close relatives and with 77-79% of the controls; the study thus included 578 cases and 1245 controls. A standardized questionnaire was used to obtain detailed information on residential history, drinking-water source, nonfarm occupational history, smoking and alcohol use, use of unpasteurized dairy products, medical conditions, family history of cancer and farm activities, including information on 24 animal insecticides and 34 crop insecticides. Relative risks were calculated by comparison to subjects who were nonfarmers, adjusting for age, vital status, state of residence, tobacco use, family history of lymphopoietic cancer, high-risk occupations and high-risk exposures. The risk for leukaemia overall was not significantly associated with reported use of any insecticide (odds ratio, 1.1; 95% CI, 0.9-1.3) among farmers. An excess risk was observed for chronic lymphocytic leukaemia (1.3; 1.0-1.8), but not for other histological types: acute nonlymphocytic leukaemia, 1.0 (0.7-1.6), chronic myelogenous, 1.0 (0.5-1.8) and acute lymphocytic, 0.8 (0.2-2.5). The risk for leukaemia tended to be greater with use of insecticides on animals than on crops. Significant excesses occurred with use on animals of natural insecticides (odds ratio, 1.5; 95% CI, 1.0-2.2) and organophosphates (1.5; 1.0-2.1). Time since first use of insecticides also influenced risk: after a 20-year latency, significant excesses of leukaemia were noted with use on animals of several insecticides, including DDT (1.4; 1.0-2.0), dichlorvos (2.4; 1.1-5.4), famphur (11.6; 1.2-107.0), nicotine (2.0; 1.2-3.4) and pyrethrins (3.8; 1.0-14.8). Nonsignificant odds ratios of 2.0 or more were observed with use of carbaryl (3.0; 0.7-3.1), coumaphos (2.3; 0.6-8.8), methoxychlor (2.1; 0.7-6.6) and toxaphene (2.6; 0.8-8.8). The relative risk for leukaemia associated with frequent use on animals (> 10 days/year) was statistically significant for dichlorvos (3.8; 1.0-14.8) and malathion (3.2; 1.0-10.0); the risk increased with frequency of use of DDT on animals, from 0.6 (0.3-1.4) for 1-4 days per year to 1.1 (0.4-2.7) for 5-9 days per year, to 2.1 (1.1-3.9) for 10 or more days per year. These estimates for agricultural exposures were not mutually adjusted.

Patients with chronic lymphatic leukaemia diagnosed in five hospitals in the middle and south-east of Sweden between 1964 and 1984 who were still alive after 1981 were compared with population controls living in the catchment areas of the hospitals (Flodin *et al.*, 1988). Subjects over 80 years or mentally disabled were excluded, leaving 111 cases (response rate,

91%) and 431 controls (response rate, 83%; replacements were sought for the 17% who did not respond). Information on exposure to ionizing radiation, DDT, solvents and engine exhausts as well as a history of previous diseases, smoking and occupation were collected using a self-administered questionnaire. Results of a stratified analysis based on a confounder score including age, sex, exposure to fresh wood, solvents, engine exhausts, DDT and horses and employment as farmer were presented. Exposure to DDT was reported by six cases and four controls; the odds ratio was 6.0 (95% CI, 1.5-23.0). [The Working Group noted the limitation of inclusion of prevalent cases because of the potential influence on recall of exposure.]

A study on Hodgkin's disease and non-Hodgkin's B-cell lymphomas was conducted in one of the areas included in the study described above. The same criteria were applied for selection of cases, and the same controls were used. There were 54 cases of Hodgkin's disease and 106 of non-Hodgkin's lymphoma (overall response rate, 97%) and 275 controls. Logistic regression analysis was carried out including sex, age, farming, exposure to fresh wood and all exposures that gave a crude odds ratio greater than 2.0. Exposure to DDT was reported by three patients with Hodgkin's disease, none with non-Hodgkin's lymphoma and three controls. The odds ratio for Hodgkin's disease was 7.5 (90% CI, 0.8-70.0) (Persson *et al.*, 1989). [The limitation of the study by Flodin *et al.* (1988) noted above also applies to this study.]

A case-control study on malignant lymphomas in northern Sweden considered primarily exposure to phenoxyacetic acid herbicides and chlorophenols (Hardell *et al.*, 1981). Cases were all men aged 25-85 years with histologically verified malignant lymphoma admitted to the control hospital in the area in 1974-78. A total of 60 cases of Hodgkin's disease and 109 of non-Hodgkin's lymphoma were matched to 338 population controls (responses available from 335) by age, sex, place of residence, vital status and year of death for deceased cases and controls. Information from self-administered questionnaires was supplemented by telephone interviews when the data were incomplete. A total of 22 cases and 26 controls reported exposure to DDT [odds ratio, 1.8; 95% CI, 1.0-3.2]. Seven cases and 11 controls reported exposure to DDT and not to phenoxyacetic acid herbicides [odds ratio, 1.6; 95% CI, 0.6-4.1]. Information on use of DDT was not presented separately for patients with Hodgkin's disease and those with non-Hodgkin's lymphoma.

Four case-control studies in Sweden assessed the risk of soft-tissue sarcoma alone, primarily in association with exposure to phenoxyacetic acid herbicides and chlorophenols (Hardell & Sandström, 1979; Eriksson *et al.*, 1981; Hardell & Eriksson, 1988; Eriksson *et al.*, 1990). Exposure was assessed by methods similar to those described above, using questionnaires mailed to subjects or next-of-kin. For subgroups of the subjects, information was supplemented with telephone interviews.

A case-control study in northern Sweden included 52 male cases of histologically reviewed soft-tissue sarcoma (100% response) and 206 population controls (99% response), matched for age, sex, place of residence and year of death for deceased cases and controls (Hardell & Sandström, 1979). Four cases and 14 controls reported exposure to DDT (crude odds ratio, 1.2 [95% CI, 0.4-3.7]).

A population-based case-control study in southern Sweden included 110 cases of histologically verified soft-tissue sarcoma and 219 controls (responses obtained from all but

one), matched for age, place of residence and year of death for dead cases and controls (Eriksson *et al.*, 1981). Seven cases and 11 controls reported exposure to DDT [crude odds ratio, 1.3; 95% CI, 0.5-3.4].

A population-based case-control study in northern Sweden included 54 male cases of soft-tissue sarcoma (responses obtained from all but one) (Hardell & Eriksson, 1988). Two control groups were used: one was population-based, with 311 subjects (94% response) matched for age and place of residence, and the second consisted of 179 cases of malignant disease (94% response) diagnosed in the same period as the cases. Six cases, 19 population-based controls and eight cancer controls reported exposure to DDT [crude odds ratio, 1.9; 95% CI, 0.7-5.0 (population controls); 2.7; 0.9-7.8 (cancer controls)]. Crude odds ratios for exposure to DDT without exposure to phenoxyacetic acid herbicides were [0.6 (0.1-5.0)] for population controls and [1.2 (0.1-11.6)] for cancer controls.

All male patients diagnosed with histologically confirmed soft-tissue sarcoma between 1978 and 1986 were identified from a regional cancer registry in central Sweden. Interviews were completed with 218 (92%) of the cases identified. One control per case was drawn from the National Population Registry matched on age, sex, vital status and county of residence; 212 controls (89%) of those selected were interviewed. Twelve controls who were contacted could not complete the questionnaire and were replaced by the next person on the population register. Subjects or next-of-kin completed a 12-page questionnaire regarding exposures of interest; these data were supplemented by telephone interviews for subjects employed in agriculture, forestry, horticulture, carpentry and sawmills. The odds ratios for soft-tissue sarcoma were 0.61 (95% CI, 0.34-1.1) for potential exposure to DDT and 0.52 (0.19-1.4) for potential exposure to pesticides other than DDT or mercury seed dressings (Eriksson *et al.*, 1990).

2.3.2 *Other cancers*

A proportionate analysis of occupational mortality in Washington State, USA, identified a 30% increased risk for respiratory cancer among orchardists (Milham, 1983), and a case-control study was undertaken on mortality from respiratory cancer in Washington State in 1968-80 (Wicklund *et al.*, 1988). Death certificates were selected that contained the occupational codes for orchardists, orchard labourers and brush pickers, and farm owners and tenants. Cases were men who had died from respiratory cancer, and potential controls were men who had died from other causes, matched by county of residence, year of death, age at death and occupational code. An attempt was made to contact surviving next-of-kin or other informants. Interviews were obtained for 87.1, 79.6 and 60.5%, respectively, of the three occupational groups. On the basis of the information obtained, orchardists were limited to men who had been involved in orchard work for at least 10 years or 25% of their working history or had been associated with at least one orchard of five or more acres [> 2 ha]. Information on occupational exposures and smoking was obtained from a structured questionnaire. If the informant was unable to recall whether a specific pesticide had been sprayed by the deceased but was able to recall the precise year of his orchard work, a 'presumed' history of spraying a particular pesticide was obtained. Lead arsenate was used by orchardists before 1945 and was replaced by DDT subsequently; thus, if a deceased man had worked prior to 1945, he was presumed to have a positive history of lead arsenate

spraying, and if he had worked after 1945 he was presumed to have a positive history of DDT spraying. Information was obtained for all but 7% of the 155 cases and 4.9% of the 155 matched controls. A total of 89 cases and 89 controls were assumed to have had exposure to DDT. When men exposed to DDT but not to lead arsenate were considered, there were 33 cases and 29 controls, and the odds ratio (adjusted for smoking) was 0.91 (95% CI, 0.40-2.1). [The Working Group noted that the unexposed group included men for whom details on exposure to DDT were not available, which may have biased the odds ratio towards the null.]

