

Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid

In June, 2015, 26 experts from 13 countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of the insecticides lindane and 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT), and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). These assessments will be published as Volume 113 of the IARC Monographs.¹

The insecticide lindane was classified as “carcinogenic to humans” (Group 1). Lindane, the γ -isomer of hexachlorocyclohexane, has been used extensively for insect control in agriculture and for treatment of human ectoparasites. Occupational exposures have occurred among agricultural workers and pesticide applicators; however, the use of lindane is now banned or restricted in most countries. Lindane is lipophilic, readily absorbed via all routes of exposure, and distributes widely in the body.

Epidemiological cohort and case-control studies of non-Hodgkin lymphoma in several countries provided sufficient evidence in humans for the carcinogenicity of lindane. The US Agricultural Health Study,² a large prospective cohort study with detailed exposure assessment, reported statistically significant increases in non-Hodgkin lymphoma risk with increasing occupational exposure to lindane. Population-based case-control studies in the mid-western USA and Canada also reported consistently positive associations.^{3,4}

Sufficient evidence in experimental animals for the carcinogenicity of lindane was provided by several studies of dietary administration in mice, with lindane consistently increasing the incidence of benign or malignant liver tumours. There is strong evidence that lindane causes

immunosuppressive effects that can operate in humans.

The insecticide DDT was classified as “probably carcinogenic to humans” (Group 2A). DDT was used for the control of insect-borne diseases during World War 2; subsequently it was widely applied to eradicate malaria and also used in agriculture. Although most uses of DDT apart from disease vector control were banned from the 1970s, human exposure to DDT and to its metabolite 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) still occurs, mainly as a consequence of biological persistence leading to exposure through diet. DDT is readily absorbed and is distributed in the body by lymphatic and blood circulation, with a preference for lipid-rich tissues.

Associations between cancer and exposure to DDT have been investigated in more than 100 cohort and case-control studies from diverse countries. Nested and population-based case-control studies in China reported strong, dose-related associations between liver cancer and blood DDT level after adjustment for potential confounders.⁵⁻⁷ No excess risk of liver cancer was reported in a historical cohort study⁸ of men who sprayed DDT during a malaria-control campaign in Italy. In studies on non-Hodgkin lymphoma, positive associations were reported in several cohort and case-control studies in North America and Europe,^{2,9,10} while other studies found no association.⁸ Several case-control studies in the USA and Europe reported positive associations between DDT or DDE and testicular cancer, including a large case-control study¹¹ nested in a US military cohort. Although more than 40 studies conducted since 1993 were reviewed, no clear association was found between breast cancer and DDT or DDE measured in samples of

blood or adipose taken in adulthood; however, the possible importance of early-life exposure to DDT remains unresolved. Studies on non-Hodgkin lymphoma and cancers of the liver and testis provided limited evidence in humans for the carcinogenicity of DDT.

Numerous studies in mice, rats, and hamsters (mainly oral administration) provided sufficient evidence in experimental animals for the carcinogenicity of DDT and its metabolites DDE and 1-chloro-4-[2,2-dichloro-1-(4-chlorophenyl)ethyl]benzene (DDD). In mice, 12 studies gave positive results, some for multiple tumour sites, with DDT consistently increasing the incidence of benign and malignant liver tumours; lymphoma incidence was also increased in three studies. In rats, DDT increased the incidence of benign and malignant liver tumours in four studies. In hamsters, DDT significantly increased the incidence of adrenal cortex adenoma in two studies. In rodents, the metabolites DDE and DDD induced liver tumours in two studies each.

