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Meeting Report: Occupational Exposures in Insecticide Application and Some Pesticides

INTRODUCTION

THE LATEST in the series of *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* is the product of the deliberations of scientists from 19 countries (see list of participants at the end of this article), who met in Lyon, France, on 16–23 October 1990. They evaluated the evidence on the carcinogenicity of 17 pesticides, and for occupational exposures in insecticide application [1] using the standardised wording and groupings established within the *Monographs* [2]; the degrees of evidence for carcinogenicity for the different exposures were evaluated as outlined in Table 1.

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BACKGROUND

Pesticides are now used throughout the world—to varying degrees, depending on the dominating crops in a country, its stage of economic development, climatic conditions and the prevalence of pests. Crops are affected by pests and by competition from weeds; the trend towards large-scale monoculture of new plant species and cultivars, in which natural, indigenous insect predators play no role, has increased the problem. Crop losses due to pests can range from 10% in developed countries up to as much as 75% in developing countries. Furthermore, pesticides are in widespread use in urban areas for the control of disease vectors. Thus, worldwide consumption of pesticides in the mid-1980s was about 3 million tonnes; of these, herbicides accounted for 46%, insecticides for 31% and fungicides for 18%.

Table 1. Occupational exposures in insecticide application and some pesticides

Exposure	Degree of evidence for carcinogenicity		Overall evaluation‡
	Humans	Animals	
Insecticides			
Occupational exposures in spraying and application of nonarsenical insecticides	Limited	—	2A*
Aldicarb	No data	Inadequate	3
Chlordane	Inadequate	Sufficient	2B
DDT	Inadequate	Sufficient	2B
Deltamethrin	No data	Inadequate	3
Dichlorvos	Inadequate	Sufficient	2B
Fenvalerate	No data	Inadequate	3
Heptachlor	Inadequate	Sufficient	2B
Permethrin	No data	Inadequate	3
Fungicides			
Captafol	No data	Sufficient	2A†
Pentachlorophenol	Inadequate	Sufficient	2B
Thiram	Inadequate	Inadequate	3
Ziram	No data	Limited	3
Herbicides			
Atrazine	Inadequate	Limited	2B†
Monuron	No data	Limited	3
Picloram	No data	Limited (tech. grade)	3
Simazine	Inadequate	Inadequate	3
Trifluralin	Inadequate	Limited (tech. grade)	3

*Arsenic and arsenic compounds are carcinogenic to humans [2].

†The supporting evidence from other relevant data influenced the making of the overall evaluation.

‡Explanation of terms used in the evaluation—Group 1: The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans; Group 2A: The agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans; Group 2B: The agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans; Group 3: The agent (mixture, exposure circumstance) is not classifiable as to its carcinogenicity to humans; Group 4: The agent (mixture, exposure circumstance) is probably not carcinogenic to humans. More precise information on the classification scheme is contained in the preamble to the *Monograph*.

Use of pesticides in public health and in agriculture involves handling formulated products, mixing them for spraying, spraying them, eventually disposing of excess material and cleaning spray equipment. Applicators generally prepare formulations for use themselves, and the final product and patterns of use differ in different parts of the world. Workers in developing countries may have particularly heavy exposure to pesticides, owing to inadequate working conditions (lack of protective clothing, unsafe practices for spraying and storing pesticides) and deficient sociocultural conditions (illiteracy, inefficient garbage disposal and sewage systems). Heavy exposure may also occur during production in such countries, as working conditions are often less stringently controlled than in developed countries and, owing partly to high temperatures, protective clothing is not worn. Residues in food and water are another potential sources of exposure, but the levels of pesticides found are several orders of magnitude lower than those associated with production and application.