Two case-control studies in Sweden examined the risks for colon cancer (Hardell, 1981) and nasal and nasopharyngeal cancer (Hardell *et al.*, 1982), primarily in relation to exposure to phenoxyacetic acid herbicides and chlorophenols. The same control group, consisting of 541 people, was used in these two studies and in two previous studies conducted by the same group (Hardell & Sandström, 1979 [see above]; Hardell *et al.*, 1981). There were 154 cases of colon cancer and 71 cases of nasal and nasopharyngeal cancer. Odds ratios for exposure to DDT, without controlling for other agricultural exposures, were [0.8; 0.4-1.7] for colon cancer and [1.2; 95% CI, 0.5-2.9] for nasal and nasopharyngeal cancer. In the study of colon cancer, exposure to DDT was also analysed after excluding subjects who had been exposed to phenoxyacetic acids and chlorophenols; the odds ratio was [0.5; 0.2-1.6].

Men aged 25-80 who had been diagnosed with liver cancer between 1974 and 1981 and reported to the Department of Oncology, Umeå, Sweden, were included in another case-control study (Hardell *et al.*, 1984). Microscope slides were reviewed for the 166 assembled cases, and 103 cases of primary liver cancer were retained for the study; 206 population-based controls were matched to cases on age and residence. Information on exposure was obtained as in previous studies (see Hardell & Sandström, 1979); responses were obtained for 102 cases and 200 controls. The analysis was restricted to the 98 cases of hepatocellular or cholangiocellular carcinoma. Odds ratios for exposure to DDT, without controlling for other agricultural exposures, were [0.4; 95% CI, 0.1-1.1] for exposure to DDT in farming and [1.3; 0.4-4.0] for exposure to DDT in forestry.

A total of 240 cases of brain glioma were collected from two hospitals in Milan, Italy, between 1983 and 1984. Patients with non-glioma brain tumours (465) and patients with non-neoplastic neurological diseases (277) recruited from the same hospitals and matched for age and sex to the cases formed two series of controls [response rates not given]. Subjects were asked about their occupational history as well as their use of fertilizers, herbicides and insecticides or fungicides. Exposure of farmers to insecticides or fungicides gave an odds ratio of 2.0 (95% CI, 1.2-3.2) using all controls and of 2.1 (1.3-3.6) using only cancer controls (Musicco *et al.*, 1988).

2.3.3 *Childhood cancer*

A case-control study of brain tumours in Baltimore, MD, USA, included all cases under 20 years of age diagnosed in 1965-75, and two groups of controls—one selected from birth certificates of the state and one from children with other malignancies. Controls were matched individually to cases on sex, race and date of birth; cancer controls were also matched on date of diagnosis. Interviews were conducted with 84 of 127 (66%) identified cases; interviews with controls yielded 73 matched pairs with population controls and 78 matched pairs with cancer controls. Parents were interviewed with respect to environmental

exposures, including insect exterminations in the household, as well as child and family characteristics. A matched-pair analysis was conducted. Insect extermination was more common in houses of cases with respect to population controls (odds ratio, 2.3 [95% CI, 0.9-6.6]) but not to cancer controls (1.2 [0.5-2.8]) (Gold *et al.*, 1979).

The results of the case-control studies are summarized by site in Tables 7-9.

3. Other Relevant Data in Humans

3.1 Toxic effects

The toxicology of insecticides in humans has been reviewed (Hayes, 1982).

[The Working Group noted that useful information on chronic illness resulting from human exposure to insecticides is limited (WHO, 1990). The reasons include variable exposure to insecticides, the large number of compounds used (also in combination), the presence of many confounding factors, and the lack of sensitive, specific endpoints for different types of toxicity. Consequently, it seems unlikely that broad surveys in which exposure is not characterized will be adequate to identify the effects of insecticides. Several reports infer that insecticides have chronic effects, but because of constraints such as those described above and often because of the lack of an appropriate epidemiological design, the results cannot be interpreted. Well-designed studies of occupational exposures, combined with appropriate biomonitoring procedures, are perhaps the only way of collecting information on this issue.]

Some of the studies that purport to show an association between adverse health effects and exposure to insecticides are listed below. Disorders of the cardiovascular system (Bezugly & Gorskaya, 1976; Fokina & Bezugly, 1978; Kaskevich, 1980), nervous system (Bezugly *et al.*, 1973); sensory organs, respiratory system (Muminov & Fershtat, 1973; Barthel, 1974; Werner *et al.*, 1978) and reduced lung function (Kolpakov, 1979; Lings, 1982) have been reported following exposure to pesticides (including specified and unspecified insecticides). Skin disorders, including dermatitis (Wassermann *et al.*, 1960; Mirakhmedov & Yusupov, 1973; Takahashi *et al.*, 1975; Nagata *et al.*, 1976a; Tsugane *et al.*, 1978; Yokoyama *et al.*, 1978), headache, nausea (Tsugane *et al.*, 1978; Yokoyama *et al.*, 1978) and blood disorders (Bezugly *et al.*, 1973; Nakajima & Kawabata, 1977) have also been reported.

Abnormal electroencephalograms were observed in some but not all studies on farm workers exposed to organochlorine, organophosphorus and carbamate insecticides (Kontek *et al.*, 1971; Horiguchi, 1973; Horiguchi *et al.*, 1976a,b).

Altered liver enzyme activities have been reported among pesticide workers exposed to organophosphorus pesticides alone or in combination with organochlorine and/or other pesticides (Liska & Tildyova, 1974; Dzhaparov & Karimov, 1978).

Table 7. Case-control studies on malignant lymphomas containing information on insecticide exposure

Reference	Location	Cancer	No. of exposed cases/controls	Relative risk	95% CI	Comments
Hoar *et al.* (1986)	Kansas, USA	Non-Hodgkin's lymphoma	54/275	1.5	0.9–2.4	Insecticides; not adjusted for herbicide use
			24/99	1.1	0.6–2.2	Adjusted for herbicide use; farmers only
Hoar Zahm *et al.* (1988)	Kansas, USA	Hodgkin's disease	38/275	0.8	0.5–1.4	Insecticide use
			32/214	0.9	0.5–1.5	Insecticide use on animals
			25/132	1.1	0.6–1.9	Insecticide use on crops Unadjusted for other agricultural exposures
Hoar Zahm *et al.* (1990)	Nebraska, USA	Non-Hodgkin's lymphoma	104/321	1.1	0.7–1.6	Insecticides; not adjusted for herbicide use
			NA	2.4	NA	Organophosphates; adjusted for 2,4-D use Risks rose with days per year of organophosphate insecticides after adjustment for herbicides
Woods *et al.* (1987); Woods & Polissar (1989)	Washington, USA	Non-Hodgkin's lymphoma	NA	1.6	0.7–3.8	Chlordane
			NA	1.8	1.0–3.2	DDT
			NA	1.6	0.5–5.1	Chlordane for farmers only
			NA	1.7	0.9–3.3	DDT for farmers only Not adjusted for other agricultural exposures
Persson *et al.* (1989)	Sweden	Non-Hodgkin's lymphoma	0/3	–	–	DDT exposure
Persson *et al.* (1989)	Sweden	Hodgkin's disease	3/3	7.5	0.8–70.0	DDT, adjusted for some agricultural exposures; 90% CI
Hardell *et al.* (1981)	Sweden	Malignant lymphoma	22/26	[1.8]	[1.0–3.2]	DDT, crude risk calculated from data in paper. Not adjusted for other agricultural exposures
			7/11	[1.6]	[0.6–4.1]	Crude risk for DDT, without exposure to phenoxyacetic acid herbicides

NA, not available

Table 8. Case-control studies of soft-tissue sarcomas containing information of insecticide exposure

Reference	Location	No. of exposed case/controls	Relative risk	95% CI	Comments
Hoar Zahm *et al.* (1988)	Kansas, USA	50/275	1.3	0.8–2.2	Insecticide use
		46/214	1.6	0.9–2.5	Insecticide use on animals
		14/132	0.8	0.4–1.6	Insecticide use on crops Not adjusted for other agricultural exposures
Woods *et al.* (1987)	Washington, USA	NA	0.96	0.2–4.8	Chlordane
		NA	1.1	0.4–3.2	DDT Not adjusted for other exposures
Hardell & Sandström (1979)	Sweden	4/14	1.2	[0.4–3.7]	DDT Crude risk calculated from data in paper; not adjusted for other agricultural exposures
Eriksson *et al.* (1981)	Sweden	7/11	[1.3]	[0.5–3.4]	DDT Crude risk calculated from data in paper; not adjusted for other agricultural exposures
Hardell & Eriksson (1988)	Sweden	6/19	[1.9][a]	[0.7–5.0]	DDT
		6/8	[2.7][b]	[0.9–7.8]	Crude relative risk calculated from data in paper; not adjusted for other agricultural exposures
		1/10	[0.6][a]	[0.1–5.0]	Crude risk for exposure to DDT and not phenoxyacetic acid
		1/3	[1.2][b]	[0.1–11.6]	
Eriksson *et al.* (1990)	Sweden	6/11	0.52	0.19–1.4	Pesticides other than DDT and mercury seed dressings
		22/33	0.61	0.34–1.1	DDT Not adjusted for other agricultural exposures

