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Pesticides and Cancer - Recent Results from Epidemiological Studies

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Abstract

Pesticides are used to prevent and destroy pests in agriculture and forestry but also in homes, private and public gardens, and on domestic animals. Although pesticides have benefits such as increasing yield by protecting crops from weeds and insects, and preventing transmission of diseases such as malaria by killing mosquitoes, some pesticides have been linked to adverse health outcomes, including cancer. Most epidemiological studies on pesticides in relation to cancer have been carried out on farmers and agricultural workers, and are almost exclusively conducted in high-income countries. The IARC monographs have evaluated the evidence and classified a large number of pesticides in terms of their carcinogenic potential. In 2015 eight pesticides were evaluated, in which the insecticide lindane was classified as carcinogenic to humans (Group 1). More pesticides may be classified as carcinogenic to humans in the future; i.e. when the on-going large studies taking place in different parts of the world, with improved exposure assessment and longer follow-up, will provide further results and better evidence together with experimental data, and more epidemiological studies from low and middle income countries become available. Well-designed exposure assessment studies are a prerequisite to study the link between use of pesticides and morbidity. For informed decisions on cancer control and prevention, reliable data on exposure of workers and the general population are needed, in particular in Africa where agricultural activities expand.

Introduction

Pesticides are mainly used in agriculture, including crop and animal production, and forestry but also in homes, private and public gardens, along roads to keep vegetation off, on domestic animals, in medicine (lice and mycosis control), as well as in disease-vector control programs. The main reason for using pesticides is to prevent and destroy pests on plants, animals, humans, and in various locations. World-wide over 1 billion people are occupationally exposed to pesticides, and it has been estimated that more than 2.5 billion kg of pesticide active ingredients are applied annually (Alavanja 2009).

Pesticides represent a large group of compounds and mixtures and can be classified in different ways, notably by target organism (e.g., herbicides, insecticides, fungicides, and rodenticides), chemical structure (e.g. organochlorine, organophosphate), physical state (e.g. fumigant = gaseous), and level of hazard (e.g. WHO's Ia=extremely hazardous, Ib=highlyhazardous, II=moderately hazardous, III=slightly hazardous) (International Programme on Chemical Safety 2009;United States Environmental Protection Agency 2015;United States Environmental Protection Agency 2016).Although pesticides have benefits such as increasing yield by protecting crops from weeds and insects, and preventing transmission of diseases such as malaria by killing mosquitoes, some pesticides have been linked to adverse health outcomes, including cancer, non-malignant respiratory diseases, reproductive and neurological disorders, and developmental problems in children.

Cancers tend to develop over a long time, so the relevant time-period for environmental and occupational exposures involved in the cancer development commonly starts several decades earlier than the onset of disease. Hence, it is challenging to study the carcinogenic effects of pesticides in humans because of the large number of active ingredients (>900), which are used only part of the year, often have been mixed, and their use has changed over time. Studies attempting to reconstruct past use of individual pesticides in participants can suffer from fading recall which can introduce a serious limitation if past exposure is collected after cancer onset, as diseased and disease-free subjects could differ in their efforts to remember past use (Schuz *et al.* 2003).

This complexity in exposure assessment is one of the reasons why many studies are only able to report the effects of "pesticides" as a group rather than specific active ingredients. The results of these studies provide inadequate evidence in view of the need of regulating the use of specific hazardous pesticides. Cohort studies with baseline and prospective exposure assessment including questionnaires, environmental and bio-specimens collections are more suitable for bio- monitoring of exposures, validation of self-reports, and better discriminate among multiple occurring pesticides exposures.

Most epidemiological studies on pesticides in relation to cancer have been carried out on farmers and agricultural workers, many of them directly exposed through pesticide application (Alavanja *et al.* 2014). Indirect exposure through re-entry tasks such as pruning or harvesting has also been documented (Baldi et al. 2014). Cancer incidence in subjects living close to cultivated land and presumed exposed to pesticide drift also contribute to the literature (Ward *et al.* 2006). Few studies have included workers exposed at pesticide production plants (Bueno de Mesquita *et al.* 1993; Ruder&Yiin 2011;van Amelsvoort et al. 2009). Farmers generally experience lower incidence rates of some common cancers such as lung, bladder and colon than the general population. At the same time, farmers experience higher incidence rates of leukemia, multiple myeloma, non-Hodgkin lymphoma (NHL), lip, stomach, skin, brain, and prostate cancers (Blair & Freeman 2009;MacFarlane *et al.* 2010).

