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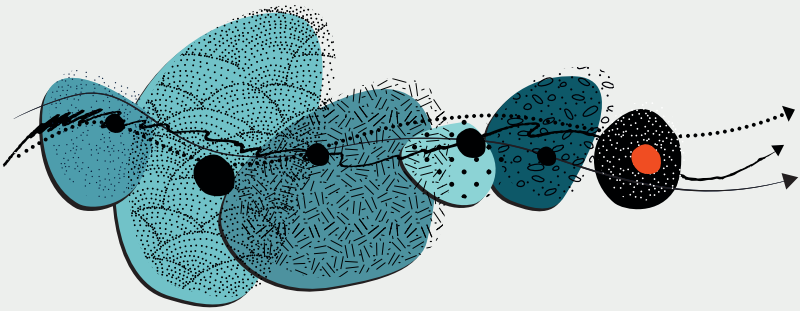

Summary

Effects of pesticides on health

New data

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978-2-7598-2721-3
DOI: 10.1051/978-2-7598-2721-3

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Summary

Effects of pesticides on health

New data

This document presents a summary of the work of a group of experts brought together by the French National Institute for Health and Medical Research (Inserm) to conduct a collective expert review (see Annex 1) on the effects of pesticides on human health, originally published in French.[1]

The review was performed at the request of five Directorates General of the French government: the Directorate General for Risk Prevention, the Directorate General for Health, the Directorate General for Labor, the Directorate General for Research and Innovation, and the General Secretariat of the Ministry of Agriculture and Food.

This work, based on the academic literature available as of the first quarter of 2020, updates a collective expert report entitled *Pesticides : Effets sur la santé* published by Inserm in 2013. Over 5,300 documents were compiled through searches of various bibliographic databases including PubMed/Medline, Scopus, and Cairn (see Annex 2) and through complementary literature searches carried out by the experts.

The work was coordinated by the Collective Expert Reports Unit of Inserm, which is part of its Public Health Thematic Institute.

To cite this document:

Inserm. Effects of pesticides on health: New data. Summary. Collection Expertise collective. Montrouge: EDP Sciences, 2022.

Access collective expert reports online at:
https://www.ipubli.inserm.fr/handle/10608/1
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1. Inserm. Pesticides et effets sur la santé: Nouvelles données. Collection Expertise collective. Montrouge: EDP Sciences, 2021.

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Acknowledgements

We thank Bertrand BED'HOM and Isabelle JOUET, rapporteurs for the Inserm Ethics Committee, for their critical comments on the report.

We thank Olivier CUSSENOT[4] (Service d'urologie, Hôpital Tenon, Paris) for his critical reading of the chapter on prostate cancer.

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4. Olivier CUSSENOT proofread the chapter on prostate cancer entitled "*Exposition aux pesticides et au chlordécone, Risque de survenue d'un cancer de la prostate*" in its form published in February 2019 available at: https://www.inserm.fr/information-en-sante/expertises-collectives/pesticides-effets-sur-sante [accessed May 17, 2021].

Executive summary

A pesticide is any substance used to kill, repel, or control certain forms of plant or animal life that are considered to be pests. Concerns have been raised over their possible effects on human health and, more broadly, on the environment, both for pesticides that are currently authorized as well as for those used in the past (some of which are environmentally persistent). To better assess their effects on health, Inserm was called upon in 2018 by the Directorates General of five ministries to update a collective expert report entitled "*Pesticides: Effets sur la santé*" published by the institute in 2013.

This collective expert report provides a review of current knowledge in the field through a critical analysis of the international scientific literature published since 2013. More than 5,300 documents were assembled and analyzed by a multidisciplinary group of experts. The report begins with a sociological analysis of the mounting concerns over pesticides and a presentation of knowledge on the exposure of the French population to pesticides. It then addresses some twenty pathologies, including neuropsychological and motor development disorders in children, cognitive and anxiety-depression disorders in adults, neurodegenerative diseases, and cancers in children and adults. A final section is devoted to the specific active substances chlordecone and glyphosate, and to the family of succinate dehydrogenase inhibitor (SDHi) fungicides. The presumption of a link between pesticide exposure and the development of disease is assessed based on the results of the epidemiologic studies evaluated and is qualified as strong, moderate or weak. These findings are placed into context with those of toxicological studies to evaluate the biologic plausibility of the observed links.

Occupational exposure

Considering studies of professionals that handle or are in frequent contact with pesticides and who are a priori the most exposed, the experts confirm the **strong presumption of a link** between pesticide exposure and six pathologies: non-Hodgkin lymphoma (NHL), multiple myeloma, prostate cancer, Parkinson's disease, cognitive disorders, as well as certain respiratory system disorders (chronic obstructive pulmonary disease and chronic bronchitis). For NHL, a **strong presumption of a link** was established with certain active substances (malathion, diazinon, lindane, DDT) and with a chemical family of pesticides (organophosphates), while strong links were identified for Parkinson's disease and cognitive disorders with organochlorine and organophosphate insecticides, respectively. These essentially involve pesticides for which the studies relied on biomarkers for quantifying exposure. Toxicological studies on the mechanisms of action of these pesticides confirm they are likely to contribute to the health effects identified by the epidemiological studies.

Moderate links were identified between occupational exposure to pesticides and Alzheimer's disease, anxiety-depression disorders, certain cancers (leukemia, central nervous system, bladder, kidney, and soft tissue sarcomas), asthma and wheezing, and thyroid disorders.

Exposure during pregnancy or childhood

Epidemiological studies of pediatric cancers led to a conclusion of a **strong presumption of a link** between pesticide exposure during childhood as well as maternal exposure to pesticides during pregnancy (due to occupational or residential use) and the risk of certain pediatric cancers, in particular leukemia and central nervous system tumors.

Mother-child cohort studies point to a link between occupational or environmental pesticide exposure during pregnancy and the risk of neuropsychological and motor development

disorders in children. It is difficult to identify the specific active substances involved, although a **strong presumption of a link** is found for certain families of pesticides, notably organophosphate insecticides as well as pyrethroids (whose use has increased as a substitute for organophosphates). The link between organophosphates and alterations in sensory functions, as well as motor and cognitive capacities in children is confirmed, and recent studies on pyrethroids establish a link between exposure during pregnancy and risk of internalized behavior problems in children such as anxiety. Experimental toxicology findings in rodents suggest the immature blood-brain barrier is highly permeable to pyrethroids during early developmental stages, supporting the biologic plausibility of this link. Moreover, recent exposure studies have shown that these insecticides, that are used in both agriculture as well as domestic settings, lead to frequent contamination of interior environments.

Exposure of residents in agricultural areas

Populations residing in agricultural areas may be affected by drift of products applied on crops. Indeed, studies suggest an influence of the proximity to agricultural zones and residential contamination by pesticides that is variable depending on the substances, their mode of application and the methods used to evaluate exposure. Ecological and case-control studies with geolocalization based on characterization of agricultural activity in the vicinity of addresses of residence suggest a link between exposure of residents living near agricultural land and Parkinson's disease and also between residential proximity to pesticide application zones (radius <1.5 km) and behavioral traits related to autism spectrum disorders in children. However, these studies have important limitations related to fine assessment of exposure and the absence of individual data, which makes the **strength of this presumption weak**.

Focus on chlordecone, glyphosate and succinate dehydrogenase inhibitors

Chlordecone, an insecticide used in the French West Indies in the past, persists today in the islands natural environments. The consumption of contaminated foodstuffs has led to the widespread contamination of the population. The **strong presumption of a link** between exposure to chlordecone in the general population and the risk of prostate cancer is confirmed. Based upon a consideration of all epidemiological and toxicological data available, the experts conclude there is convincing evidence of a causal relationship.