[a]Population controls
[b]Cancer controls

Table 9. Case-control studies of other cancers containing information on insecticide exposure

Reference	Location	Cancer[a]	No. of cases/ controls	Relative risk	95% CI	Comments
Morris *et al.* (1986)	USA	Multiple myeloma	28/25	2.6	1.5–4.6	Pesticides
			2/5	[1.0]	[0.2–5.1]	Organophosphorus
			9/8	[2.8]	[1.1–7.0]	Organochlorines
Boffetta *et al.* (1989)	USA	Multiple myeloma	12/25	1.6	0.7–3.7	Pesticides and herbicides; adjusted for other exposures
			4/17	1.0[b]	0.3–3.1	Exposed nonfarmers
			8/20	1.7[b]	0.8–4.0	Unexposed farmers
			8/8	4.3[b]	1.7–10.9	Exposed farmers
Brown *et al.* (1990)	Iowa and Minnesota, USA	Leukaemia	250/588	1.1	0.9–1.3	Use of any insecticide
		ALL	5/588	0.8	0.2–2.5	Adjusted for vital status, age, state, tobacco, family history of lymphopoietic cancer, high-risk occupations, high-risk exposures
		CLL	122/588	1.3	1.0–1.8	
		AML	58/588	1.0	0.7–1.6	
		CML	20/588	1.0	0.5–1.8	
Flodin *et al.* (1988)	Sweden	Chronic lymphatic leukaemia	6/4	6.0	1.5–23.0	DDT; adjusted for other exposures
Wiklund *et al.* (1988b)	USA	Respiratory	33/29	0.91	0.40–2.1	DDT Both cases and controls were orchard workers
Hardell *et al.* (1981)	Sweden	Colon	9/40	[0.8]	[0.4–1.7]	DDT Crude risk calculated from data in paper; not adjusted for other agricultural exposures
		Colon	3/21	[0.5]	[0.2–1.6]	DDT Crude risk calculated from data in paper; for exposure to DDT and not phenoxyacetic acids or chlorophenols
Hardell *et al.* (1982)	Sweden	Nose, nasopharynx	6/40	[1.2]	[0.5–2.9]	DDT Crude risk calculated from data in paper; not adjusted for other agricultural exposures

Table 9 (contd)

Reference	Reference	Cancer	No. of cases/ controls	Relative risk	95% CI	Comments
Hardell *et al.* (1984)	Sweden	Primary liver	4/20	[0.4]	[0.1–1.1]	DDT Crude risk calculated from data in paper; not adjusted for other agricultural exposures; farmers
		Primary liver	5/8	[1.3]	[0.4–4.0]	DDT Crude risk calculated from data in paper; not adjusted for other agricultural exposures; foresters
Musicco *et al.* (1988)	Italy	Brain	37/55 37/31	2.0 2.1	1.2–3.2 1.3–3.6	All controls Tumour controls only Insecticides and fungicides
Study of children						
Gold *et al.* (1979)	USA	Brain	19/10 21/19	2.3[c] 1.2[d]	[0.9–6.6] [0.5–2.8]	Exterminations in house

[a]ALL, acute lymphocytic leukaemia; CLL, chronic lymphocytic leukaemia; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia
[b]Crude odds ratio
[c]Population controls
[d]Cancer controls

3.2 Reproductive and developmental effects in humans

In an ecological study, all cases of cleft lip or cleft palate occurring among white, liveborn singletons in rural areas in Iowa or Michigan (USA) in 1974-75 were identified, together with a 2% sample of all livebirths, who served as controls. Cases and controls were assigned an exposure score based on the proportion of hectares of land on which insecticides or herbicides were used for pest control, by county. An odds ratio of 2.9 (95% CI, 1.5-5.4) was found in Iowa, indicating that the risk of cleft lip or cleft palate was almost three times higher in children born in counties with a high proportion of cropland treated with insecticides or herbicides, compared to other counties. In Michigan, the odds ratio was 1.7 (95% CI, 1.0-2.8). The study did not distinguish between insecticides and herbicides (Gordon & Shy, 1981). [The Working Group noted that the study has the limitations of ecological analyses.]

A study on a population of 8867 people (2951 men and 5916 women) engaged in floriculture in Colombia and exposed to 127 different types of pesticides has been reported. Information on reproductive outcomes before and after employment in the industry was collected by means of a detailed interview. The odds ratio for spontaneous abortion after employment in floriculture was 2.2 (95% CI, 1.8-2.7) among female workers and 1.8 (1.2-2.8) among wives of male workers. The odds ratios for premature birth were 1.9 (1.6-2.2) and 2.8 (2.0-3.8), respectively. The authors point out difficulties in the interpretation of their findings, particularly in regard to recall bias. They did not analyse fungicides and insecticides separately (Restrepo *et al.*, 1990).

In a study of 12 couples (wife and husband) employed in grape gardens in India and of 15 comparable but unexposed couples, reproductive histories were collected. There were 14 spontaneous abortions (44% of 32 pregnancies) and one stillbirth in the exposed group and three spontaneous abortions (8% of 40 pregnancies) and no stillbirth in the unexposed group. The excess of abortions was significant ($p < 0.05$). The workers were exposed to several pesticides, including DDT, lindane, parathion, dichlorvos and dieldrin (Rita *et al.*, 1987).

3.3 Genetic and related effects

Only those studies that provide information on exposure to insecticides were considered. Nevertheless, interpretation of the observed effects was impeded by two fundamental problems: the lack, in almost all studies, of quantitative information on exposure to insecticides and the multiplicity of exposures. People exposed occupationally to insecticides during spraying and application handle large numbers of pesticide formulations, only a proportion of which may be insecticide formulations. Within these formulations, so-called inert ingredients usually form the bulk of the materials, and many of these are biologically highly reactive substances. Consequently, it is difficult or impossible to attribute effects observed in sprayers and applicators specifically to insecticide formulations or even to any named pesticidal component.

3.3.1 *Cytogenetic studies*

Sixteen agricultural workers who had been exposed predominantly to insecticides (mainly the organophosphorus compounds, demeton, ethyl parathion, trichlorfon and naled) in the USA, with a mean exposure time of 12 years, were compared with 16 controls with a

variety of occupations not involving pesticides. Blood samples were taken off-season and mid-season from both groups, and 25 metaphase-arrested lymphocytes from each person were scored on each occasion for chromatid breaks and gaps. The frequency of chromatid breaks in mid-season samples was increased from 0.44 ± 0.22 (SD) in the control group to 1.56 ± 0.29 in the exposed group (Yoder *et al.*, 1973). There was no difference in the occurrence of chromatid gaps either off-season or mid-season or of chromatid breaks in off-season samples. [The Working Group noted that no attempt was made to control for confounding factors such as tobacco smoking, that small numbers of cells were scored from each person and that individual results were not reported.]

The effects of low levels of the insecticide fumigant, ethylene dibromide, upon the frequencies of sister chromatid exchange and chromosomal aberrations were examined among forestry workers in mainland USA (Steenland *et al.*, 1985) and papaya workers in Hawaii (Steenland *et al.*, 1986). Blood samples were taken from 14 forestry workers who sprayed pine trees before and after exposure (8-h time-weighted average, 80 ppb [616 μg/m^3], with a peak of up to 281 ppb [2164 μg/m^3]) and compared with those from six unexposed controls. No effect of exposure to ethylene dibromide was observed, although smoking did increase the frequency of sister chromatid exchange. A group of 60 papaya workers exposed to ethylene dibromide at a geometric mean of 88 ppb [678 μg/m^3] (8-h time-weighted average), but with peak exposures of up to 262 ppb [2017 μg/m^3], were compared with a control group of 42 workers from a nearby sugar mill. The two groups were matched for age, tobacco, marijuana and coffee use and race. No difference was found in the total frequencies of either chromosomal aberrations or sister chromatid exchange. The frequency of the latter, however, was increased in men who smoked either tobacco or marijuana, and that of chromosomal aberrations showed an increasing trend with age.

Floriculturists (36 men and women) in Argentina involved in spraying various pesticides, including organophophosphates, carbamates and organochlorines, were studied for chromosomal aberrations and sister chromatid exchange. Symptoms of chronic intoxication were observed in 21 workers. The control group consisted of 15 healthy scientists and technicians. A significant difference was seen in sister chromatid exchange frequencies between the symptomatic and non-symptomatic floriculturists as well as between a matched group of controls and sprayers. The frequency of only dicentric and ring type chromosomal aberrations was increased when the whole group of floriculturists and controls was compared (Dulout *et al.*, 1985).