In this short review we will provide an overview of the current state of knowledge regarding exposure to pesticides and increased risk of different cancers, based on the IARC monographs and relevant projects. A number of on-going projects at IARC and elsewhere are also presented to illustrate what type of research is still needed.

Results of the recent IARC Monographs volumes 112-113

The IARC monographs programme, the monographs often referred to as the "encyclopaedia of carcinogens", is one of the main pillars of work at the International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization, situated in Lyon in France. Interdisciplinary working groups of expert scientists from all over the worldare invited to evaluate all published scientific literature on different domains documenting the potential carcinogenicity of specific agents, including studies of cancer in humans, animal bio-assays and mechanisms of carcinogenesis. The working groups evaluate the carcinogenicity of chemicals, complex mixtures, occupational exposures, physical agents, biological agents, and lifestyle factors, and classify them as carcinogenic to humans (Group 1), probably carcinogenic to humans (Group 2A), possibly carcinogenic to humans (Group 2B), not classifiable as to its carcinogenicity to humans in Group 3, or probably not carcinogenic to humans (Group 4)(IARC 2015). National and international health agencies worldwide use the IARC Monographs as a source of scientific information on known or suspected carcinogens, and as a scientific support for their programs and actions to prevent exposure to known or suspected carcinogens. Table 1 shows all pesticides evaluated by the IARC Monographs until date.

During 2015, the IARC monograph assembled two meetings with experts from 18 countries to evaluate the evidence on eight different pesticides that are or have been used widely around the world.

Insecticides

Lindane was classified as carcinogenic to humans (Group 1) based on sufficient evidence of carcinogenicity in humans (Loomis et al. 2015). Several epidemiological cohort and case control studies in different countries have shown associations with increased risk of NHL(McDuffie *et al.* 2001; Blair *et al.* 1998;Alavanja *et al.* 2014). Lindane is a well-known endocrine disruptor and has been used for insect control in agriculture and for treatment of external parasites on humans (US Food and Drug Administration 2013;WHO 2013). Lindane is now banned or restricted in most countries, for example in France it was banned for agriculture in1998 but still used in construction material until 2007 (INVS and AFSSET 2009; INRS 2014;).

DDT or 1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane is a well-known insecticide that has been used widely in agriculture to treat a large panel of insects, and in the most recent years mainly for control of insect-borne diseases, notably malaria (WHO Media centre 2006). Most uses of DDT have been banned since the 1970s, however human exposure still occurs mostly because of its bio persistence leading to exposure through diet (IARC Working Group, Lyon, 2-9 June 2015). The effects of DDT and its metabolites have been investigated in many epidemiological studies around the world and in relations to various cancer types, e.g. NHL, liver and testicular cancers; positive associations have been observed but chance and bias could not be excluded with reasonable confidence (evidence of carcinogenicity in humans classified as limited), in particular regarding early-life exposure in relation to breast cancer (McGlynn et al. 2006;Persson et al. 2012; Zhao et al. 2012). The evidence in animal experiments (mice, rats and hamsters) provided sufficient evidence for carcinogenicity and showed strong evidence that DDT affects several key characteristics influencing cancer development that can operate in humans. Consequently, overall, DDT was classified as probably carcinogenic to humans (Group 2A) (IARC Working Group, Lyon, 2-9 June 2015).