With regard to the herbicide glyphosate, the expert review found a **moderate presumption of a link** to an increased risk of NHL. An excess of risk is suggested for multiple myeloma and leukemia, but the results are less solid (**weak presumption of a link**). An analysis of toxicological studies show that mutagenicity tests on glyphosate are generally negative, whereas genotoxicity tests are generally positive, findings consistent with an induction of oxidative stress. Experimental carcinogenesis studies in rodents show an excess of cases but they are not convergent. They report different types of tumors, arising in either males or females, and only at very high doses or in certain strains. Other mechanisms of toxicity (intergenerational effects, disruption of microbiota) are reported in the scientific literature, and it would be interesting to take these into consideration during regulatory assessment procedures.

For SDHi fungicides, which disrupt mitochondrial function by inhibiting the activity of an enzyme complex (SDH) involved in cellular respiration, there are presently no epidemiological data on the possible health effects of these substances in the setting of either professional or environmental exposure. Toxicological and mechanistic studies show that some SDHi fungicides could be considered as endocrine disruptors, at least in the animal models tested (zebrafish). While these substances are non-genotoxic, some show carcinogenic effects in rodents but the finding is disputed on the basis of a mechanism of action

that cannot be extrapolated to humans. Additional research is needed to improve the assessment of the carcinogenic potential of SDHi fungicides (and more generally that of non-genotoxic compounds), and to fill significant gaps in the human data through reinforcement of biomonitoring and exploitation of existing cohorts.

In conclusion, this expert report highlights the importance of periodically re-evaluating knowledge in this field. The identification and confirmation of a strong presumption of a link between certain pathologies and pesticide exposure should guide public action to better protect the population. These questions relating to the links between pesticide exposure and the development of certain diseases have become increasingly complex, and concerns have emerged from the literature regarding the indirect effects of certain pesticides on human health through their effects on ecosystems. The interdependence at issue should be further studied and integrated, along with social and economic aspects, to inform decision-making when developing public health policies.

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Annexes

Foreword

The use of pesticides raises public health issues involving many different diseases and populations. The latter includes, for example, agricultural workers as well as workers in other sectors such as parks or gardens, residents of agricultural areas, individuals who use pesticide products at home and the general consumer. The controversies surrounding pesticides have increased over the past decade, particularly with respect to their use in agriculture and their effects on the health of farmers, individuals living near agricultural land, and consumers of treated products. The mounting concerns over pesticide exposure have been extensively reported in the specialist and general media, and have taken on inextricably scientific and political dimensions.

In April 2018, Inserm was asked by five Directorates General of the French government to update a collective expert report entitled "*Pesticides: Effets sur la santé*" published by the Institute in 2013. The scientific literature has expanded considerably over this time, and this report draws on the latest data to provide an updated assessment of knowledge on the impact of pesticide exposure on human health. It was written by a group of 12 experts from several disciplines including epidemiology, toxicology, exposure science, and sociology. In addition to analyzing the literature on pesticides in general, it also fulfils a specific request from the commissioning bodies to examine two substances that have become particularly controversial in recent years. The first is glyphosate, whose authorization renewal is currently being considered at the European Union level, and the second is chlordecone, an insecticide long used in Guadeloupe and Martinique that is suspected of causing prostate cancer. Succinate dehydrogenase inhibitor (SDHi) fungicides, which are currently the subject of much debate, are also discussed in a separate chapter.

The group of experts selected diseases and health events for which sufficient new data had been published over the intervening six years to justify an update of the previous collective expert report. In some cases, if the conclusions were already sufficiently robust, the group of experts updated only the areas that had evolved over this period. In other cases, if the results were more uncertain or there were few publications, all of the data produced since 2013 were analyzed. Diseases that were not examined in 2013, and for which sufficient data are available, have been considered including breast cancer, kidney and bladder cancer, soft tissue and visceral sarcomas, respiratory disease, thyroid disorders, and endometriosis. The expert group first drew on data from epidemiologic studies of populations exposed to pesticides for each disease or health event examined. This was complemented by an analysis of the findings of toxicology studies to assess the biologic plausibility of the identified links and to define in mechanistic terms the relationships between the health problems in question and specific active substances.

For each disease or health event examined, a brief definition and some background information is provided followed by a summary of the findings of the 2013 collective expert report. As with the previous report, the presumption of a link between pesticide exposure and the occurrence of a disease is categorized as strong (++), moderate (+), or weak (±). The degrees of presumption are evaluated in accordance with the following general principles adapted from Wigle *et al.* (2008) and a report from the US National Academy of Medicine (formerly US Institute of Medicine) published in 2000,[5] which were also used in the 2013 Inserm collective expert report:

5. Wigle DT, Arbuckle TE, Turner MC, *et al.* Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. *J Toxicol Environ Health B Crit Rev* 2008; 11: 373-517 and Institute of Medicine (US) Committee on the Assessment of Asthma and Indoor Air. Clearing the Air: Asthma and Indoor Air Exposures. Washington (DC): National Academies Press (US); 2000. Chapter 2: Methodological considerations in evaluating the evidence. https://www.ncbi.nlm.nih.gov/books/NBK224476/ [consulted June 29, 2020].

- (++) the presumption of the link is strong if there is a high-quality meta-analysis showing a statistically significant association, or several high-quality studies from different groups showing statistically significant associations;

- (+) the presumption of the link is moderate if there is at least one high-quality study showing a statistically significant association;

- (±) the presumption of the link is weak if the studies are of insufficient quality or have inconsistent findings, or do not have sufficient statistical power to conclusively support the existence of an association.

The degrees of presumption represent a framework of reasoning that provides for some flexibility at the discretion of the group of experts. For example, if a meta-analysis exists but it is based on studies that are limited in number or are heterogeneous, the group of experts may assign it limited weight when assessing the presumption of the link. Conversely, a rigorous case-control study based on very good characterization of exposure may be considered more informative and more robust than several cohort studies of moderate quality in which characterization of exposure is based on a questionnaire.

In addition, many of the results that show an association between a disease and occupational pesticide exposure are derived from the US Agricultural Health Study (AHS) cohort, which gives it considerable weight in evaluating the presumption of a link for many active substances. The AHS cohort is a key study in this area due to its prospective design and size. However, like any study, it has certain limitations: *i*) the 50 pesticides analyzed (mainly insecticides and herbicides) reflect the specific agricultural profiles of Iowa and North Carolina (mainly field crops and livestock farming); *ii*) the subjects are primarily white male farmers exposed during pesticide application, and as such, it does not inform on the effects of indirect contact with substances, notably in the context of crop re-entry tasks; and *iii*) the pesticides used are identified solely by self-reporting using

questionnaires with the names of the active substances and indicative examples of the brand names of commercial products. The results derived from this cohort are therefore weighted depending on the quality and number of studies available and the specific features of the disease in question, with these limitations varying in importance.

Toxicology data from the scientific literature are analyzed to assess the biologic plausibility of a link between exposure to an active substance and the development of disease, but also to flag effects that have not been observed or investigated in the epidemiologic studies. These data are derived from the fields of biochemistry, cell biology, genetics, histology, and physiology on the basis of *in silico*, *in vitro*, and *in vivo* models (molecular modeling, cell and tissue lines, and animal testing). The following aspects were taken into consideration: *i*) the relevance of the experimental models; *ii*) the level of exposure; and *iii*) the coherence of the findings relating to the underlying mechanisms of toxicity. One of the goals of this approach is to identify adverse outcome pathways (AOPs) for a chemical agent, i.e. to describe a logical sequence of causally linked events at different levels of biologic organization caused by exposure to this agent that leads to a harmful effect on the health of humans or wildlife.

This expert report begins with a sociologic analysis of the mounting concerns over pesticides and a review of data on exposure of the French population to pesticides. The analysis is then divided into four sections. The first explores the link between exposure to pesticides and neuropsychological and motor development disorders in children, followed by neurologic disorders in adults including cognitive impairment, anxiety and depression, and neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis). The second section looks at cancer in children and adults, and includes a section focusing on chlordecone and the risk of prostate cancer. The third section is devoted to other health events not examined in the previous expert report including respiratory health, thyroid disorders, and endometriosis. Finally, the last section

deals with the active substance glyphosate, as well as the family of succinate dehydrogenase inhibitor (SDHi) fungicides.