In a study from Hungary, 80 male workers were involved in mixing and spraying pesticides (80 formulations were recorded, including insecticides such as organophosphates, organochlorines, pyrethroids and carbamates). At least 12 weeks' continuous contact with pesticides was recorded during the spraying season. A group of 24 administrative workers and mechanics served as controls. A significant increase in the frequency of chromosomal aberrations was seen in the group of pesticide workers as compared with controls; that of chromosome-type aberrations increased with duration of exposure (Páldy *et al*,. 1987).

Forty producers of potted plants (17 smokers) working in greenhouses in Argentina and exposed to a mixture of organophosphorus, organochlorine, carbamate and some miscellaneous pesticides, were examined for chromosomal aberrations (Dulout *et al.*, 1987). The control group consisted of 32 healthy hospital blood donors (10 smokers) with no known

exposure to pesticides. Since some of the control individuals showed toxic symptoms that are seen after chronic exposure to pesticides, a second control group was selected consisting of 12 blood donors (six smokers) with no symptom of exposure. No difference was observed between the control groups with respect to frequency of chromosomal aberrations or between the producers of potted plants and the controls as a whole.

The frequencies of chromosomal aberrations in 15 vineyard workers in India who were exposed to seven insecticides (DDT, lindane, quinalphos, metasystox, parathion, dichlorvos and dieldrin) and two fungicides (dithane M_{45} and copper sulfate) were compared with those in 10 controls of similar age and socioeconomic status, but not exposed to pesticides (Rita *et al.*, 1987). The proportion of metaphase cells with chromatid breaks was significantly increased in the exposed group.

In another Hungarian study, 55 male workers were involved in spraying and applying pesticides in greenhouses, plastic tents and open fields. Among the pesticide formulations, various organophosphates, carbamates and pyrethroids were listed. The control group consisted of 60 male blood donors. A slight increase in the frequency of chromosomal aberrations was recorded among the open-field sprayers; however, the values for closed-space workers were at the control level (Nehéz *et al.*, 1988).

Cotton field workers (pesticide mixers and sprayers) in India were studied for the effects of exposure to pesticides (particularly insecticides) on the frequency of chromosomal aberrations (Rupa *et al.*, 1989a) and of sister chromatid exchange (Rupa *et al.*, 1989b). Peripheral lymphocytes were examined from 50 smokers and compared with those from 20 nonsmokers and 27 smokers, none of whom were occupationally exposed to pesticides. The frequency of chromosomal aberrations was significantly increased in the pesticide-exposed group as compared with either of the control groups. Sister chromatid exchange frequencies showed similar responses to both smoking and pesticides exposure; there was a trend towards an increasing number of sister chromatid exchanges with years of exposure to pesticides.

In a study of chromosomal aberrations, 52 nonsmoking cotton-field workers exposed to pesticides (mainly insecticides) were compared with 25 controls. The insecticides mentioned included malathion, methyl parathion, dimethoate, DDT and fenvalerate. The prevalence of chromosomal aberrations was significantly increased in the group of workers, and there was a positive trend with duration of exposure (Rupa *et al.*, 1989c).

Fumigation of phosphine produced from aluminium or magnesium phosphide pellets is used commonly in the grain industry to control beetles. Of 24 professional fumigant applicators, nine were exposed to phosphine alone (mean level, 2.97 mg/m^3 in grain bin areas; average duration of exposure, over 20 min daily). This group had a five-fold higher frequency of chromosomal deletions than the control subjects, and the frequency of breaks was also significantly increased. Chromosome banding analysis showed that chromosomal rearrangements were six times more frequent in the exposed workers than in the controls. Sister chromatid exchange frequency was not increased. In lymphocytes *in vitro*, no sister chromatid exchange was induced, but the frequency of chromosomal aberrations was increased in a dose-related manner (Garry *et al.*, 1989).

Carbonell *et al.* (1990) studied 27 agricultural workers in Spain who had used insecticides such as fenvalerate, deltamethrin and methomyl. No sister chromatid exchange was induced.

The results of studies on cytogeneticity are summarized in Table 10.

3.3.2 *Urine mutagenicity studies*

Urine samples were taken from 12 greenhouse owners (11 men and 1 woman) who daily sprayed fungicides and insecticides (dichlorvos, orthene (acephate) and pentac (dienochlor) mentioned) in greenhouses in central New York for 1-40 years. The samples, collected 8 h after spraying, and control samples taken three days later were tested for mutagenicity using *Salmonella typhimurium* (strains TA100 and TA98) both with and without an exogenous metabolic system. No increase in mutagenic activity was detected in urine from seven subjects. Three subjects who had elevated urine mutagenicity had been working with poor protection. Two of the subjects reported smoking during the days of sample collection (Shane *et al.*, 1988).

San *et al.* (1989) and See *et al.* (1990) assayed the urine of nonsmoking orchardists in Canada using chromosomal aberrations in Chinese hamster ovary cells as the endpoint. People were exposed to organophosphates among other pesticides. Chromosome damaging activity was significantly elevated in samples collected during the pesticide spraying season as compared to samples collected during the non-spraying season or to urine samples from nonsmoking controls.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Chemicals have been used to control insects for centuries but have come into widespread use only within the past century, with the development of a variety of synthetic insecticides. Of the several hundred chemicals that have been applied for insecticidal purposes, fewer than one hundred have been used extensively.

The principal classes of compounds that have been used as insecticides are organochlorine, organophosphorus, carbamate and pyrethroid compounds and various inorganic compounds. Insecticides comprise a higher proportion of the total pesticide usage in developing countries than in developed countries.

Insecticides are applied by aerial spraying and by various ground-based techniques, ranging from hand-held sprayers and dusters to vehicle-mounted hydraulic sprayers, air sprayers, foggers and power dusters.

Occupational exposures occur in the mixing and loading of equipment and in the spraying and application of insecticides. Absorption resulting from dermal exposure is the most important route of uptake for exposed workers.

4.2 Carcinogenicity in humans

4.2.1 *Descriptive and ecological studies*

Several death certificate case-control studies in the USA evaluated cancer risks in association with ecological measures of insecticide exposure. The risk for multiple myeloma

Table 10. Summary of results from cytogenetic biomonitoring studies on pesticide applicators

Job description	Exposure data	Insecticides listed	Number of subjects (exposed/ controls)	Cytogenetic effect[a]		Reference
				CA	SCE	
Crop dusters, formulators, spray rig operators, farmers in Idaho, USA	Mean exposure time, 12 years	Organophosphates (10), organochlorines (5), phenolics (1), carbamates (1)	16/16	+	ND	Yoder *et al.* (1973)
Floriculturists in Argentina	Chronic intoxication symptoms in 21 individuals, at least 10 years of employment	Organophosphates (5), organochlorines (7), carbamates (5)	36/15	(+)	+	Dulout *et al.* (1985)
Pesticide mixers and field sprayers in Hungary	0.2–15 years of exposure; long exposure group, 11–15 years	80 different formulations: insecticides (organophosphates, pyrethroids), herbicides, fungicides	80/24	+	ND	Páldy *et al.* (1987)
Growers of potted plants in Argentina	Haematological tests normal, cholinesterase decreased in only 3/40; employment time, > 10 years	About 40 different formulations: organophosphates (3), organochlorines (3), permethrin, carbamates (5), and other pesticides	40/32	-	ND	Dulout *et al.* (1987)
Vineyard workers in India	5–15 years of exposure	Various (9) pesticides used throughout the year including 7 insecticides (e.g., DDT, dichlorvos, lindane, parathion)	15/10	+	ND	Rita *et al.* (1987)
Farmers and greenhouse workers in Hungary	Better protection in greenhouse than in open field; most exposed for 2–10 years	Various formulations of agrochemicals (insecticides: organophosphates (7), carbamates (3), pyrethroids (5); fungicides)	55/60	(+)	ND	Nehéz *et al.* (1988)
Mixers and sprayers of pesticides in cotton fields in India	Several years of exposure, 8 h/day; 9 months/year; all cotton-field workers were smokers	Insecticides (11) including DDT, BHC, malathion, fenvalerate, cypermethrin	50/47	+	+	Rupa *et al.* (1989a,b)

Table 10 (contd)

Job description	Exposure data	Insecticides listed	Number of subjects (exposed/ controls)	Cytogenetic effect[a]		Reference
				CA	SCE	
Mixers and sprayers of pesticides in cotton fields in India	Several years of exposure, 8 h/day; 9 months/year; all cotton-field workers were non-smokers	Insecticides (11) including: DDT, BHC, malathion, fenvalerate	52/25	+	ND	Rupa *et al.* (1989c)
Fumigant applicators in grain industry	Daily exposure over 20 min in closed space with phosphine at 0.4–5.8 mg/m^3	Groups exposed to phosphine alone (n = 9) and to phosphine and other pesticides (n = 15)	9/24	+	–	Garry *et al.* (1989)
Horticultural and floricultural workers in Spain	Over 10 years of work in family enterprises	Various pesticides, including insecticides (methomyl, fenvalerate, deltamethrin)	27/28	ND	–	Carbonell *et al.* (1990)

[a]CA, chromosomal aberration; SCE, sister chromatid exchange; +, statistically significant positive result; (+), suggestive positive result; –, negative result; ND, no data

tended to be greater for farmers residing in counties where insecticides were more heavily used, but that for leukaemia did not.