The insecticides malathion and diazinon were also classified as probably carcinogenic to humans (Group 2A) (IARC Working Group, 2015). Malathion is used in agriculture, public health, and residential insect control and continues to be produced in large volumes throughout the world. There was limited evidence of malathion causing cancer in humans. Case-control analyses of occupational exposures have reported positive associations with NHL and prostate cancer; although no increased risk of NHL was observed in the large US Agricultural Health Study cohort (AHS) (Eriksson *et al.* 2008; Band *et al.* 2011;Koutros et al. 2013;McDuffie *et al.* 2001;Waddell et al. 2001). Diazinon has been used for control of insects in homes and gardens and in agriculture. The use of this insecticide has been reduced in different parts of the world but is still employed in many countries (IFA 2013). There was limited evidence of diazinon causing cancers in humans, some positive associations have been observed for NHL, leukaemia, and lung cancer

(McDuffie *et al.* 2001;Waddell *et al.* 2001; Jones *et al.* 2015). Diazinon induced DNA or chromosomal damage in animal experiments and in vitro.

The insecticides tetrachlorvinphos and parathion were classified as possibly carcinogenic to humans (Group 2B) (IARC Working Group, Lyon, 3-10 March 2015). Tetrachlorvinphosis banned in the European Union (EU), while in the USA it continues to be used on domestic animals to kill ectoparasites. The evidence of carcinogenicity from human studies was scarce, while there was sufficient evidence from animal experiments in mice and rats, and some positive studies showing genotoxicity and increased cell proliferation (Parker *et al.* 1985). Parathion use is severely restricted in the USA and the EU. Some occupational studies have shown associations with several cancers but the evidence in humans remains inadequate, while the evidence in animals (mice, rats) was considered sufficient (Guyton *et al.* 2015).

Herbicides

The herbicide Glyphosate was classified as probably carcinogenic to humans (Group 2A).It is used in more than 750 different pesticide formulations for agriculture, forestry, urban, and domestic applications, and has the highest global production volume of all herbicides; the agricultural use has increased steeply since the development of crops that have been genetically modified to make them resistant to glyphosate. The evidence of carcinogenicity (NHL) for glyphosate in humans was limited (McDuffie *et al.* 2001; De Roos et al. 2003; Eriksson *et al.* 2008;Weichenthal *et al.* 2010), while the evidence from animal experiments showed sufficient evidence in studies on mice. Glyphosate has been detected in blood and urine from agricultural workers, indicating absorption. Glyphosate formulations have also induced DNA and chromosomal damage in mammals, and in human and animal cells in vitro. One study reported increases in blood markers of chromosomal damage (micronuclei) in residents of several communities after spraying of glyphosate formulations (Bolognesi *et al.* 2009).

The widely-used herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) was classified as possibly carcinogenic to humans (Group 2B), based on epidemiological studies providing inadequate evidence; animal experiments that provided limited evidence; and mechanistic studies in-vivo and in-vitro that provided strong evidence that 2,4-D induces oxidative stress that can operate in humans, and moderate evidence that 2,4-D causes immune-suppression (Kogevinas et al. 1995; Burns et al. 2011; IARC Working Groupa, 2015;).

Table 1. Pesticides classified by the IARC *Monographs* in the Volumes 1-115

CAS No	Agent	Group	Volume	Year
000060-35-5	Acetamide	2B	7, Sup 7, 71	1979
000116-06-3	Aldicarb	3	53	1991
000309-00-2	Aldrin	3	5, Sup 7	1987
000057-06-7	Allylisothiocyanate	3	73	1999
000061-82-5	Amitrole *(NB: Overall evaluation down graded to Group 3 with supporting evidence from other relevant data)*	3	79	2001
000084-65-1	Anthraquinone	2B	101	2012
000140-57-8	Aramite	2B	5, Sup 7	1987
007440-38-2	Arsenic and inorganic arsenic compounds	1	23, Sup 7, 100C	2012
001912-24-9	Atrazine *(NB: Overall evaluation downgraded to Group 3 with supporting evidence from other relevant data)*	3	73	1999