The various chapters of the expert report present the analysis of the literature conducted by the experts in each of their disciplines based on the bibliography made available to them. The present document is a summary of the full expert report, and was collectively written and validated by the group. The principal conclusions are presented in tabular form, with shading used to indicate new findings in relation to the 2013 collective expert report. Key studies are noted in the table legends, and the term "without distinction" means that the studies did not discriminate between various families of pesticides or active substances. For greater concision, the tables in this summary present only the new findings and those where the presumption of a link is classified as strong or moderate. Readers may consult the full expert report for additional details and references. Also available in the French full expert report, but not discussed here, are two chapters focusing on lung cancer and on the French AGRIculture and CANcer (AGRICAN) cohort. These were contributed by external scientists who presented their analysis of the literature to the expert group and wrote the chapters that are published as 'communications' in the final expert report.[6]

6. The responsibility for the analyses and views expressed in these communications rests solely with their authors.

Summary

Mounting concerns about the effects of pesticides on health

Pesticides, a generic term derived from the Latin "*pestis*" (plague) and "*caedere*" (to kill), are widely used in agriculture to improve product yield, quality, and appearance by destroying organisms that are considered to be harmful, such as insects, fungi, and weeds.[7] While there exists a long-documented history of concerns about the effects of pesticides on human health, political conflicts related to these issues have now reached unprecedented levels in France. These conflicts are being driven both by protest movements and by competition among authorities to control public policies designed to protect the populations exposed to these products.

In France, such mobilizations first emerged in the field of occupational health. A transformation took place through which the cases of individual sick workers became a common cause for farmers who saw themselves as pesticide victims, and who with the help of families, environmental activists, and legal professionals, founded the association "Phyto-Victimes" in 2011. Several associations are now speaking out against the health risks to workers in the agricultural and agri-food sectors, and calling for compensation for the harm they have experienced and for stricter regulation of pesticides. This emergence of advocacy is the result of several joint sociological and political dynamics, notably the loss of influence of historic agricultural trade unions and the productivist model of agriculture, and changes

7. The various classifications and chemical families of pesticides (insecticides, fungicides, herbicides, organochlorines, organophosphates, thiocarbamates, pyrethroids, etc.) are not covered in this document. Readers are invited to refer to the summary or to Chapter 1 "*Notions générales sur les pesticides et sur leurs utilisations en France*" of the collective expert report entitled "*Pesticides: Effets sur la santé*" published by Inserm in 2013 [document in French].

in farming families who are increasingly critical of pesticides. At the same time, local resident groups have also formed in arboriculture and viticulture regions calling for spraying to be restricted near their homes. These diverse social movements are connected to movements that promote organic food and condemn the dangers of synthetic pesticides.

All of these social, economic, and political changes in rural and agricultural areas have contributed to raising the profile of the health effects of pesticides far beyond the scientific literature in the fields of epidemiology and toxicology. The social movements they have driven have been extensively covered by the general media, particularly when they have involved court cases that can be used by journalists to develop a narrative around complex medical issues by focusing, for example, on the opposition between the populations exposed to pesticides and the companies that market these products. More generally, mobilizations by farmers and local residents denouncing the dangers of pesticides have ensured this issue is a firm fixture on the political agenda, and have made it a key component of discussions about the future of agricultural sectors, as was demonstrated by the 2017 French National Food Conference.

In this context, a growing number of public institutions have taken up this issue, far beyond the administrative actors in the agricultural sector who have historically been responsible for it. For many years, agricultural institutions were principally responsible for administrative regulation of pesticides. The situation has since changed considerably, and institutions outside the field of agriculture have become increasingly important in this area of public policy. This is the case of the *Agence française de sécurité sanitaire de l'alimentation* (AFSSA, French Food Safety Agency), which merged with the *Agence française de sécurité sanitaire de l'environnement et du travail* (AFSSET, French Agency for Environmental and Occupational Health & Safety), and has since become the *Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail* (ANSES, French Agency for Food, Environmental and Occupational Health &

Safety). In general, for public authorities, this is a time of profound questions about the way in which the risks of pesticides are assessed and managed.

The mounting body of scientific evidence demonstrating the impact of pesticides on human health is heightening social and political conflicts over these products and their regulation. The scientific data produced in recent years (including articles published in scientific journals, studies conducted by manufacturers or by contract research organizations commissioned by manufacturers...) on the links between pesticides and health often appear contradictory and do not point to simple courses of action for resolving the problems identified.

Regulatory risk assessment of pesticides is based primarily on experimental toxicology data. These are used to determine acceptable exposure doses in humans for each active substance, and to determine the conditions of use for controlled application of the commercial products. The methods of this risk assessment have evolved over time toward ever greater codification. This is the result of a transnational history combining science, politics and economics. Discussions within the Organization for Economic Co-operation and Development (OECD) led to the adoption of international guidelines for generating toxicity data that is admissible for the pre-marketing risk assessment of pesticides. Harmonization efforts have been made at the European Union level as well. The European Food Safety Authority (EFSA), which assesses the dietary risks of pesticides, has produced a set of guidelines for all Member States, although risk assessment of commercial formulations are up to the discretion of each nation. This process of regulatory risk assessment has resulted in the systematic production of substantial toxicity data for all marketed pesticides. Over the last few years, however, this system has come under extensive criticism. Some of the criticisms, particularly those leveled by environmental social movements, denounce the lack of transparency and an overgenerous interpretation of the right to trade secrets. Other critics claim that manufacturers in the sector, and certain scholarly

societies that they fund, influence the negotiations that take place prior to the adoption of the guidelines, which may therefore be biased in their favor. In addition, the toxicity data produced by manufacturers for the purposes of risk assessment are primarily used to assess the effects of exposure to individual pesticides, and cannot be used to assess the effects of generalized and simultaneous exposure to a variety of products. Similarly, certain factors, such as transgenerational effects and sexual dimorphism, appear to be little or poorly taken into account in the risk assessment of pesticides. More broadly, several social science studies have highlighted the risk of an increasing separation between regulatory toxicology, which is governed by the guidelines set by the OECD and risk assessment agencies, and academic toxicology research.

In keeping with these developments, another source of knowledge on the effects of pesticides on human health emerged: epidemiologic studies, which take an observational approach to study populations, and use statistical tools to identify risk factors for human health. The publications resulting from these studies have provided important warning signals on the risks associated with exposure to pesticides. In particular, they have shown excess incidence of Parkinson's disease, certain hematologic malignancies, and prostate cancer among agricultural worker populations exposed to pesticides. However, these epidemiologic data receive little consideration in the regulatory procedures for assessing the risks of pesticides, with the agencies responsible often pointing to their methodological limitations. For situations where organized and structured data on actual pesticide usage is lacking, epidemiologists have developed culture-exposure matrices for each crop that can be used to obtain more accurate and/or less biased exposure data and more robust results. These matrices, along with active and passive dosimetry tools, can be used to establish the probability, frequency and intensity of exposure to each pesticide. Epidemiologists have also set up prospective cohort studies enabling long-term follow-up of exposed populations. While these innovations open up the prospect of

epidemiologic data that can be more easily interpreted, the fact remains that the data currently available raise numerous questions and are not always able to provide definitive answers.

The mounting concerns over the effects of pesticides on population health have been paralleled and fueled by increasing scientific literature on the subject, and the request that gave rise to this collective expert review lies at the confluence of all these elements.