The future use of pesticides depends on a number of factors. The need for pest control is indisputable, but this must be balanced against the hazards they represent to other organic life, including man, the subsequent effects on the environment and the availability of alternative, less hazardous methods. Acute morbidity and mortality associated with exposure to pesticides varies greatly. In Sri Lanka, deaths from exposure to pesticides in 1975–1980 accounted for about 1000 out of 13 000 annual hospital admissions, and similar observations were made in Indonesia, Malaysia and Thailand [3, 4]. The few studies available indicate that intentional poisonings (mainly suicides) are the most common acute effects followed by occupational poisonings and accidental poisonings. In selected groups of South East Asian and Latin American farmers using pesticides, as many as 30% had signs of subclinical poisoning [5]. Questions have been asked for many years about the longer-term effects of pesticides. The only group that has been shown to be causally associated with human cancer, however, is arsenical insecticides [2]. The task of the latest IARC Working Group was to evaluate studies on the carcinogenicity of a number of other pesticides.

EVALUATIONS

Evaluation of the carcinogenic risk of occupational exposures among applicators of insecticides (other than arsenicals, which have already been evaluated in the *IARC Monographs* programme [2]) was particularly difficult, partly because of the self-imposed restriction to consider only reports in which exposure to insecticides by application was mentioned. The few studies

of workers exposed during the manufacture of insecticides and the many studies of agricultural workers in general, or of exposure to pesticides in general, were not evaluated, even when common sense indicated that the primary exposure would have been to insecticides. This selection process left a surprisingly small number of reports, given that many insecticides have been in common use since the early 1950s. Chemical insecticides came into widespread use with the development of a variety of synthetic products. They are applied by aerial spraying and by various ground techniques, ranging from hand-held sprayers and dusters to hydraulic sprayers, air sprayers, foggers and power dusters mounted on vehicles. Applicators are thus exposed primarily *via* inhalation and dermal routes.

Cohort studies provide the strongest evidence that application of non-arsenical insecticides is associated with increased risk for cancer. Two of these showed significant excesses of lung cancer: standardised mortality ratio (SMR) 1.8, 95% confidence interval (CI) 1.4–2.4, as calculated by the Working Group from data given in the report [6, 7]; and SMR 1.4, 95% CI 1.1–1.6 [8]. Two cohorts showed rising risks with duration of exposure [6, 7, 9], whereas another cohort study showed a deficit of lung cancer risk [10, 11]. A number of case-control studies of multiple myeloma and other tumours of B-cell origin showed small excess risks among people exposed to insecticides [12–14].

These studies fell short of providing sufficient evidence that these occupational exposures entail a carcinogenic risk, however, since in the cohort studies there were only small numbers of workers in the subgroups with the longest exposure; furthermore, the possibility could not be ruled out that applicators in some of the studies may have been exposed to arsenical insecticides, and, in the case-control studies, potential confounding by other agricultural exposures had not been explored fully. After lengthy discussion, the Working Group therefore classified spraying and application of nonarsenical insecticides as entailing exposures that are probably carcinogenic (group 2A).

The evidence for the carcinogenicity of eight individual insecticides was also evaluated. For aldicarb (used only in agriculture), deltamethrin, fenvalerate and permethrin (synthetic pyrethroids used in agriculture, in homes and gardens and to protect stored crops), no epidemiological data were available, and the few experimental studies reviewed were considered to provide inadequate evidence of carcinogenicity in animals. The Working Group therefore considered that these four products were not classifiable as to their carcinogenicity to humans (group 3). The other four insecticides evaluated were chlordane and heptachlor (which usually occur together) dichlorvos and DDT.