000133-06-2	Captan	3	30, Sup 7	1987
002425-06-1	Captafol *(NB: Overall evaluation upgraded to Group 2A with supporting evidence from other relevant data)*	2A	53	1991
000063-25-2	Carbaryl	3	12, Sup 7	1987
000143-50-0	Chlordecone (i.e., Kepone)	2B	20, Sup 7	1987
000057-74-9	Chlordane	2B	79	2001
006164-98-3	Chlordimeform	3	30, Sup 7	1987
000510-15-6	Chlorobenzilate	3	30, Sup 7	1987
000563-47-3	3-Chloro-2-methyl-1-propene, technical-grade	2B	115	2016
000101-21-3	Chloropropham	3	12, Sup 7	1987
	Chlorophenoxy herbicides *(e.g., 2,4-D & 2,4,5-T)*	2B	41, Sup 7	1987
001897-45-6	Chlorothalonil	2B	73	1999
010380-28-6	Copper 8-hydroxyquinoline	3	15, Sup 7	1987
052918-63-5	Deltamethrin	3	53	1991
000094-75-7	2,4-D	2B	113	2015
000050-29-3	DDT (i.e., 4,4'-Dichlorodiphenyltrichloroethane)	2A	113	2015
002303-16-4	Diallate	3	30, Sup 7	1987
000333-41-5	Diazinon	2A	112	2015
000096-12-8	1,2-Dibromo-3-chloropropane	2B	20, Sup 7, 71	1999
000541-73-1	*meta*-Dichlorobenzene	3	73	1999
000095-50-1	*ortho*-Dichlorobenzene	3	73	1999
000106-46-7	*para*-Dichlorobenzene (i.e., *para*-chloroaniline)	2B	73	1999
000078-87-5	1,2-Dichloropropane	3	41, Sup 7, 71	1999
000542-75-6	1,3-Dichloropropene (technical -grade) (i.e., Telone)	2B	41, Sup 7, 71	1999
000062-73-7	Dichlorvos	2B	53	1991
000115-32-2	Dicofol	3	30, Sup 7	1987
000060-57-1	Dieldrin	3	5, Sup 7	1987
000075-60-5	Dimethylarsinic acid (i.e., Cacodylic acid)	2B	100C	2012
000079-44-7	Dimethylcarbamoyl chloride *(NB: Overall evaluation upgraded to Group 2A with supporting evidence from other relevant data)*	2A	12, Sup 7, 71	1999
000072-20-8	Endrin	3	5, Sup 7	1987
000106-93-4	Ethylene dibromide *(NB: Overall evaluation upgraded to Group 2A with supporting evidence from other relevant data)*	2A	15, Sup 7, 71	1999
000096-45-7	Ethylenethiourea *(NB: Overall evaluation downgraded to Group 3 with supporting evidence from other relevant data)*	3	79	2001
051630-58-1	Fenvalerate	3	53	1991
014484-64-1	Ferbam	3	12, Sup 7	1987
002164-17-2	Fluometuron	3	30, Sup 7	1987
001071-83-6	Glyphosate	2A	112	2015

000076-44-8	Heptachlor	2B	79	2001
000118-74-1	Hexachlorobenzene	2B	79	2001
	Hexachlorocyclohexanes*(other than Lindane, its gamma isomer)*	2B	20, Sup 7	1987
000070-30-4	Hexachlorophene	3	20, Sup 7	1987
000087-68-3	Hexachlorobutadiene	3	73	1999
000058-89-9	Lindane	1	113	2015
000121-75-5	Malathion	2A	30, Sup 7, 112	2015
012427-38-2	Maneb	3	12, Sup 7	1987
000072-43-5	Methoxychlor	3	20, Sup 7	1987
000074-83-9	Methyl bromide	3	41, Sup 7, 71	1999
000093-15-2	Methyleugenol	2B	101	2012
000074-88-4	Methyl iodide	3	41, Sup 7, 71	1999
000298-00-0	Methyl parathion	3	30, Sup 7	1987
002385-85-5	Mirex	2B	20, Sup 7	1987
000150-68-5	Monuron	3	53	1991
000086-88-4	1-Naphthylthiourea (ANTU)	3	30, Sup 7	1987
001836-75-5	Nitrofen (technical-grade)	2B	30, Sup 7	1987
	Non-arsenical insecticides (occupational exposures in spraying and application of)	2A	53	1991
000056-38-2	Parathion	2B	30, Sup 7, 112	2015
000087-86-5	Pentachlorophenol (see Polychlorophenols)		53, 71	1999
052645-53-1	Permethrin	3	53	1991
000090-43-7	*ortho*-Phenylphenol	3	73	1999
001918-02-1	Picloram	3	53	1991
000051-03-6	Piperonylbutoxide	3	30, Sup 7	1987
	Polychlorophenols and their s odium salts (mixed exposures) *(e.g.,2,4,5-& 2,4,6-Trichlorophenol)*	2B	53, 71	1999
023746-34-1	Potassium bis(2-hydroxyethyl)dithiocarbamate	3	12, Sup 7	1987
000122-42-9	Propham	3	12, Sup 7	1987
000082-68-8	Quintozene (Pentachloronitrobenzene)	3	5, Sup 7	1987
000122-34-9	Simazine	3	73	1999
000148-18-5	Sodium diethyldithiocarbamate	3	12, Sup 7	1987
000132-27-4	Sodium *ortho*-phenylphenate	2B	73	1999
000095-06-7	Sulfallate	2B	30, Sup 7	1987
008001-50-1	Terpenepolychlorinates (i.e., Strobane)	3	5, Sup 7	1987
022248-79-9	Tetrachlorvinphos	2B	30, Sup 7, 112	2015
000137-26-8	Thiram	3	53	1991
008001-35-2	Toxaphene (Polychlorinated camphenes)	2B	79	2001
000052-68-6	Trichlorfon	3	30, Sup 7	1987
001582-09-8	Trifluralin	3	53	1991
000315-18-4	Zectran	3	12, Sup 7	1987
012122-67-7	Zineb	3	12, Sup 7	1987
000137-30-4	Ziram	3	53	1991