Exposure of the French population to pesticides

The available data on environmental contamination indicate the widespread presence of pesticides and their metabolites and degradation products in France. There are many different sources of contamination, including treatment of crops, animals, and farm and storage buildings in the agricultural sector, which is the main consumer of pesticides in France (90% of the quantity sold), non-agricultural use of pesticides in the maintenance of transport infrastructure (such as roads, railways, and airports), domestic use (such as parasite and insect control), and wood treatment. Measures have recently been taken to reduce certain sources of exposure, with a ban on the use of synthetic pesticides for the maintenance of public spaces (such as parks and green spaces) in 2017, and a ban on their use by private individuals in 2019.

Contamination of outdoor environments

In 2017, pesticides were found in 80% of groundwater bodies, with approximately a quarter of these exceeding the regulatory threshold of 0.5 μg/L for total detected and quantified pesticides and their metabolites. Of the nearly 300 substances identified, half were herbicides and 40% are currently banned. Surface water contamination is also widespread: between 2015

and 2017, 84% of measurement stations exceeded the threshold, on at least one occasion, of 0.1 µg/L for the concentration of any given pesticide considered individually. Thresholds are regularly exceeded at over a quarter of national measurement stations. With regard to marine environments, although there has been marked reductions in the levels of organochlorine pesticides recently, chlordecone contamination in the French West Indies remains a cause for concern.

Outdoor air contamination is relatively well documented, but as in almost all other countries, it is not subject to regulatory limits. The PhytAtmo database, which brings together data from 2002 to 2017, shows that between 40 to 90 active substances are detected annually, in rural or urban areas, at varying concentrations. In 2018, a national exploratory campaign analyzed 75 pesticides in air samples taken from 50 sites. The substances most frequently detected were a number of herbicides (glyphosate, prosulfocarb, S-metolachlor, pendimethalin and triallate), insecticides (chlorpyrifos-methyl and lindane), and fungicides (chlorothalonil and folpet). The results of this study were used to prioritize in-depth analyses on lindane (detected in almost 80% of samples), and systematic monitoring of 32 substances, including 9 that are banned.

Soils are also contaminated, but in the absence of regulatory monitoring, only fragmentary data are available. Locally elevated levels of lindane and atrazine were found in northern France in 2008, and a recent study in the Deux-Sèvres region found the presence of the herbicide diflufenican, the insecticide imidacloprid, and the fungicides boscalid and epoxiconazole in over 80% of soil samples from pastures and cereal crops.

In recent years, national organizations and networks have made efforts to structure and organize environmental contamination data. Further work in this area is required, and must be supported in order to ensure the completeness and geographic and temporal representativeness of these data.

Contamination of the food chain

Foodstuffs are governed by regulatory and monitoring systems that set, among other restrictions, maximum residue limits (MRLs) for pesticides. In 2016, an EFSA analysis of nearly 7,000 food samples marketed in France (half of French origin) found that 6.4% were non-compliant, exceeding the MRL for at least one pesticide. The agency concluded that, based on the current scientific knowledge: *i*) the likelihood of acute exposure to pesticide residues exceeding the concentrations likely to cause adverse health effects was low, and that *ii)* long-term dietary exposure to the pesticides that were monitored was unlikely to pose a risk to consumer health. However, it should be noted that few scientific studies exist on the long-term effects of chronic exposure, as these are particularly difficult to conduct. In France, the *Études de l'alimentation totale* (TDS, Total Diet Studies) have analyzed foods on the French market "as consumed". The TDS2 study in 2011, which included an analysis of approximately 300 pesticides in over 1,200 samples, reported that 37% of samples contained at least one detected residue. However, just one exposure scenario (to dimethoate in the case of significant consumption of cherries) posed a risk of exceeding the acceptable daily intake. In 2016, the Infant Total Diet Study (iTDS) analyzed food products intended for children. Of the 309 samples tested for 469 substances, 67% contained at least one detected residue, but a risk analysis did not identify active substances of concern to human health. Although potential food-related risks appear to be controlled based on the current state of knowledge, the analyses on which such assessments are predicated do not take into account the impact of exposure to combinations of pesticides ("cocktail effects"). There is therefore a need to acquire integrated data and models that better reflect the complex nature of exposure.

Contamination of indoor environments

Domestic use of pesticides can result in direct exposure of residents during use, along with contamination of the indoor

environment, as substances may remain in the air and dust. Long neglected, the contribution of this source of exposure appears to be significant in France. Pesticide use by private individuals was examined in the Pesti'home study, which found that 75% of households reported using pesticides in the previous year. These included various pyrethroid insecticides (notably permethrin, cypermethrin, and tetramethrin). The households that used pesticides the most frequently were also those with the greatest number of products, and over a quarter of households had stocks of at least one banned product. These findings point to the need for greater vigilance and to inform the general public on the use and storage of these products.

Contamination of indoor environments primarily results from direct use of pesticides in the home, release of substances from treated materials, and from contaminated outdoor air. Studies conducted by two national observatories in the 2000s documented indoor air contamination by pesticides. The most common substances found were permethrin, lindane, and to a lesser extent other organochlorines (DDT/DDE, α-endosulfan), and organophosphates (chlorpyrifos, diazinon, and fenthion). Dust has also been used to study the contamination of indoor environments. A study in schools (between 2013 and 2017), and in dwellings inhabited by young children (between 2008 and 2009) found many pesticides present (permethrin, lindane, DDE, cypermethrin and chlorpyrifos), with profiles consistent with those observed in the air.

Contamination of homes and proximity to agricultural areas

Many questions have been raised about levels of exposure to pesticides and the potential risks to local residents of agricultural areas. Around twenty studies have explored these issues, either by measuring pesticides in different matrices (air, soil, and urine) or by considering proximity to agricultural areas as a proxy for exposure.

Three French studies have measured agricultural pesticides in household dust or urine samples from local residents. Numerous pesticides of agricultural origin were detected, but a lack of temporal precision does not permit firm conclusions to be drawn regarding the contribution of nearby agricultural activity to the exposure. North American studies looking at this issue, which also have methodological limitations, have produced inconsistent results with half of them finding no correlation between distance from crops and pesticide concentrations in household dust.

Other studies have used a methodology incorporating both spatial and temporal data to characterize pesticide exposure in greater detail. For example, in the United Kingdom, one such study found no increase in urinary pesticide concentrations in individuals living within 100 m of fields in the 2 days following pesticide treatment. A study in Wallonia showed a reduction in pesticide deposition in soils as a function of time as well as distance from the treated zones. Finally, in a study of local residents living near flower bulb fields in the Netherlands, pesticide concentrations were higher within 250 m from the fields than within 500 m, particularly outside homes but also indoors, and more markedly during application periods. Although limited, the available data suggests an influence of proximity to agricultural areas on the contamination of homes by pesticides. However, this influence varies depending on the substances, their method of application, and the environmental or biologic matrices used to estimate exposure.

What then are the impacts of household exposure to pesticides on human health? Some of the existing studies in this area are based on an approach that considers the proximity of homes to agricultural areas as a proxy for exposure. These mainly consist of "ecological" studies designed to correlate a health effect measured in geographic units with indicators of agricultural activity (farm density, crop area, quantity of pesticides used...) defined for these same units, and case-control studies based on characterization of the agricultural activity near geolocated residential

addresses. For example, these approaches have previously been used in studies of Parkinson's disease, bladder cancer, and central nervous system tumors, and are being used in two ongoing French studies: the Geocap Agri study on childhood cancers, and the ELFE (French Longitudinal Study from Childhood) cohort study. The advantage of these types of studies is that they are able to include a large number of participants, are based on objective indicators of exposure, and are generally less expensive to run than studies that use questionnaires or analytical tests to evaluate exposure. However, due to their nature, they present significant limitations in relation to the assessment of exposure (for example, it is difficult to incorporate changes in agricultural activities, residential history is rarely available, there is little discussion regarding the accuracy of geocoding, and they do not take into account uses of agricultural pesticides), and the lack of individual data. Refinement of these approaches should allow for better assessment of residential pesticide exposure in agricultural areas, and estimation of health risks.