4.2.2 *Cohort studies*

A cohort of workers from a large pest control company in the USA had an excess lung cancer risk. Similarly, in a cohort of licensed pest control workers from Florida, there was significantly increased mortality from lung cancer, which was particularly high among workers licensed for 20 years or more; a nonsignificant excess risk for brain cancer was also seen. A follow-up of deaths among plant protection workers and agronomists in eastern Germany showed an increased risk of lung cancer which also increased with length of exposure; survey data indicated that the smoking habits of these pesticide workers were similar to those of the general population.

Among farmers licensed for pesticide use in the Piedmont region of Italy, increased risks for skin cancer and malignant lymphomas were reported; lung cancer incidence was not studied.

A cohort of licensed pesticide applicators in Sweden showed excess risks for cancers of the lip and testis, a slight excess risk for Hodgkin's disease, and risks similar to those of the general population for non-Hodgkin's lymphoma and soft-tissue sarcoma. Overall, there was a deficit of lung cancer risk that was probably related to the lower smoking rates of the applicators.

In a study of a large cohort of grain millers in the USA, flour-mill workers had excess risks for non-Hodgkin's lymphoma and pancreatic cancer; the risk for lung cancer was not increased.

4.2.3 *Case-control studies*

The risk for non-Hodgkin's lymphoma rose with frequency of use of organophosphorus insecticides among farmers in Nebraska, an association that could not be accounted for by use of phenoxyacetic acid herbicides. In Kansas, the risk increased slightly with frequency of use of insecticides as a group. In a study in Washington State, non-Hodgkin's lymphoma was associated with potential contact with chlordane and DDT. DDT use was also associated with non-Hodgkin's lymphoma in one of two studies in Sweden.

Multiple myeloma was associated with use of pesticides (particularly organochlorine insecticides) in a study in the USA. The risk for multiple myeloma was also elevated among farmers in the USA exposed to unspecified herbicides and pesticides.

The results of six studies in Sweden and the USA on soft-tissue sarcoma in association with exposure to insecticides were inconsistent.

Chronic lymphocytic leukaemia has been associated with use of insecticides in the USA and with use of DDT in Sweden.

The risk for brain cancer was associated with exposure to insecticides and fungicides in farmers in Italy.

Overall, the strongest evidence that exposure to nonarsenical insecticides causes cancer in humans comes from the cohort studies of applicators. Two of these studies showed significant excesses of lung cancer. Two showed rising risks with duration of exposure,

whereas the third showed an inverse association. These findings were based on small numbers in the subgroups with the longest exposure, and applicators in some of these studies had potential contact with arsenical insecticides. Some case-control studies of multiple myeloma and other tumours of B-cell origin show small excesses among people exposed to insecticides. In most studies, however, potential confounding by other agricultural exposures had not been fully explored.

4.3 Other relevant data

In a study in India, an excess of spontaneous abortions was reported among couples exposed to several pesticides in grape gardens. In a population in Colombia, where exposure to many different pesticides occurred, increased risks for spontaneous abortion and decreased birth weight were reported.

Several studies on the cytogenetic effects of work with pesticide formulations are described. Only in the case of ethylene dibromide and phosphine was exposure to a single, identified insecticide: No cytogenetic effect was observed with exposure to ethylene dibromide, while a significant excess of chromosomal aberrations was observed among the phosphine fumigators. All other studies were of workers handling not only a mixture of insecticide formulations but also other pesticide formulations. The majority of these studies reported increases in the frequency of chromosomal aberrations and/or sister chromatid exchange among the exposed workers. With the exceptions noted above, in no instance, however, could the involvement of non-insecticides be eliminated.

4.4 Evaluation[1]

There is *limited evidence* that occupational exposures in spraying and application of nonarsenical insecticides[2] entail a carcinogenic risk.

Overall evaluation

Spraying and application of nonarsenical insecticides[2] entail exposures that *are probably carcinogenic to humans (Group 2A).*

5. References

Adamis, Z., Antal, A., Fuezesi, I., Molnár, J., Nagy, L. & Susán, M. (1985) Occupational exposure to organophosphorus insecticides and synthetic pyrethroid. *Int. Arch. occup. environ. Health, 56,* 299-305

Alavanja, M.C.R., Rush, G.A., Stewart, P. & Blair, A. (1987) Proportionate mortality study of workers in the grain industry. *J. natl Cancer Inst., 78,* 247-252

Alavanja, M.C.R., Blair, A. & Masters, M.N. (1990) Cancer mortality in the US flour industry. *J. natl Cancer Inst., 82,* 840-848

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

[2]Arsenic and arsenic compounds are carcinogenic to humans (IARC, 1987). This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group.

Ames, R.G., Brown, S.K., Mengle, D.C., Kahn, E., Stratton, J.W. & Jackson, R.J. (1989) Cholinesterase activity depression among California agricultural pesticide applicators. *Am. J. ind. Med., 15,* 143-150

Anon. (1981) *Basic Pesticide Equipment Manual,* Helena, MT, Department of Agriculture

Baker, E.L., Jr, Zack, M., Miles, J.W., Alderman, L., Warren, M., Dobbin, R.D., Miller, S. & Teeters, W.R. (1978) Epidemic malathion poisoning in Pakistan malaria workers. *Lancet, i,* 31-34

Barthel, E. (1974) Pulmonary fibroses in persons exposed to pesticides (Ger.). *Z. Erkr. Atmungsorg., 141,* 7-17

Barthel, E. (1976) High incidence of lung cancer in persons with chronic occupational exposure to pesticides in agriculture (Ger.). *Z. Erkr. Atm.-Org., 146,* 266-274

Barthel, E. (1981a) Increased risk of lung cancer in pesticide-exposed male agricultural workers. *J. Toxicol. environ. Health, 8,* 1027-1040

Barthel, E. (1981b) Cancer risk in pesticide-exposed agricultural workers (Ger.) *Arch. Geschwulstforsch., 51,* 579-585

Bezugly, V.P. & Gorskaya, N.Z. (1976) The role of the complex of organochlorine and organophosphorus pesticides in the development of atherosclerosis (Russ.). *Vrach. Delo., 2,* 99-102

Bezugly, V.P., Odintsova, I.L. & Gorskaya, N.S. (1973) Morphological composition of the blood in persons working with a complex of organochlorine and organophosphorus pesticides (Russ.). *Vrach. Delo, 11,* 134-138

Blair, A. & Thomas, T.L. (1979) Leukemia among Nebraska farmers: a death certificate study. *Am. J. Epidemiol., 110,* 264-273

Blair, A. & Watts, D. (1980) Bladder cancer and dairy farming (Letter to the Editor). *J. occup. Med., 22,* 576-577

Blair, A. & White, D.W. (1981) Death certificate study of leukemia among farmers from Wisconsin. *J. natl Cancer Inst., 66,* 1027-1030

Blair, A., Grauman, D.J., Lubin, J.H. & Fraumeni, J.F., Jr (1983) Lung cancer and other causes of death among licensed pesticide applicators. *J. natl Cancer Inst., 71,* 31-37

Blair, A., Hoar Zahm, S., Cantor, K.P. & Stewart, P.A. (1989) Estimating exposure to pesticides in epidemiological studies of cancer. In: Wang, R.G.M., Franklin, C.A., Honeycutt, R.C. & Reinert, J.C., eds, *Biological Monitoring for Pesticide Exposure. Measurement, Estimation, and Risk Reduction* (ACS Symposium Series 382), Washington DC, American Chemical Society, pp. 38-46

Boettiger, L.E. (1979) Epidemiology and aetiology of aplastic anemia. *Haematol. Bluttransfus., 24,* 27-37 (116)

Boffetta, P., Stellman, S.D. & Garfinkel, L. (1989) A case-control study of multiple myeloma nested in the American Cancer Society prospective study. *Int. J. Cancer, 43,* 554-559

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

Burmeister, L.F., Van Lier, S.F. & Isacson, P. (1982) Leukemia and farm practices in Iowa. *Am. J. Epidemiol., 115,* 720-728

Burmeister, L.F., Everett, G.D., Van Lier, S.F. & Isacson, P. (1983) Selected cancer mortality and farm practices in Iowa. *Am. J. Epidemiol., 118,* 72-77

Cantor, K.P. (1982) Farming and mortality from non-Hodgkin's lymphoma: a case-control study. *Int. J. Cancer, 29,* 239-247

Cantor, K.P. & Blair, A. (1984) Farming and mortality from multiple myeloma: a case-control study with the use of death certificates. *J. natl Cancer Inst.*, *72*, 251-255