There is strong evidence that DDT affects several mechanisms that can operate in humans. Immunosuppression has been consistently observed in numerous experimental systems, including human cells in vitro. DDT, DDD, and DDE increased oxidative stress in human peripheral blood mononuclear cells and stimulated human colon cancer and liver cancer cell proliferation in vitro and in xenografted mice. Oestrogenic effects and androgen-receptor antagonism were consistently observed in numerous experimental systems including human cells in vitro.¹² Anti-oestrogens blocked oestrogenic effects of DDT in human breast cancer cells and in mice.¹³ Progesterone receptor activation



Lancet Oncol 2015

Published Online

June 23, 2015

[http://dx.doi.org/10.1016/S1470-2045\(15\)00081-9](http://dx.doi.org/10.1016/S1470-2045(15)00081-9)

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Of the working group members, LR received an honorarium and travel expenses for providing advice on future epidemiological research to a Scientific Advisory Group on Epidemiology of the European Crop Protection Association and MTS has received payment for consulting and testimony from US law firms and research support from the US Council for Education and Research on Toxicants. All other working group members declare no competing interests. The representatives declare no competing interests. Of the observers, JSB is a former Dow Chemical Co employee, owns Dow Chemical Co stock, and is a consultant to the 2,4D Research Data Task Force; JEG has received funding from the 2,4D Research Data Task Force; and SAMM is a consultant to the 2,4D Research Data Task Force. The Industry Task Force II on 2,4-D Research Data (Task Force) is an industry consortium whose members hold registrations for the active ingredient 2,4-D. The Task Force members include Dow AgroSciences LLC, Nufarm Ltd, and Agro-Gor Corporation, a US corporation jointly owned by Albaugh Incorporated (USA) and PBI-Gordon Corporation (USA). All members of the IARC/WHO Secretariat declare no competing interests.

was seen in vitro. Evidence of sex-hormone disruption in exposed men and women was unclear.

Since its introduction in 1945, 2,4-D has been widely used to control weeds in agriculture, forestry, and urban and residential settings. Occupational exposures to 2,4-D can occur during manufacturing and application, while the general population can be exposed through food, water, dust, residential application, and during spraying. In humans, 2,4-D is eliminated largely unchanged in the urine.

Cancer risks associated with exposure to 2,4-D have been evaluated in population-based case-control studies and in cohort studies of workers manufacturing and applying pesticides. Due to the potential for confounding, studies involving exposure to mixed herbicides or to herbicides containing dioxin were regarded as uninformative about the carcinogenicity of 2,4-D. Neither a nested case-control analysis¹⁴ of an international cohort of workers who manufacture and spray herbicides nor a historical cohort study¹⁵ of 2,4-D manufacturing workers in the USA found strong or consistent increases in non-Hodgkin lymphoma in relation to 2,4-D exposure, but the latter study gave some indication of increased risk in the highest categories of estimated exposure. Population-based case-control studies of 2,4-D exposure in relation to lymphoma and leukaemia reported mixed results. The Working Group conducted a meta-analysis of 11 studies that showed no association of non-Hodgkin lymphoma with ever-exposure to 2,4-D, although the results appeared to be sensitive to whether the studies adjusted for other pesticides. The consensus of the Working Group was that there is inadequate evidence in humans for the carcinogenicity of 2,4-D, although a substantial minority considered that the evidence was limited.

The carcinogenicity of 2,4-D has been assessed in multiple rodent bioassays and in an observational study of pet dogs. In female mice, single subcutaneous injections of the isooctyl ester of 2,4-D increased the incidence of reticulum-cell sarcoma.¹⁶ In male rats, 2,4-D in the diet induced a positive trend in the incidence of rare brain astrocytomas.¹⁷ The Working Group concluded that there was limited evidence in experimental animals for the carcinogenicity of 2,4-D due to methodological concerns regarding the positive studies, although a substantial minority judged the evidence to be sufficient.

Mechanistic studies provided strong evidence that 2,4-D induces oxidative stress that can operate in humans and moderate evidence that 2,4-D causes immunosuppression, based on in-vivo and in-vitro studies.

In considering all the relevant scientific data, the Working Group classified 2,4-D as “possibly carcinogenic to humans” (Group 2B).

We declare no competing interests.

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