Additional Important Resources and On-Going Studies on Pesticides around the World

A systematic review and a series of meta-analyses were carried out to explore the relationship between NHL and occupational exposure to agricultural pesticide active ingredients (n=80) and chemical groups (n=21). Estimates of associations between pesticides and cancer were extracted from 44 papers, all derived from studies conducted in high-income countries between 1964 and 2007. Random effects meta-analyses showed that phenoxy herbicides, carbamate insecticides, organophosphorus insecticides and the active ingredient lindane, were positively associated with NHL. Analyses by NHL subtypes, possible to investigate only in a handful of the studies, showed that B cell lymphoma was positively associated with phenoxy herbicides and the organophosphorus herbicide glyphosate. Diffuse large B-cell lymphoma was positively associated with phenoxy herbicide exposure. The authors concluded that further investigations of a larger variety of pesticides and in more geographic areas, especially in low- and middle-income countries are needed. (Schinasi & Leon 2014).

AGRICOH

AGRICOH is a consortium of agricultural cohort studies initiated by the US National Cancer Institute (NCI) and coordinated by the International Agency for Research on Cancer (IARC) since October 2010 (Leon et al. 2011). Currently, 28 cohorts from 12 countries in 5 continents comprise AGRICOH. The joining studies are from South Africa (n=2), Canada (3), Chile (n=1), Costa Rica (n=2), USA (n=7), Australia (n=2), Republic of Korea (n=1), New Zealand (n=2), Denmark (n=1), France (n=3), Norway (n=3) and the UK (n=1)(IARC 2016). The objective of the consortium is to promote collaboration and pooling of data to study the association between a wide range of agricultural exposures and health outcomes. On-going projects investigate cancer incidence for 25 cancer sites in male and female agricultural workers (8 cohorts in 6 countries); risk of hematolymphopoetic neoplasms, including several sub-types,in association with application of 33 active ingredients (including14 chemical groups, 3 cohorts from France, Norway and USA, >3,000 incident cancers); exposure to pesticides through application and re-entry and risk of invasive breast cancer in female farmers and spouses of male farmers; exposure to pesticides in applicators and risk of prostate cancer; and exposure to endotoxin and lung cancer.