Chlordane and heptachlor have been used since the mid-1950s; they are now used primarily for the underground control of termites. Cases of cancer, especially of the haematopoietic system, have been associated with domestic exposure to these compounds; however, epidemiological studies have shown inconsistent, small excess risks for cancers at these sites. Rates of mortality from lung cancer were slightly increased in two cohort studies of pesticide applicators [8, 9] and in one of chlordane/heptachlor manufacturers [15]. Although termite control operators probably have greater exposure to these compounds than other applicators, the excess risk for lung cancer in one study [8] occurred only among the other applicators. The Working Group therefore considered that these studies provided inadequate evidence for the carcinogenicity to humans of chlordane and heptachlor. In contrast to these inconsistent findings, those of experimental studies were uniform in showing increases in the incidence of hepatocellular neoplasms in mice and of thyroid neoplasms in rats. Other tumours were induced in rats in further experiments. These results thus provide sufficient evidence for the carcinogenicity of the two compounds in experimental animals. The overall evaluations, based on the epidemiological and experimental results, are that both chlordane and heptachlor are possibly carcinogenic to humans (group 2B).

Dichlorvos, used in crop protection, in veterinary medicine and in the control of insects in homes and other buildings, was evaluated in only one case-control study of leukaemia [13], subsequent to the report of a series of cases of haematopoietic disorders in children said by their parents to have been exposed to this substance at home. The case-control study also found an association, but there were few exposed subjects, and they had potential exposure to many pesticides. Experimental studies, however, showed rare oesophageal tumours and a dose-related increase in the incidence of tumours of the forestomach in treated mice. Rats developed papillomas of the forestomach, mononuclear-cell leukaemia and pancreatic adenomas. Taking the two sets of data together, the Working Group classified dichlorvos as possibly carcinogenic to humans (group 2B).

DDT has been used since 1943 as an insecticide in many situations; it has been used extensively for the control of vectors of malaria, typhus, yellow fever and sleeping sickness, and also on food crops. As a result, DDT is now ubiquitous in the environment: it is highly persistent and has been found in soil, sediments, foods and organic tissues. Its use is banned in some countries and has been restricted since the 1970s in many others to the control of vector-borne diseases.

The results of epidemiological studies of DDT are suggestive of a carcinogenic effect, but there are limitations in the way in which exposure was assessed and only small, inconsistent excess risks were found. The numbers of cases of respiratory tract cancer seen among cohorts exposed to DDT, for instance, were only slightly greater than those seen in unexposed people; and in most of the case-control studies of lymphatic and haematopoietic tumours, potential exposure to other pesticides was not taken into account. The Working Group therefore considered that there was inadequate epidemiological evidence for the carcinogenicity of DDT. As for chlordane, heptachlor and dichlorvos, however, studies in experimental animals gave sufficient evidence for its carcinogenicity: liver tumours were induced in mice and rats in a number of studies. The overall evaluation, therefore, was that DDT is possibly carcinogenic to humans (group 2B).

The four fungicides evaluated by the Group were captafol, pentachlorophenol, thiram and ziram.

Captafol has been used since 1962 to control fungal diseases in fruit, vegetables and other plants. The carcinogenicity of this compound in humans has not been studied. It was tested, however, in one study in mice and in two in rats by oral administration. In mice, it produced a high incidence of adenocarcinomas of the small intestine and of vascular tumours of the heart and spleen—unusual tumours in inbred mice; it also induced hepatocellular carcinomas. In rats, captafol induced renal and hepatic tumours. These results were considered to provide sufficient evidence for the carcinogenicity of this compound in experimental animals. Within the usual IARC classification system, the combination of no epidemiological data and strong evidence in animals would result in a categorisation of 2B; however, captafol was also found to be active in a wide

range of tests for genetic and related effects, including a generally insensitive test in which dominant lethal mutation was induced in rats treated *in vivo* [16]. The Working Group took into consideration this supporting evidence and made the overall evaluation that captafol is probably carcinogenic to humans (group 2A).

Pentachlorophenol, introduced in the 1930s, has been used in large quantities, mainly as a wood preservative and is presently a widespread environmental pollutant. Although in one cohort study the incidences of cancers of the skin, lip, mouth and pharynx and of leukaemia were increased among sawmill workers [17], pentachlorophenol constituted only a small proportion of the chlorophenols to which the workers were exposed. The results of case-control studies were conflicting, with no increased risk for soft-tissue sarcoma seen in one study [18] and an increase in another [19]. No increased risk was seen for non-Hodgkin lymphoma [20] and a slightly increased risk for multiple myeloma [21]. These findings were considered to represent inadequate evidence of carcinogenicity. In experimental animals, however, dose-related increases in the incidence of liver tumours, adrenal tumours and malignant vascular tumours of the liver and spleen were seen in mice, providing sufficient evidence for carcinogenicity. The overall evaluation was therefore that pentachlorophenol is possibly carcinogenic to humans (group 2B).