Measurement of pesticide levels among the general population in France

Measuring the concentration of a pesticide or its metabolites in biologic matrices is often considered a gold standard method for assessing exposure. The results provide information on the body burden of a substance by integrating all routes and sources of exposure. A distinction is made between internal matrices (such as blood and adipose tissue) and external matrices (such as urine and feces). Internal matrices are useful for measuring persistent compounds with a half-life of several weeks to several years. They are however of limited use in characterizing past exposure, which is restricted to a few years or months prior to sampling. With regard to external matrices, urine is most commonly used, particularly for measuring compounds with a half-life of several days to a few hours, but urine output and elimination kinetics must be considered when interpreting the results. There is

increasing interest in alternative external matrices. Hair is one interesting example because its growth also makes it possible to estimate the period(s) of exposure, but interpretation of results is challenging due to limited understanding of the toxicokinetic processes affecting accumulation. Meconium (the first feces of the newborn) is of great interest for examining fetal exposure to substances, but is subject to the same problems. Developments in analytical chemistry have made it possible to identify and quantify a large number of substances. Appropriate selection of the matrix and analytes still however represents a major area of investigation, including the identification of as-yet unknown metabolites.

Exposure assessment studies performed on the general population report widespread exposure to multiple pesticides.[8] Some of these are national in scope, but are currently limited to a few groups of chemicals. The environmental component of the French National Nutrition and Health Study in 2006-2007 found levels of organochlorines comparable to those observed abroad, while levels of pyrethroids and, to a lesser extent, organophosphates, were higher than in the United States or Germany. Studies derived from the national ELFE cohort also confirmed the widespread presence of pyrethroids in 2011 and demonstrated low or no exposure to organophosphates and triazines. The initial results from the ESTEBAN study, which includes over 3,500 adults and children, are expected in 2021 and will advance knowledge in this area.

Academic studies conducted at the regional level also exist that are more comprehensive in terms of pesticide coverage, but also more exploratory given the uncertainties associated with the selected biologic matrices. Three studies from the PELAGIE mother-child cohort have reported the ubiquitous presence of organophosphates and pyrethroids among participants, along with the presence of triazines in around 30% of mothers. A

8. Estimated levels of occupational contamination and the methods and tools for measuring occupational exposure are described in detail in the 2013 collective expert report, and will not be readdressed here.

study of meconium samples collected from around fifty healthy neonates found the presence of chlorpyrifos, diazinon, propoxur and isoproturon in the majority of the samples. Finally, analysis of hair clippings from a subcohort of the ELFE study detected 122 substances at least once, and a minimum of 25 substances in each sample. The most common pesticides were pyrethroids and organophosphates, but all 18 chemical groups examined were found, demonstrating the presence of complex cocktails of pesticides. It is important to remember that while the detection of a pesticide or its metabolites in a biologic matrix is clear evidence of exposure, it does not allow for any interpretation of toxicity and health effects without an analysis of all available toxicology and epidemiology data.

Neurologic diseases and neuropsychological disorders

This section presents an analysis of the scientific literature published since 2013 on the role of pesticides in the development of neurologic diseases and neuropsychological disorders. It is organized by theme and by the population concerned, and focuses on the effects of pesticide exposure during the prenatal period, and in particular on child neuropsychological and motor development. It then addresses neurologic diseases in adults, including a number of neurodegenerative diseases (Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis), cognitive impairment, and anxiety and depression.

Child neuropsychological and motor development

In the 2013 collective expert report, child health was discussed in relation to maternal exposure during pregnancy by studying pregnancy outcome events including spontaneous abortion, congenital defects, low birth weight and duration of pregnancy.

It also explored disorders presenting after birth affecting the reproductive system, metabolism and growth, psychomotor and intellectual development, behavior, and the development of cancers.

Some of this research fits within the developmental origins of health and disease concept, which suggests that subtle, clinically silent modifications in certain health parameters occurring in early life in response to a toxic event/agent, may lead to more significant impairments or diseases later in life.[9] Certain periods of life, particularly those involving development, such as pregnancy, early childhood, and puberty, are recognized as "windows of vulnerability" to the effects of a toxic event or agent.

The group of experts decided to focus this update on the links between pre- and post-natal exposure to pesticides and child neuropsychological and motor development, child behavior, and childhood cancers (in the section on "Cancers" below), since these are the area in which the most research has been published and where the most significant progress has been made.

Particular attention was paid to studies that included robust, reliable tools for measuring exposure and health parameters, and that considered major confounding factors as well as the temporal consistency between the exposure and the health event of interest. In some studies, estimates of exposure are based on measuring biomarkers that combine all routes of exposure (dermal, dietary, and respiratory) and sources of exposure (agricultural, occupational, domestic activities...) without distinction. Those studies focusing on child neuropsychological and motor development or behavior are typically mother-child cohort studies involving long-term follow-up of pregnant women and their children. While essential for this area of research, these studies are rare given the time and cost involved.

9. Charles MA, Delpierre C, Bréant B. *Le concept des origines développementales de la santé : Évolution sur trois décennies.* Med Sci 2016; 32: 15-20.

The developing brain is particularly sensitive to exposure to toxic agents. For certain toxins, such as lead and mercury, numerous studies have shown that the consequences of pre-natal exposure on neuropsychological and motor development are not limited to those evident at birth, but instead may be more subtle and emerge later during childhood. Poorer performance, sensory deficits, and learning delays or disabilities in school-age children can place individuals at a disadvantage and ultimately have consequences for society as a whole.

Exposure to organophosphate insecticides

A large number of studies using biomarkers of exposure have now investigated the impact of exposure to organophosphate insecticides during pregnancy on child neuropsychological development. The first cohort studies including follow-up of women during pregnancy and their children were described in the previous expert review in 2013; these cohort studies were conducted in the United States among ethnic minorities or low-income groups and found cognitive deficits up to 7 years of age associated with prenatal exposure to organophosphate insecticides.

These findings were not subsequently confirmed at later ages in the same cohort studies, or in two of the four more recent European and North American studies. Poorer cognitive performance among school-age children and impaired psychomotor development and visual acuity in young children have however been observed in recent cohort studies with some of the highest levels of exposure in the literature: the majority from Asia, and one from Europe.

While variability in levels of exposure may partly explain differences between the studies, several hypotheses may shed light on the apparent inconsistency of the results: *i*) a possible reversibility of effects via compensatory mechanisms acquired with age or by cognitive stimulation over the course of the child or adolescent's life; *ii*) the existence of social and/or ethnic

vulnerability to pesticide exposure; *iii*) the reduction in the use of organophosphate insecticides over the past two decades; and *iv*) variation in sources of exposure and/or the combinations (cocktails) of organophosphate insecticides present in agricultural and domestic products.

Two cohort studies, following children up to 14 years of age, have confirmed the potential impairment of children's social abilities, with behavioral traits related to autism spectrum disorders observed up to adolescence, in association with prenatal exposure to organophosphate insecticides. Animal and mechanistic models for studying the neurotoxicity of organophosphate insecticides were discussed in the previous expert review of 2013 (see the chapter entitled "*Mécanismes d'action neurotoxique des pesticides*") and confirmed the biologic plausibility of developmental neurotoxicity, in particular for the organophosphate insecticide chlorpyrifos. For chlorpyrifos, an Asian cohort study found no effect on the psychomotor development of children at 3 years of age, while one of the US cohort studies confirmed a link with the fine motor skills of children aged 9-13 years. However, no new studies have been published to date in humans that strengthen the link suggested by the 2013 expert review specifically for malathion and methyl parathion (organophosphate family) and propoxur (carbamate family).