The Agricultural Health Study (AHS)

AHS provided results for several cancer sites and pesticides in the recent IARC monographs, and is an important study on cancer within AGRIGOH. AHS is a prospective cohort study in Iowa and North Carolina in the USA,followingover52,000 licensed private pesticide applicators (farmers) and 32,000 farm spouses, as well as almost 5,000 commercial applicators, since the mid-1990s. This study, which documented historical past exposure at enrolment and updated exposure information on use of individual pesticides during three cycles of follow-up, continues to provide insights on cancer risk and various other health outcomes in occupationally exposed workers (the pesticide applicators), their environmentally exposed spouses, and their children growing up on farms (Alavanja *et al.* 2014; Jones *et al* 2015;Weichenthal et al. 2010). Pesticides not yet evaluated by IARC have been studied and positive associations with cancer and exposure-response patterns have been reported for 7 additional pesticides currently registered in Canada and/or the United States (alachlor, chlorpyrifos, dicamba, S-ethyl-N,N-dipropylthiocarbamate, imazethapyr, metolachlor, pendimethalin). Although, epidemiologic evidence outside the AHS remains limited with respect to most of the observed associations, animal toxicity data support the biological plausibility of relationships observed at least for alachlor, metolachlor, and pendimethalin (Weichenthal *et al.* 2010). A number of "satellite" studies have been developed for example to study the biological mechanisms underlying observed associations. In 2010 the study of Biomarkers of Exposure and Effect in Agriculture (BEEA)was initiated within AHS.As of mid-2014 1,233 male farmers over 50 years of age have been enrolled in the BEEA study. During a home visit, participants were asked to complete a detailed interview about recent agricultural exposures and provide samples of blood, urine, and since 2013 house dust was also measured (Hofmann *et al.* 2015).

AGRICAN

Another large study included in AGRICOH is the French Agriculture and Cancer (AGRICAN) study, a cohort of active and retired male and female farm owners and workers, also including non-agricultural populations, living in eleven areas of France. Enrolment of over 180,000 individuals (54 % males, 54 % farm owners, 50 % retired) members of the health insurance plan for the agricultural sector took place between 2005 and 2007 by participants filling in a postal questionnaire at baseline documenting historical crop cultivation and animal production as well as work-related tasks comprising pesticide treatment (Leveque-Morlais *et al.* 2015). AGRICAN is linked with population-based cancer registries in France to estimate cancer risk in relation to crops cultivated and specific tasks while for the estimate of cancer risk associated with individual pesticides the use of crop exposure matrices has been used (Brouwer *et al.* 2016).

CLIC

Childhood cancer is rare, as well as occupational pesticide exposure in the general population; therefore it has been difficult to study the effects of parental exposure in relation to cancer risk in the offspring in single studies. The Childhood Leukemia International Consortium (CLIC) is a multi-national collaboration of case-control studies of childhood leukaemia. Results from analyses of 13 studies in CLIC have shown that maternal pesticide exposure during pregnancy was associated with a higher risk of acute myeloid leukaemia in their offspring, and that paternal pesticide exposure around conception was associated with T-cell acute lymphoblastic leukaemia in their children (Bailey *et al.* 2015).

Studies on Pesticides in Africa

In Africa, a substantial number of studies concern pesticides but only one in relation to cancer risk.Many studies are cross-sectional focusing on knowledge, attitudes and practices, and show that practices vary considerably between farms and by type of farm, and revealing unnecessary exposure in vulnerable working population (Karunamoorthi *et al.* 2011; Lekei *et al.* 2014b;Lekei et al. 2014c;Negatu *et al.* 2016). A number of studies measured pesticides in the environment (Dalvie et al. 2014;Garrison et al. 2014;Ogbeide et al. 2015;Olutona *et al.* 2016). Other studies investigate outcomes with shorter latency than cancer, for example acute poisoning, spontaneous miscarriages, respiratory and neurobehavioral outcomes (Naidoo *et al.* 2011; London *et al.* 2012; Rohlman et al. 2012;Lekei *et al.* 2014a; Hanssen *et al.* 2015). To our knowledge one hospital based case-control study on leukaemia and NHL has been carried out in Egypt, although it was a small study (n=130 cases) with rather imprecise exposure assessment (Salem *et al.* 2014).

Challenges in Exposure Assessment

Retrospective exposure assessment is critical, and commonly used, in epidemiological studies. Several attempts have been made to improve the precision, validity and depth of these determinations by carefully documenting multiple sources of data on use of pesticides in agriculture. Here below we present two studies from France: PESTIMAT, which attempts to improve information on pesticide usage, and SIGEXPO, which attempts to develop methods to estimate environmental exposures to pesticides.