Carbonell, E., Puig, M., Xamena, N., Creus, A. & Marcos, R. (1990) Sister chromatid exchange in lymphocytes of agricultural workers exposed to pesticides. *Mutagenesis*, *5*, 403-405

Carman, G.E., Iwata, Y., Pappas, J.L., O'Neal, J.R. & Gunther, F.A. (1982) Pesticide applicator exposure to insecticides during treatment of citrus trees with oscillating boom and airblast units. *Arch. environ. Contam. Toxicol.*, *11*, 651-659

Clarkson, T.W., Friberg, L., Nordberg, G.F. & Sager, P.R., eds (1988) *Biological Monitoring of Toxic Metals*, New York, Plenum

Comer, S.W., Staiff, D.C., Armstrong J.F. & Wolfe, H.R. (1975) Exposure of workers to carbaryl. *Bull environ. Contam. Toxicol.*, *13*, 385-391

Copley, K. (1987) Dow studies measure applicator exposure. *Grounds Maint.*, *22*, 42, 46

Copplestone, J.F., Fakhri, Z.I., Miles, J.W., Mitchell, C.A., Osman, Y. & Wolfe, H.R. (1976) Exposure to pesticides in agriculture: a survey of spraymen using dimethoate in the Sudan. *Bull. World Health Organ.*, *54*, 217-223

Corrao, G., Calleri, M., Carle, F., Russo, R., Bosia, S. & Piccioni, P. (1989) Cancer risk in a cohort of licensed pesticide users. *Scand. J. Work Environ. Health*, *15*, 203-209

Coye, M.J., Lowe, J.A. & Maddy, K.J. (1986) Biological monitoring of agricultural workers exposed to pesticides: II. Monitoring of intact pesticides and their metabolites. *J. occup. Med.*, *28*, 628-636

Culver, D., Caplan, P. & Batchelor, G.S. (1956) Studies of human exposure during aerosol application of malathion and chlorthion. *Arch. ind. Health*, *13*, 37-50

Davis, J.E., Stevens, E.R., Staiff, D.C. & Butler, L.C. (1983) Potential exposure to diazinon during yard applications. *Environ. Monit. Assess.*, *3*, 23-28

Devine, J.M., Kinoshita, G.B., Peterson, R.P. & Picard, G.L. (1986) Farm worker exposure to terbufos [phosphorodithioic acid, *S*-(*tert*-butylthio)methyl *O,O*-diethyl ester] during planting operations of corn. *Arch. environ. Contam. Toxicol.*, *15*, 113-119

Dover, M.J. (1985) *A Better Mousetrap: Improving Pest Management for Agriculture*, Washington DC, World Resources Institute

Dulout, F.N., Pastori, M.C., Olivero, O.A., Cid, M.G., Loria, D., Matos, E., Sobel, N., de Bujan, E.C. & Albiano, N. (1985) Sister-chromatid exchanges and chromosomal aberrations in a population exposed to pesticides. *Mutat. Res.*, *143*, 237-244

Dulout, F.N., Pastori, M.C., Cid, M.G., Matos, E., von Guradze, H.N., Maderna, C.R., Loria, D., Sainz, L., Albiano, N. & Sobel, N. (1987) Cytogenetic analysis in plant breeders. *Mutat. Res.*, *189*, 381-386

Dzhaparov, A.K. & Karimov, V.A. (1978) State of metabolites and the activity of carbohydrate metabolizing enzymes in patients with chronic organochlorine and organophosphorus pesticide poisoning (Russ.). *Gig. Tr. prof. Zabol.*, *11*, 28-29

Eriksson, M., Hardell, L., Berg, N.O., Möller, T. & Axelson, O. (1981) Soft-tissue sarcomas and exposure to chemical substances: a case-referent study. *Br. J. ind. Med.*, *38*, 27-33

Eriksson, M., Hardell, L. & Adami, H.-O. (1990) Exposure to dioxins as a risk factor for soft tissue sarcoma: a population-based case-control study. *J. natl Cancer Inst.*, *82*, 486-490

Fenske, R.A. (1987) Assessment of dermal exposure to pesticides: a comparison of the patch technique and the video imaging/fluorescent tracer technique. In: Greenhalgh, R. & Roberts, T.R., eds, *Pesticide Science and Technology* (Proceedings of the 6th International Congress on Pesticides Chemistry), Oxford, Blackwell Scientific Publishers, pp. 579-582

Flodin, U., Fredriksson, M., Persson, B. & Axelson, O. (1988) Chronic lymphatic leukaemia and engine exhausts, fresh wood, and DDT: a case-referent study. *Br. J. ind. Med.*, *45*, 33-38

Foa, V., Emmett, E.A., Maroni, M. & Colombi, A. (1987) *Occupational and Environmental Chemical Hazards, Cellular and Biochemical Indices for Monitoring Toxicity*, Chichester, Ellis Horwood

Fokina, K.V. & Bezugly, V.P. (1978) Role of combinations of organochlorine and organophosphorus pesticides in the development of cerebral atherosclerosis (Russ.). *Vrach. Delo*, *4*, 19-23

Franklin, C.A. (1989) Biological monitoring for pesticide exposure. In: Wang, R.G.M., Franklin, C.A., Honeycutt, R.C. & Reinert, J.C., eds, *Biological Monitoring for Pesticide Exposure. Measurement, Estimation, and Risk Reduction* (ACS Symposium Series 382), Washington DC, American Chemical Society, pp. 2-5

Franklin, C.A., Muir, N.I. & Moody, R.P. (1986) The use of biological monitoring in the estimation of exposure during the application of pesticides. *Toxicol. Lett.*, *33*, 127-136

Freeborg, R.P., Daniel, W.H. & Konopinski, V.J. (1985) Applicator exposure to pesticides applied to turfgrass. In: Honeycutt, R.C., Zweig, G. & Ragsdale, N.N., eds, *Dermal Exposure Related to Pesticide Use: Discussion of Risk Assessment* (ACS Symposium Series 273), Washington DC, American Chemical Society, pp. 287-295

Garry, V.F., Griffith, J., Danzl, T.J., Nelson, R.L., Whorton, E.B., Krueger, L.A. & Cervenka, J. (1989) Human genotoxicity: pesticide applicators and phosphine. *Science*, *246*, 251-255

Gold, R.E. & Holcslaw, T. (1985) Dermal and respiratory exposure of applicators and residents to dichlorvos-treated residences. In: Honeycutt, R.C., Zweig, G. & Ragsdale, N.N., eds, *Dermal Exposure Related to Pesticide Use: Discussion of Risk Assessment* (ACS Symposium Series 273), Washington DC, American Chemical Society, pp. 253-264

Gold, E., Gordis, L., Tonascia, J. & Szklo, M. (1979) Risk factors for brain tumors in children. *Am. J. Epidemiol.*, *109*, 309-319

Gold, R.E., Leavitt, J.R.C. & Ballard, J. (1981) Effect of spray and paint-on applications of a slow-release formulation of chlorpyrifos on German cockroach control and human exposure. *J. Econ. Entomol.*, *74*, 552-554

Gordon, J.E. & Shy, C.M. (1981) Agricultural chemical use and congenital cleft lip and/or palate. *Arch. environ. Health*, *36*, 213-220

Hardell, L. (1981) Relation of soft-tissue sarcoma, malignant lymphoma and colon cancer to phenoxy acids, chlorophenols and other agents. *Scand. J. Work Environ. Health*, *7*, 119-130

Hardell, L. & Eriksson, M. (1988) The association between soft tissue sarcomas and exposure to phenoxyacetic acids. *Cancer*, *62*, 652-656

Hardell, L. & Sandström, A. (1979) Case-control study soft tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. *Br. J. Cancer*, *39*, 711-717

Hardell, L., Eriksson, M., Lenner, P. & Lundgren, E. (1981) Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. *Br. J. Cancer*, *43*, 169-176

Hardell, L., Johansson, B. & Axelson, O. (1982) Epidemiological study of nasal and nasopharyngeal cancer and their relation to phenoxy acid or chlorophenol exposure. *Am. J. ind. Med.*, *3*, 247-257

Hardell, L., Bengtsson, N.O., Jonsson, U., Eriksson, S. & Larsson, L.G. (1984) Aetiological aspects on primary liver cancer with special regard to alcohol, organic solvents and acute intermittent porphyria—an epidemiological investigation. *Br. J. Cancer*, *50*, 389-397

Haskell, P.T., ed. (1985) *Pesticide Application: Principles and Practice*, Oxford, Clarendon Press

Haverty, M.I., Page, M., Shea, P.J., Hoy, J.B. & Hall, R.W. (1983) Drift and worker exposure resulting from two methods of applying insecticides to pine bark. *Bull. environ. Contam. Toxicol., 30*, 223-228

Hayes, W.J., Jr (1982) *Pesticides Studied in Man*, Baltimore, Williams & Wilkins Co.