Exposure to pyrethroid insecticides

The epidemiologic literature focusing on the role of pyrethroid insecticides in child neuropsychological and motor development is recent and follows an increase in their use as a substitute for organophosphate insecticides. The majority of these studies involved mother-child cohorts, and used urinary biomarkers to measure exposure. The results are consistent across the studies, regardless of the context, and suggest an increase in child behavioral disorders, particularly internalized disorders (such as anxiety) associated with prenatal exposure to pyrethroids. With

regard to their effects on cognitive abilities in children, the results are less persuasive. No specific active substances could be identified from this literature.

Families and active ingredients associated with excess risk of impaired child neuropsychological and motor development*: results of biomarker studies in pregnant women

Exposure during pregnancy	Impairment observed in children	Presumption of a link
Organophosphates		
Without distinction	Impaired motor and cognitive abilities and sensory function	++
	Behavioral traits related to autism spectrum disorders	+ [a]
Chlorpyrifos	Impaired motor and cognitive abilities	+ [b] Interaction with *PON1*
Malathion Methyl-parathion	Impaired motor and cognitive abilities	+ [c] Interaction with *PON1*
Carbamates/ Thiocarbamates		
Propoxur	Impaired motor and cognitive abilities	+ [c]
Pyrethroids		
Without distinction	Internalized behavioral disorders such as anxiety	++
	Impaired motor and cognitive abilities	±
Organochlorines**		
Chlordecone	Impaired fine motor skills	+ [d]

++ based on the results of eighteen cohort studies of organophosphates, strengthens the 2013 results; based on the results of three cohort studies for pyrethroids New data
+ [a] based on the results of two cohort studies New data; + [b] based on the results of two additional cohort studies compared to 2013; + [c] no new studies since 2013; + [d] based on the results of one cohort study, results from 2013
± based on the results of five studies (positive and negative) New data
* includes psychomotor and mental development, cognitive performance, and behavior
** The scientific literature on the other organochlorines has not been re-examined.
PON1: paraoxonase 1

A link between exposure to pyrethroid insecticides during childhood and an increase in externalized behavioral disorders in children (such as attention deficit with/without hyperactivity, and aggression) has been observed in several cross-sectional studies, but their conclusions concerning the possible causality of the association are limited.

While several toxicology studies have effectively demonstrated the impact of pyrethroid pesticides on voltage-dependent sodium channels, targeted in insects, numerous other relevant modes of action have also been identified: dysfunction of several types of calcium channels and increased dopamine transporter expression. These mechanisms have been observed at low doses used *in vivo* and *in vitro* and in association with an impact on animal behavior.

Animal studies conducted at various stages of development show that brain levels of deltamethrin are inversely proportional to age, suggesting that the greater sensitivity to pyrethroid insecticides in younger organisms could be explained by a hyperpermeable blood-brain barrier. The toxicology literature since 2013 describes novel mechanisms of action (proteosomal targeting of proteins, epigenetic modifications), and points also to potential synergistic effects of pyrethroids that could explain the effects of these substances often used in combination, and that represent avenues for further research. Ultimately, all of the data on mechanisms of action provide arguments to support the role of prenatal exposure to pyrethroid insecticides in the development of neuropsychological and motor disorders in children.

Residential exposure to pesticides

The exposure of the general population to pesticides through agricultural use near residential locations is particularly difficult to evaluate. Several studies have used geocoded residential addresses during pregnancy or childhood to estimate distances from agricultural use and the intensity of local agricultural use of pesticides. These reported an elevated risk of intellectual

disabilities and of behavioral traits related to autism spectrum disorders in children associated with residential proximity (<1.5 km) to agricultural activities. In particular, associations are found with organophosphate, pyrethroid, and carbamate families of pesticides, consistent with studies using biomarkers of exposure. In relation to domestic use of products during pregnancy for control of insects or other pests, the level of evidence for possible impairment to neuropsychological and motor development in children remains weak.

Presumption of a link between exposure to pesticides and neuropsychological and motor development in children: results from non-biomarker studies in pregnant women

Exposure during pregnancy	Impairment observed in children	Presumption of a link
Non-occupational exposure (domestic use, residential proximity to agricultural zones treated with pesticides)	Impaired motor and cognitive abilities	+
	Behavioral traits related to autism spectrum disorders	± [a]
Occupational exposure to pesticides (without distinction)	Impaired motor and cognitive abilities	± [b]

+ based on the results of two cohort studies and one case-control study (but inadequate measurement of exposure) New data

± [a] based on the results of a case-control study New data; ± [b] based on the results of two cross-sectional studies, results from 2013

Finally, it should be noted that few studies have looked at the link between maternal occupational exposure and psychomotor and intellectual development and behavior in children in France or elsewhere. It was not possible to update this literature for this new expert review.

Cognitive impairment in adults

Cognition is a complex brain process that involves memory, attention, judgment, understanding, and reasoning. Some environmental agents are able to disrupt cognition, probably by interfering with neurotransmitters. The potential impact of pesticides on cognition was suggested by the clinical identification of chronic impairment of cognitive function following acute poisoning with organophosphate insecticides. These findings were followed by observational studies that revealed chronic neurologic manifestations after acute poisoning, as measured by poorer performance in various tests evaluating visual attention, memory, and abstract reasoning. Subsequently, other studies have examined the delayed effects of chronic exposure, in the absence of acute poisoning, generally among individuals using organophosphates, but also organochlorines and pyrethroids.

The 2013 collective expert review identified some forty epidemiologic studies on the impact of pesticide exposure on cognition. These included four prospective cohort studies, while the remainder were mostly cross-sectional in design. Around fifteen original research studies and two meta-analyses have since been published.

Three studies of agricultural workers (in Ethiopia, China, and the Agricultural Health Study in the United States), provide new data on the effect of acute pesticide poisoning on cognitive performance, measured some time after exposure. Although it was sometimes difficult to distinguish the effects of acute exposure from those of chronic exposure among occupational users, these three studies further strengthened the conclusions regarding a link between acute pesticide poisoning (mainly organophosphates) and poorer cognitive performance in the areas of visual attention, memory, and abstract reasoning.

With respect to the delayed effects of occupational pesticide exposure on cognition, eight new cross-sectional studies and four cohort studies have been published since 2013. The cross-sectional studies were conducted in a wide range of countries

(Iran, China, Saudi Arabia, Chile, Sweden, and the USA). Half of these involved occupational users only (horticultural and agricultural workers, Gulf War veterans, and individuals working in mosquito control), while the others considered individuals living near crops (vines and citrus fruit), the rural population (in China) or the general population (in the United States and Sweden). The pesticides studied were mainly organophosphates, but also pyrethroids and organochlorines. The studies of effects on occupational users and local residents all concluded that cognitive performance was reduced, as measured by various tests.

The studies of the general population also found poorer performance, with the exception of the cross-sectional National Health and Nutrition Examination Survey (NHANES, USA), in which exposure was estimated from biomarkers of exposure (urinary pesticide metabolites).

Four new prospective analyses have been conducted in France, the United States and Greece. Two of them focused on occupational exposure: one among workers in the pesticide production industry (chlorpyrifos) in the United States and the other among wine growers in France. The production industry study found no association between the exposure of workers, who were followed up for one year, and cognitive decline. The French cohort study (PHYTONER) analyzed the results of cognitive tests after 4 years of follow-up from nearly a thousand wine growers, estimating exposure to eleven organophosphates using a culture-exposure matrix and field study-based algorithms. Cumulative exposure was associated with poorer cognitive performance, particularly for working memory and processing speed, but with no dose-response relationship. Two other prospective analyses have examined cognitive decline among elderly people living near agricultural areas. The first of these was a Californian study of people aged 60 years and over, living near areas treated with organophosphates, followed up for a 10-year period for cognitive decline and onset of dementia. The second was a Greek cohort study of people aged 65 years and over,

living near pesticide-treated fields. These two studies found poorer cognitive performance in these elderly local residents.