PESTIMAT

PESTIMAT is a crop-exposure matrix aimed to reconstitute parameters of pesticide exposure in

France since 1950. PESTIMAT is composed of tables crossing crops and active ingredients by year and providing the following indices of exposure: (1) probability (proportion of farmers having used the active ingredients); (2) frequency (number of treatment days); and (3) intensity (application rate of the active ingredients in kg/ha). Indices of exposure were obtained by combining information from six sources: (i) registration and withdrawal information from the French Ministry of Agriculture; (ii) information from agricultural bodies on products marketed; (iii) agricultural recommendations by the Plant Health Protection body; (iv) treatment calendars provided by farmers; (v) data from associations of farmers; and (vi) data from the industry. To date, 529 active ingredients used between 1950 and 2010 are included in PESTIMAT, i.e. 160 fungicides, 160 herbicides, and 209 insecticides. Taking into account duration of use and determinants of intensity, PESTIMAT allowsdetermination of exposure scores and of estimates for dose-effect relationships in epidemiological studies, information supporting causality in epidemiologic inquiries (Blanc-Lapierre *et al.* 2013; Baldi *et al.* 2015;).

SIGEXPO

Approaches based on Geographic Information Systems (GIS) have been developed and used in the USA to assess environmental exposure to pesticides based on the proximity of households to farmlands (Ritz 2003;Rull and Ward, et al 2006; Nuckols *et al.* 2007; Ritz & Rull 2008;).The SIGEXPO project aims to identify the main determinants of the environmental exposure to pesticides to develop a GIS metric adapted to the French context. One component of the project consisted of collecting indoor dust samples from 239 households in three zones near agricultural areas and one urban area, i.e. floor wipes and dust traps for recent/current dust, and door/window sill wipes for "old dust".

About 150 pesticides were detected in households located within 1000m from farmlands. In terms of frequency of detection, about one third of these represented banned compounds (probable reemission from crops and construction materials), and at least one third were related to domestic practices. Preliminary results showed that there were significant impacts of agricultural practice of surrounding areas on indoor dust contamination; there was also significant impact of natural barriers and meteorological conditions such as vegetation and wind.

Even though farmers are generally healthier than the general population and experience lower incidence rates of some cancers, higher incidence rates of leukaemia, multiple myeloma, other lymphomas, lip, stomach, skin, brain, and prostate cancers have been consistently observed (Blair and Freeman 2009). Pesticides are not likely to fully explain the cancer and other disease patterns observed among farmers because exposures vary by type of agriculture, and many other hazardous exposures may be present on farms including diesel engine exhaust, organic dusts, and solvents.More and better studies in the future need to focus on the full range of exposures to significantly improve our understanding of the cancer patternsand their aetiologyamong farmers.

More pesticides may be classified as carcinogenic to humans in the future; i.e. when the on-going large studies with better precision with regard to exposure assessment and longer follow-up will provide further results and better evidence. The evidence for a large number of specific pesticides is currently insufficient, particularly from epidemiological studies, to evaluate their potential carcinogenic risk to humans. Schinasi and Leon emphasised that studies from Africa were missing in their literature review and meta-analyses (Schinasiand Leon 2014). As agricultural activities expand in Africa, monitoring exposure to pesticides for example via registration of use, and ensuring work-safety standards, will require well designed exposure assessment studies, which are also indispensable to study the link between use of pesticides and any morbidity.

In conclusion, while various pesticides are used ubiquitously around the world, there is emerging scientific evidence that some of them are related to an increased risk of cancer. The evidence comes mainly from studies in those working with pesticides, i.e. agricultural workers or pesticide applicators, and much more data needs to be collected on possible harmful effects from exposure to lower doses than occupationally related ones. This applies particularly for pesticide drift from farmland to residential areas or pesticide residues in food or water. When defining preventive measures in the future it will be important to take into account local circumstances, i.e. the benefits of using specific pesticides as well as the availability of alternatives. For informed decisions on cancer control reliable data on exposure of workers and the general population are needed.

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