Hayes, A.L., Wise, R.A. & Weir, F.W. (1980) Assessment of occupational exposure to organophosphates in pest control operators. *Am. ind. Hyg. Assoc. J., 41*, 568-575

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

Hoar Zahm, S., Blair, A., Holmes, F.F., Boysen, C.D. & Robel, R.J. (1988) A case-referent study of soft-tissue sarcoma and Hodgkin's disease. Farming and insecticide use. *Scand. J. Work Environ. Health, 14*, 224-230

Hoar Zahm, S., Weisenburger, D.D., Babbitt, P.A., Saal, R.C., Vaught, J.B., Cantor, K.P. & Blair, A. (1990) A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology, 1*, 349-356

Horiguchi, Y. (1973) Studies on the influence of organophosphorus pesticides on the central nervous system. Part 2. Effects on the human body (Jpn.). *J. Jpn. Assoc. rural Med., 22*, 294-295

Horiguchi, Y., Yanagisawa, T., Ide, H. & Sasaki, K. (1976a) Studies on the effect of organophosphorus pesticides in the human central nervous system (Jpn.). *J. Jpn. Assoc. rural Med., 25*, 627-628

Horiguchi, Y., Yanagisawa, T., Sasaki, K., Ide, H., Ueki, S., Abe, E. & Kurosawa, K. (1976b) Neurological studies on the treatment of organophosphorus insecticide intoxication. Part 5. Electroencephalographic study of pesticide applicators (Jpn.). In: [Studies on the Effects of Pesticides on Living Bodies], pp. 68-70

IARC (1980) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 23, *Some Metals and Metallic Compounds*, Lyon, pp. 39-141

IARC (1986) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 6, *Genetic and Related Effects: An Updating of Selected* IARC Monographs *from Volumes 1 to 42*, Lyon, pp. 296-300

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, pp. 100-106

Joyce, R.J.V. (1985) Application from the air. In: Haskell, P.T., ed., *Pesticide Application: Principles and Practices*, Oxford, Clarenden Press, pp. 118-152

Kaskevich, L.M. (1980) On the character of pre-clinical changes under the effect of a complex of chloro- and phosphororganic pesticides (Russ.). *Vrach. Delo, 4*, 105-107

Kolpakov, I.E. (1979) Demonstration of early changes in the respiratory function and gas exchange of workers exposed to pesticides. *Gig. Tr. prof. Zabol., 1*, 36-37

Kontek, M., Marcinkowska, B. & Pietraszek, Z. (1971) Electroencephalograms in farmers professionally exposed to pesticides (Pol.). *Med. Prac., 22*, 433-440

Korsak, R.J. & Sato, M.M. (1977) Effects of chronic organophosphate pesticide exposure on the central nervous system. *Clin. Toxicol., 11*, 83-95

Kurtz, D.A. & Bode, W.M. (1985) Application exposure to the home gardener. In: Honeycutt, R.C., Zweig, G. & Ragsdale, N.N., eds, *Dermal Exposure Related to Pesticide Use: Discussion of Risk Assessment* (ACS Symposium 273), Washington DC, American Chemical Society, pp. 139-162

Leavitt, J.R.C., Gold, R.E., Holcslaw, T. & Tupy, D. (1982) Exposure of professional pesticide applicators to carbaryl. *Arch. environ. Contam. Toxicol., 11*, 57-62

Lings, S. (1982) Pesticide lung: a pilot investigation of fruit-growers and farmers during the spraying season. *Br. J. ind. Med., 39*, 370-376

Liska, D. & Tildyova, K. (1974) Study of the changes of activity of some enzymes in the blood of pilots and engineers exposed to organophosphorus pesticides (Czech.). *Cesk. Hyg., 19*, 289-295

Loevinsohn, M.E. (1987) Insecticide use and increased mortality in rural central Luzon, Philippines. *Lancet, i*, 1359-1362

Lotti, M. (1989) Neuropathy target esterase in blood lymphocytes: monitoring the interaction of organophosphates with a primary target. In: Wang, R.G.M., Franklin, C.A., Honeycutt, R.C. & Reinert, J.C., eds, *Biological Monitoring for Pesticide Exposure. Measurement, Estimation, and Risk Reduction* (ACS Symposium Series 382), Washington DC, American Chemical Society, pp. 117-123

MacMahon, B., Monson, R.R., Wang, H.H. & Zheng, T. (1988) A second follow-up of mortality in a cohort of pesticide applicators. *J. occup. Med., 30*, 429-432

Maddy, K.T., Knaak, J.B. & Gibbons, D.B. (1986) Monitoring the urine of pesticide applicators in California for residues of chlordimeform and its metabolites 1982-1985. *Toxicol. Lett., 33*, 37-44

Maitlen, J.C., Sell, C.R., McDonough, L.M. & Fertig, S.N. (1982) Workers in the agricultural environment: dermal exposure to carbaryl. In: Plimmer, J.R., ed., *Pesticide Residues and Exposure* (ACS Symposium Series 182), Washington DC, American Chemical Society, pp. 83-103

Marinova, G., Osmakova, D., Dermendzhieva, L.L., Khadzhikolev, I., Chakurova, O. & Kaneva, Y. (1973) Professional injuries—pesticides and their effects on the reproductive function of women working with pesticides (Hung.). *Akush. Ginecol. (Sofia), 12*, 138-140

Maroni, M. (1986) Organophosphorus pesticides. In: Alessio, L., Berlin, A., Boni, M. & Roi, R., eds, *Biological Indicators for the Assessment of Human Exposure to Industrial Chemicals*, Luxembourg, Commission of the European Communities, pp. 47-77

Matthews, G.A. (1985) Application from the ground. In: Haskell, P.T., ed., *Pesticide Application: Principles and Practice*, Oxford, Clarendon Press, pp. 95-117

Milham, S., Jr (1983) *Occupational Mortality in Washington State, 1950-1979* (DHHS (NIOSH) Publication No. 83-116), Cincinnati, OH, National Institute for Occupational Safety and Health

Mirakhmedov, U.M. & Yusupov, B.Y. (1973) Clinical aspects of dermatoses caused by poisonous chemicals in agricultural workers (Russ.). *Gig. Tr. prof. Zabol., 17*, 48-49

Morgan, D.P., Lin, L.I. & Saikaly, H.H. (1980) Morbidity and mortality in workers occupationally exposed to pesticides. *Arch. environ. Contam. Toxicol., 9*, 349-382

Morgan, M.S., Phillips, G.S. & Kirkpatrick, E.M. (1989) Convenient field sampling method for monitoring volatile compounds in exhaled breath. In: Wang, R.G.M., Franklin, C.A., Honeycutt, R.C. & Reinert, J.C., eds, *Biological Monitoring for Pesticide Exposure. Measurement, Estimation, and Risk Reduction* (ACS Symposium Series 382), Washington DC, American Chemical Society, pp. 56-69

Morris, P.D., Koepsell, T.D., Daling, J.R., Taylor, J.W., Lyon, J.L., Swanson, G.M., Child, M. & Weiss, N.S. (1986) Toxic substance exposure and multiple myeloma: a case-control study. *J. natl Cancer Inst., 76*, 987-994

Moseman, R.F. & Oswald, E.O. (1980) Development of analytical methodology for assessment of human exposure to pesticides. In: Harvey, J., Jr & Zweig, G., eds, *Pesticide Analytical Methodology* (ACS Symposium Series 136), Washington DC, American Chemical Society, pp. 251-257

Muminov, A.I. & Fershtat, V.N. (1973) The status of the upper respiratory tract in people working with combinations of organophosphorus and organochlorine pesticides (Russ.). *Vestn. Otorinolaringol., 35*, 96

Musicco, M., Sant, M., Molinari, S., Filippini, G., Gatta, G. & Berrino, F. (1988) A case-control study of brain gliomas and occupational exposure to chemical carcinogens: the risk to farmers. *Am. J. Epidemiol., 128*, 778-785

Nagata, H., Izumiyama, T., Kamata, K., Takano, S., Saito, M., Suzuki, K., Tajiri, H., Kobayashi, S. & Kurotani, S. (1976) Results of multiphase health examination of pesticide applicators in grape and apple orchards with combined pesticides (Jpn.). *J. Jpn. Assoc. rural Med., 25*, 196-197

Nakajima, H. & Kawabata, M. (1977) Health examination results from a model rural village in Yamaguchi Prefecture (Jpn.). *J. Jpn. Assoc. rural Med., 26*, 177

Nehéz, M., Boros, P., Ferke, A., Mohos, J., Palotás, M., Vetró, G., Zimányi, M. & Dési, I. (1988) Cytogenetic examination of people working with agrochemicals in the southern region of Hungary. *Regul. Toxicol. Pharmacol., 8*, 37-44

Nigg, H.N. & Stamper, J.H. (1983) Exposure of spray applicators and mixer-loaders to chlorobenzilate miticide in Florida citrus groves. *Arch. environ. Contam. Toxicol., 12*, 477-482

Nye, D.E. (1986) Aerial applicator and mixer-loader exposure to cypermethrin during ULV application to cotton. In: *Proceedings of the Beltwide Cotton Production Research Conferences, Las Vegas, Nevada, January 4-9, 1986*, Memphis, TN, National Cotton Council and The Cotton Foundation, pp. 198-200