The previous collective expert review identified four reviews and a meta-analysis examining the effects of chronic pesticide exposure on cognition. These concluded that long-term exposure to pesticides is associated with cognitive impairment, an effect that is more clear in the setting of past acute poisoning. Since then, some fifteen original research studies and three reviews have been published on the subject. These include a review and two meta-analyses focused on the effects of chronic exposure to organophosphates. The authors highlight the range of different tests performed and the differences in the methods used to estimate exposures between the studies. Their conclusions are however convergent, confirming an increase in certain cognitive deficits (attention, visual and motor capacity, verbal abstraction, and perception), findings that are most consistent in the areas of memory and attention, among individuals exposed to organophosphates. A duration-response relationship was shown in the analyses performed at both the aggregate and individual level.

The other recent studies are mostly cross-sectional and compare the cognitive function of individuals poisoned by pesticides or exposed for a prolonged period of time over their working lives to that of non-exposed individuals. Most of them identify links between exposure to pesticides and cognitive decline. The majority of the associated pesticides are organophosphates, but other substances have been investigated such as pyrethroids and organochlorines, which have also been shown to be associated with impaired cognitive function. Over the past few years, research has also been extended to populations that would appear to be less exposed than farmers, such as residents of agricultural areas and the general population, notably through the NHANES study in the United States. An effect has also been shown on cognitive performance in these populations. The longitudinal dimension of the impact of pesticides on cognitive function is an important issue given that cognitive impairment could be predictive for the development of certain dementias.

Presumption of a link between exposure to pesticides and cognitive impairment

Exposure	Populations	Presumption of a link
Pesticides*	Farmers, with or without a history of acute poisoning	++
Pesticides (without distinction)	General population or local residents of agricultural areas	+

* predominantly organophosphate insecticides
++ based on the results of a meta-analysis in 2013, two recent meta-analyses, three prospective cohort studies, and numerous cross-sectional studies Degree of presumption raised from moderate to strong
+ based on the results of two cross-sectional studies and two prospective studies New data

Anxiety and depression

The assessment of anxiety and depression disorders within populations is subject to numerous challenges, the main one being to provide a clear, consensual definition of disease entities that can be identified and enumerated using epidemiologic tools such as tests or questionnaires. As such, data on the prevalence of anxiety and depression remain contested. Almost one in ten people in France are thought to have experienced a depressive episode in the previous year, with women being affected more frequently than men. The national prevalence rate is thought to have increased in recent years. Regarding anxiety, one study reports that over 1.3 million people were treated for anxiety disorders in France between 2010 and 2014. Anxiety and depression are multifactorial in origin and develop from a complex interaction between biologic, psychologic, and environmental factors. Due to their chronic nature, comorbidities, and the stigma surrounding mental health problems, anxiety and depression can cause great distress for those affected. This can have a significant impact on work and personal life, and is associated with an increased risk of suicide or attempted suicide. The World Health Organization (WHO) estimates the suicide rate among patients experiencing a major depressive episode to be between 5 and 20%. Death by suicide may also be higher in the

agricultural population due to easier access to the most fatal methods (such as firearms, hanging, and chemical poisoning).

Numerous studies, particularly in the sociology of health, conducted in different countries, have found higher rates of depression and suicide among agricultural populations than in the general population. The specific characteristics of farming life, such as residential and social isolation and occupational challenges (physical fatigue, time pressures due to often long working days, unpredictability of seasons and weather, economic difficulties related to fluctuating agri-food prices) may contribute to anxiety and depression disorders.

The hypothesis that pesticides play a role in the development of anxiety and depression is underpinned by their possible interference with numerous neurotransmitters, such as serotonin, which play a major role in mental and behavioral processes. In the late 1970s, several observations from clinical toxicology suggested an effect of pesticides on mood (depressive symptoms, sleep disorders, anxiety and irritability) in people following acute poisoning, particularly with organophosphates.

For over thirty years, epidemiologic studies have observed similar effects from chronic occupational pesticide exposure, particularly to organophosphate insecticides. The previous collective expert review identified around thirty studies examining the association between pesticide exposure and the risk of anxiety and depression disorders. These presented a number of methodological limitations including low subject numbers, heterogeneity in the definition of disorders, and the existence of significant confounding factors, such as social isolation and economic difficulties. These studies pointed toward a higher frequency of anxiety and depression among individuals exposed to pesticides, both following acute poisoning events, and in the context of moderate but prolonged exposure. Several studies also suggested a possible association with attempted suicide, but without being able to confirm the specific role of pesticides. Analysis of the toxicology literature provides arguments in favor of a possible effect of certain substances on the central nervous

system. One example involves disruption of serotonin levels (a neurotransmitter that plays an important role in mood regulation), in response to exposure to certain pesticides, such as organophosphates.

The epidemiologic literature in this area has grown since the previous collective expert review in 2013. Three review articles were identified. The first focused on the link between pesticides and both depression and suicide, and was based on some twenty articles from 1995 to 2011, of which eleven dealt with the risk of depression and fourteen of suicide. A link between acute pesticide poisoning and depression was reported in 5 studies, with levels of risk ranging from a two-fold to a five-fold increase, while studies of chronic exposure found lower risks. An increased risk of suicide was reported by most studies, but these presented methodological limitations. Another review, focusing on organophosphates, was unable to come to a definitive conclusion regarding their association with neuropsychiatric disorders. The third publication, based on around thirty studies, reviewed the impact of high- or low-dose exposure to pesticides on the mental health of agricultural workers and emphasized the need for better characterization of both health problems and exposure.

Acute poisoning

Two new cohort studies exploring the link between acute pesticide poisoning and anxiety and depression disorders have been added to the 7 studies analyzed in the previous collective expert review. The first of these was a retrospective cohort study conducted in Great Britain among sheep farmers who used insecticides (in particular organophosphates) to control external parasites. The risk of reporting depression was increased 10-fold among individuals previously treated for pesticide poisoning, whereas no association was found among individuals who had handled these substances without a poisoning incident. The second was a prospective cohort study of South Korean farmers

who completed a depression scale as part of a face-to-face interview. Those who reported prior occupational poisoning with a pesticide had an increased risk of depressive symptoms, especially if the exposure was considered moderate to severe. These disorders were not associated with cumulative lifetime exposure. A link was found specifically with herbicides, and in particular with paraquat.

Chronic exposure

At the time of the 2013 collective expert review, the potential link between chronic pesticide exposure and neuropsychiatric disorders (in particular depression) had been examined by a dozen studies, including two with longitudinal designs. Since then, 7 cross-sectional and 5 longitudinal studies have been published, providing new insights in this area.

Cross-sectional studies have been conducted in South and Central America (coffee and tobacco crops in Brazil and vegetable crops in Mexico), Great Britain, Turkey, Bangladesh and France. The three American studies found an increase in symptoms of depression and anxiety in exposed individuals, both among agricultural workers and residents of agricultural areas. Links were also found among British sheep farmers, based on their reported symptoms. In Turkey, exposure to pesticides among men working in agriculture doubled the risk of depression. The study conducted in Bangladesh did not find a risk of depression among individuals living within 200 meters of fields. The French study, conducted as part of a case-control study of Parkinson's disease, found a link between exposure to herbicides and the existence of depression treated or managed in hospital, as reported by study participants, with an effect of exposure duration. The new cross-sectional analyses conducted in these various countries thus suggest an increase in the risk of anxiety and depression disorders in association with chronic pesticide exposure. This increase is lower than that observed in the context of acute poisoning, but may still be up to two-fold.

Three of these studies suggested links with various herbicides (including sulfonylureas, dinitroanilines, carbamates, dinitrophenols, glyphosate and picolinic acid), but not with organophosphate pesticides.