Thiram and ziram have been used since about 1930; they are used primarily as vulcanisation accelerators in the rubber industry, but are also used as fungicides on fruit and other plants. One report of an adenocarcinoma of the thyroid among 105 workers who had been engaged in the manufacture of thiram [22, 23] provides inadequate evidence of carcinogenicity; no epidemiological data were available on ziram. One study in which thiram administered to rats did not increase the incidence of tumours was also considered to provide inadequate evidence. The finding that ziram induced benign lung tumours in female mice and thyroid tumours in male rats constitutes limited evidence for its carcinogenicity in animals. On the basis of these sparse data, neither compound could be classified as to its carcinogenicity to humans (group 3).

Triazine herbicides were introduced during the 1950s for weed control, and atrazine and simazine, two members of this group, are used widely on maize and other crops. Atrazine, in particular, is used throughout the world. Seven case-control studies were considered to provide some evidence for the carcinogenicity of triazine herbicides. Two studies from an area of northern Italy showed elevated risks for ovarian tumours among women exposed to these herbicides [24, 25]. Studies in mid-western USA [13, 14, 26–29] showed small excess risks for cancers at a number of sites in association with exposure to unspecified triazine herbicides or specifically to atrazine. Complex exposures and insufficient reporting made it difficult to evaluate the carcinogenicity of individual triazines including atrazine and simazine in humans.

Two experimental studies on atrazine showed increased incidences of mammary tumours (mainly benign) in male rats and of uterine adenocarcinomas and tumours of the haematopoietic system in female rats. A preliminary report indicated that atrazine increased the incidence of lymphomas in mice. In making the overall evaluation, the Working Group also considered the fact that the increased risks for tumours known to be associated with hormonal factors, which were observed in both epidemiological and experimental studies, are consistent with the known effects of atrazine on the hypothalamic-pituitary-ovarian axis. Atrazine was thus considered to be possibly carcinogenic to humans (group 2B). Owing to lack of specific studies, simazine is not classifiable as to its carcinogenicity to humans (group 3).

Monuron, introduced in 1952, and picloram, first registered for use in 1963, both of which are herbicides, have not been the object of epidemiological studies. The results of experimental studies were inconsistent: neither monuron nor picloram had an effect on tumour incidence in mice, but monuron caused dose-related increased incidences of renal and liver-cell tumours in male rats, and picloram increased the incidence of liver-cell tumours in rats and of benign thyroid tumours in female rats. This evidence could not be evaluated, and both monuron and picloram were considered to fall into group 3.

The final pesticide evaluated was trifluralin, used since 1963 as a herbicide on pastures. Use of this compound was associated with an increased risk for non-Hodgkin lymphoma in one study in the USA [28]; no association with risk for leukaemia was seen in a larger US study [13], and a study in Italy showed no association with ovarian cancer [25]. These results were considered to constitute inadequate evidence for the carcinogenicity of trifluralin in man. One technical preparation of this herbicide increased the incidences of hepatocellular carcinomas, lung tumours and tumours of the forestomach in female mice; thyroid tumours were seen in female rats, but only at the lower dose tested. Another formulation did not increase tumour incidence in mice. This inadequate evidence from studies of human beings and the limited evidence for technical trifluralin in experimental animals make trifluralin unclassifiable as to its carcinogenicity to humans (group 3).