Ogg, C.L. & Gold, R.E. (1988) Exposure and field evaluation of fenoxycarb for German cockroach (*Orthoptera*: Blattellidae) control. *J. Econ. Entomol., 81*, 1408-1413

Páldy, A., Puskás, N., Vincze, K. & Hadházi, M. (1987) Cytogenetic studies on rural populations exposed to pesticides. *Mutat. Res., 187*, 127-132

Persson, B., Dahlander, A.-M., Fredriksson, M., Brage, H.N., Ohlson, C.-G. & Axelson, O. (1989) Malignant lymphomas and occupational exposures. *Br. J. ind. Med., 46*, 516-520

Prinsen, G.H. & Van Sittert, N.J. (1980) Exposure and medical monitoring study of a new synthetic pyrethroid after one season of spraying on cotton in Ivory Coast. In: Tordoir, W.F. & van Heemstra-Lequin, E.A.H., eds, *Field Worker Exposure During Pesticide Application* (Studies in Environmental Science No. 7), Amsterdam, Elsevier, pp. 105-120

Restrepo, M., Muñoz, N., Day, N.E., Parra, J.E., de Romero, L. & Nguyen-Dinh, X. (1990) Prevalence of adverse reproductive outcomes in a population occupationally exposed to pesticides in Colombia. *Scand. J. Work Environ. Health, 16*, 232-238

Rita, P., Reddy, P.P. & Vankatram Reddy, S. (1987) Monitoring of workers occupationally exposed to pesticides in grape garden of Andhra Pradesh. *Environ. Res., 44*, 1-5

Rupa, D.S., Reddy, P.P. & Reddi, O.S. (1989a) Frequencies of chromosomal aberrations in smokers exposed to pesticides in cotton fields. *Mutat. Res., 222*, 37-41

Rupa, D.S., Reddy, P.P. & Reddi, O.S. (1989b) Analysis of sister-chromatid exchanges, cell kinetics and mitotic index in lymphocytes of smoking pesticide sprayers. *Mutat. Res., 223*, 253-258

Rupa, D.S., Reddy, P.P. & Reddi, O.S. (1989c) Chromosomal aberrations in peripheral lymphocytes of cotton field workers exposed to pesticides. *Environ. Res., 49*, 1-6

Sabbioni, G. & Neumann, H.-G. (1990) Biomonitoring of arylamines: hemoglobin adducts of urea and carbamate pesticides. *Carcinogenesis, 11*, 111-115

Saftlas, A.F., Blair, A., Cantor, K.P., Hanrahan, L. & Anderson, H.A. (1987) Cancer and other causes of death among Wisconsin farmers. *Am. J. ind. Med., 11*, 119-129

San, R.H.C., Rosin, M.P., See, R.H., Dunn, B.P. & Stich, H.F. (1989) Use of urine for monitoring human exposure to genotoxic agents. In: Wang, R.G.M., Franklin, C.A., Honeycutt, R.C. & Reinert, J.C., eds, *Biological Monitoring for Pesticide Exposure. Measurement, Estimation, and Risk Reduction* (ACS Symposium Series 382), Washington DC, American Chemical Society, pp. 98-116

See, R.H., Dunn, B.P. & San, R.H.C. (1990) Clastogenic activity in urine of workers occupationally exposed to pesticides. *Mutat. Res., 241*, 251-259

Shane, B.S., Scarlett-Kranz, J.M., Reid, W.S. & Lisk, D.J. (1988) Mutagenicity of urine from greenhouse workers. *J. Toxicol. environ. Health, 24*, 429-437

Shugart, L.R., Adams, S.M., Jiminez, B.D., Talmage, S.S. & McCarthy, J.F. (1989) Biological markers to study exposure in animals and bioavailability of environmental contaminants. In: Wang, R.G.M., Franklin, C.A., Honeycutt, R.C. & Reinert, J.C., eds, *Biological Monitoring for Pesticide Exposure. Measurement, Estimation, and Risk Reduction* (ACS Symposium Series 382), Washington DC, American Chemical Society, pp. 85-97

Spittler, T.D. & Bourke, J.B. (1985) Potential exposure in the application of pesticides to orchard and field crops. In: Honeycutt, R.C., Zweig, G. & Ragsdale, N.N., eds, *Dermal Exposure Related to Pesticide Use: Discussion of Risk Assessment* (ACS Symposium Series 273), Washington DC, American Chemical Society, pp. 297-310

Stamper, J.H., Nigg, H.N., Mahon, W.D., Nielsen, A.P. & Royer, M.D. (1989) Applicator exposure to fluvalinate, chlorpyrifos, captan, and chlorothalonil in Florida ornamentals. *J. agric. Food Chem., 37*, 240-244

Steenland, K., Carrano, A., Clapp, D., Ratcliffe, J., Ashworth, L. & Meinhardt, T. (1985) Cytogenetic studies in humans after short-term exposure to ethylene dibromide. *J. occup. Med., 27*, 729-732

Steenland, K., Carrano, A., Ratcliffe, J., Clapp, D., Ashworth, L. & Meinhardt, T. (1986) A cytogenetic study of papaya workers exposed to ethylene dibromide. *Mutat. Res., 170*, 151-160

Takahashi, M., Akaboshi, S. & Nishiya, N. (1975) On occupational intoxication caused by pesticides in persons engaging in pesticide application for pest control (Jpn.). *Ind. Med., 17*, 52-53

Tsugane, S., Hirabayashi, H., Tajima, J., Yokoyama, T., Tsugane, Y., Sakurai, K., Nakamura, S., Ide, H. & Asanuma, S. (1978) Actual status of pesticide application and health management of pesticide applicators in vegetable-growing highlands (Jpn.). *J. Jpn. Assoc. rural Med., 27*, 446-447

Wang, H.H. & MacMahon, B. (1979) Mortality of pesticide applicators. *J. occup. Med., 21*, 741-744

Wang, R.G.M., Franklin, C.A., Honeycutt, R.C. & Reinert, J.C., eds (1989) *Biological Monitoring for Pesticide Exposure, Measurement Estimation and Risk Reduction* (ACS Symposium Series 382), Washington DC, American Chemical Society

Wassermann, M., Iliesçu, S., Mandric, G. & Horvath, P. (1960) Toxic hazards during DDT- and BHC-spraying of forests against Lymantria monacha. *Arch. ind. Health, 21*, 503-508

Werner, E., Meyer, P. & Thiele, E. (1978) Examination of the mucous membranes of the upper respiratory tract and of parotid secretion of people working in agriculture after exposure to agrochemicals (Ger.). *Z. ges. Hyg., 24*, 335-337

WHO/UNEP (1990) *Public Health Impact of Pesticides Used in Agriculture*, Geneva

Wicklund, K.G., Daling, J.R., Allard, J. & Weiss, N.S. (1988b) Respiratory cancer among orchardists in Washington State, 1968 to 1980. *J. occup. Med., 30*, 561-564

Wiklund, K., Dich, J. & Holm, L.-E. (1986) Testicular cancer among agricultural workers and licensed pesticide applicators in Sweden (Letter to the Editor). *Scand. J. Work Environ. Health, 12*, 630-631

Wiklund, K., Dich, J. & Holm, L.-E. (1987) Risk of malignant lymphoma in Swedish pesticide appliers. *Br. J. Cancer, 56*, 505-508

Wiklund, K., Dich, J. & Holm, L.-E. (1988) Soft tissue sarcoma risk in Swedish licensed pesticide applicators. *J. occup. Med., 30*, 801-804

Wiklund, K., Dich, J., Holm, L.-E. & Eklund, G. (1989) Risk of cancer in pesticide applicators in Swedish agriculture. *Br. J. ind. Med., 46*, 809-814

Wolfe, H.R., Durham, W.F. & Armstrong, J.F. (1970) Urinary excretion of insecticide metabolites. Excretion of *para*-nitrophenol and DDA as indicators of exposure to parathion. *Arch. environ. Health, 21*, 711-716

Wolfe, H.R., Armstrong, J.F. & Durham, W.F. (1974) Exposure of mosquito control workers to fenthion. *Mosquito News, 34*, 263-267

Woods, J.S. & Polissar, L. (1989) Non-Hodgkin's lymphoma among phenoxy herbicide-exposed farm workers in western Washington State. *Chemosphere, 18*, 401-406

Woods, J.S., Polissar, L., Severson, R.K., Heuser, L.S. & Kulander, B.G. (1987) Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. *J. natl Cancer Inst., 78*, 899-910

Yoder, J., Watson, M. & Benson, W.W. (1973) Lymphocyte chromosome analysis of agricultural workers during extensive occupational exposure to pesticides. *Mutat. Res., 21*, 335-340

Yokoyama, T., Yanagasawa, T., Tsugane, S., Kikuchi, Y. & Taguchi, F. (1978) Status of application of pesticides for vegetables in highland fields and the health status of farmers applying pesticides to the vegetables (Jpn.). *J. Jpn. Assoc. rural Med., 27*, 203