CONCLUDING REMARKS

The use of some of the pesticides reviewed (aldicarb, chlordane, DDT, captafol, pentachlorophenol, monuron, picloram and trifluralin) is restricted in some countries. Use of the organochlorine insecticides—DDT and chlordane—in particular reached a maximum in the 1960s and has declined since. There continues, however, to be widespread general exposure to persistent organochlorine pesticides in developing countries, especially as these compounds are known to bioaccumulate in the environment and in food chains. However, lack of data on residues in foods and other samples from these countries makes it difficult to estimate potential exposure.

Control of pests is essential for ensuring adequate yields of food crops, for the control of insect-borne diseases and for preserving wood.

Risk-benefit evaluations are not within the brief of the IARC Monographs programme. The role of the monographs is to provide objective, scientific evaluations of the degree of evidence for carcinogenicity provided by the results of studies published in the openly available, peer-reviewed scientific literature. National and international authorities may then use the monographs as one part of the body of information necessary for assessing risks and for formulating decisions about any preventive measures.

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Use of DNA Adducts in the Assessment of Occupational and Environmental Exposure to Carcinogens

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INTRODUCTION

MANY CARCINOGENS react covalently with DNA and may thereby initiate the multistage process leading to cell transformation and clinical malignancy [1]. Recently, methods have become available for the determination of DNA adducts in man [2–6]. The two principal techniques are the ^{32}P-postlabelling and immunoassay (Fig. 1). In the ^{32}P-postlabelling assay DNA is degraded enzymatically to 3′-nucleotides and a high specific activity phosphate group is introduced in the 5′-position from ATP using polynucleotide kinase [7, 8]. The adducts are analysed by thin-layer chromatography. In the immunoassay an antibody is raised against carcinogen-modified DNA or nucleotide [9, 10]. The assay of samples is usually carried out as a competitive ELISA. Both techniques are sensitive enough to allow adduct detection at levels encountered in humans. The ^{32}P-postlabelling assay may optimally detect one adduct per 10^{10} normal nucleotides [2, 3].

We have applied the above assays to humans who are either occupationally or environmentally exposed to carcinogenic compounds. In each case total white blood cells were used, and were coded in order to exclude bias.

FOUNDRY WORKER STUDIES

Air in iron foundries contains a number of carcinogens including polycyclic aromatic hydrocarbons (PAHs) [11]. Epidemiological studies from several countries have shown an excess risk of lung cancer among foundry workers and the risk appears to correlate with exposure to PAHs [11, 12].

Blood samples were drawn from foundry workers and their job descriptions were used to classify their exposures. The levels of aromatic adducts in foundry workers exceeded those in the controls. A highly significant dose-response relationship was observed both by the postlabelling [13] and immunoassay [14]. The adduct levels decreased to about one third in the course of a 4 week summer vacation indicating that they were job-related. Three different laboratories have carried out the postlabelling assays and their results correlate to a high degree [15]. A correlation was also noted between the postlabelling and immunoassay data [2].

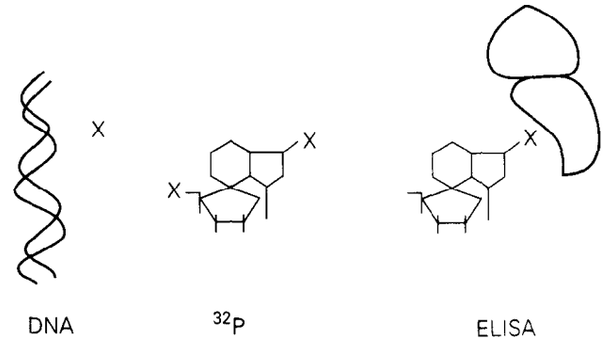

Fig. 1. Two sensitive methods, ^{32}P-postlabelling and immunoassay, for the determination of DNA adducts. X = adduct. Left, adducted DNA; middle, adducted nucleotide, digested from human DNA and postlabelled to the 5′-position with polynucleotide kinase; right, adducted nucleotide recognised by a specific antibody raised against *in vitro* adducted DNA or nucleotide.

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