Two new longitudinal analyses were conducted as part of the Agricultural Health Study, in addition to a retrospective cohort study of cereal growers in Canada and two prospective agricultural cohort studies: one in Korea and the other in Iowa. In the 2013 collective expert review, the publications on anxiety and depression within the AHS were cross-sectional in nature and found a risk of a two- or three-fold increase in depression associated with acute pesticide poisoning. Within the same cohort, longitudinal analyses have since been conducted on the incident cases between baseline and follow-up at 12 years. In men, depression was associated with the use of certain substances or pesticide families (such as fumigants, organochlorines, aluminum phosphide, ethylene dibromide, 2,4,5-T, dieldrin, diazinon, malathion, parathion, lindane, and captan), in some cases related to cumulative exposure over a working lifetime. A strong association was observed between depression and a history of pesticide poisoning. In women, there was no evidence of a link between professional use of pesticides, either by them or by their spouses, and depression, however an increased risk of depression was observed among those with a history of acute poisoning. In the cohort of Canadian cereal growers, mental health scores were negatively associated with the use of phenoxy herbicides, but no association was found with other substances, including organophosphates. In South Korea, incident cases of depressive symptoms over a period of almost 3 years occurred more commonly among men with a high exposure score – based on duration and intensity – and among those with a history of acute poisoning. In Iowa, a cohort study of 257 farmers, followed up on a quarterly basis, found an association between pesticide use and depression. All of the new longitudinal analyses conducted since the previous expert review point toward

an association between chronic pesticide exposure and the development of anxiety and depression disorders, with strong links for individuals with a history of acute poisoning. Three of these analyses suggest links with various substances.

Nine studies presented in the previous collective expert review suggested a possible link between pesticide exposure and the risk of suicide. However, these did not provide sufficient evidence to distinguish the specific role of pesticides from that of other risk factors, nor to prove the causal nature of the link. Since then, three further studies have been published: a South Korean agricultural cohort study, a case-control study in China, and an ecologic study in Brazil. In the South Korean cohort study, suicidal ideation in the year prior to the interview was up to three times more common among farmers reporting a history of acute pesticide poisoning. In China, the case-control study of individuals who had attempted to end their lives with pesticides (43 cases) revealed a higher frequency of symptoms related to organophosphate exposure, aggressiveness, and impulsivity than in the general population. The Brazilian ecologic study found excess mortality by suicide in relation to both the farming profession and the fact of living in an area where tobacco crops were present (in connection with treatments and/or nicotine poisoning). These new studies suggest a link between pesticide exposure and suicide, but, like previous work, they are limited by difficulties in ruling out confounding factors related to the agricultural setting.

In view of the epidemiologic findings, the role played by certain pesticides in relation to the central nervous system and possible interference with neurotransmitters involved in mood regulation should prompt mechanistic research.

Presumption of a link between exposure to pesticides and anxiety and depression

Exposure	Populations	Presumption of a link
Acute occupational exposure or history of pesticide poisoning (without distinction)	Farmers or applicators	+ [a]
Chronic occupational exposure to pesticides (without distinction)	Farmers or applicators	+ [b]

+ [a] based on the results of three cohort studies and cross-sectional studies
Degree of presumption raised from weak to moderate

+ [b] based on the results of four cohort studies and seven cross-sectional studies
Degree of presumption raised from weak to moderate

Alzheimer's disease

Alzheimer's disease is a neurologic condition characterized by cerebral atrophy accompanied by senile plaques (extracellular amyloid-β peptide deposits) and neurofibrillary tangles (accumulation of phosphorylated Tau protein). It is the most common cause of dementia in the elderly, affecting between 15 and 40% of persons aged 85 years and older. Other than age and female sex, the only recognized risk factor for the disease is the epsilon 4 allele of the gene coding for apolipoprotein E (APOE4). Other risk factors are suspected, including head trauma, depression, parent age, family history of dementia, vitamin B12 or folate deficiency, elevated plasma levels of homocysteine, and vascular risk factors such as hypertension. The proportion of familial cases is low (about 10%), suggesting the possible contribution of environmental factors including solvents, electromagnetic fields, lead, aluminum, and pesticides.

The 2013 collective expert review identified some 10 studies exploring the potential link between pesticides and Alzheimer's disease. The results of the case-control studies, that were based on imprecise definitions of exposure (job titles listed on death certificates, and ecologic data on pesticide use) were generally inconclusive. Complicating this, the memory problems experienced by patients make it difficult to retrace their history of

exposure to pesticides. Three existing cohort studies, which collected data on exposure prior to the onset of the disease in sufficient detail, did however identify a significant increase in risk from occupational use of pesticides. This was as high as a four-fold increase for users of defoliants and fumigants in a Canadian study, and a two-fold increase in the other two cohort studies in France and the United States. The studies, mainly carried out in an agricultural setting, did not allow for conclusions regarding certain pesticides, as they investigated insecticides and organophosphates in particular.

Recently, a meta-analysis of epidemiologic studies on the role of pesticides in Alzheimer's disease included seven studies, all identified in the previous collective expert review: three cohort studies (France, United States, and Canada) and four case-control studies (Australia, United States, and Canada), judged to be of high-quality by the authors of the meta-analysis. Based on these studies as a whole, a 34% increase in risk was calculated for individuals exposed to pesticides in an occupational setting, with no between-study heterogeneity or publication bias identified.

Three new studies have been published on the link between pesticides and Alzheimer's disease since the previous collective expert review. All were designed to assess the exposure of individuals to organochlorines using biomarkers, due to the particular difficulties encountered retracing the history of exposure in individuals with memory problems.

One Canadian prospective cohort study looked at the onset of Alzheimer's disease with follow-up of individuals aged 65 years and older. In a subsample of this cohort, exposure to pesticides was estimated from plasma levels of eleven organochlorines. After a 10-year follow-up period, no evidence was found of a link between such exposure and the onset of Alzheimer's disease.

Two new case-control studies have also been conducted, one in the United States and the other in India. In the former, a four-fold increase in the risk of Alzheimer's disease was observed in

individuals with the highest serum levels of dichlorodiphenyldichloroethylene (DDE), and a strong correlation was observed between serum DDE and levels of DDE in brain samples. In the Indian study, some organochlorines and their metabolites (β-hexachlorobenzene (β-HCH), dieldrin and p,p'-DDE) measured in blood samples, were also higher in patients with Alzheimer's disease.

Presumption of a link between exposure to pesticides and Alzheimer's disease

Exposure	Populations	Presumption of a link
Pesticides (without distinction)	Occupational users	+

+ based on the results of three prospective cohort studies in 2013, two case-control studies and a meta-analysis including the studies analyzed in 2013; the new studies do not alter the degree of presumption.

Parkinson's disease

Parkinson's disease is the most common neurodegenerative disorder after Alzheimer's disease. It is linked to the gradual loss of dopaminergic neurons in a mesencephalic structure involved in regulating the activity of the basal ganglia, the *substantia nigra pars compacta*, which plays an important role in motor control. This neuronal loss is characterized by the presence of typical neuronal inclusions (Lewy bodies) and aggregation of the protein α-synuclein. Based on *Assurance Maladie* (French health insurance) data, nearly 170,000 people are estimated to have been treated in France for Parkinson's disease in 2015 (prevalence = 2.50 per 1,000 persons) and there are approximately 25,000 new treated cases each year (incidence = 0.39 per 1,000 person-years). Overall, the incidence of Parkinson's disease is 1.5 times higher in men than in women. Given increasing life expectancy and assuming a constant incidence, the number of prevalent cases is projected to gradually increase to 260,000 by 2030: approximately 1 in 120 people over 45 years of age.

The 2013 Inserm collective expert review primarily examined the literature on the relationship between occupational pesticide

exposure and Parkinson's disease. It concluded that there was an association between occupational exposure to pesticides and Parkinson's disease, but it was more difficult to draw conclusions regarding the effect of specific pesticides. In its 2013 and 2016 reports, the European Food Safety Authority (EFSA) came to the same conclusion. According to the most comprehensive and detailed meta-analysis available at the time, the association was particularly strong for herbicides and insecticides. Among the herbicides, some studies found an association with paraquat and 2,4-D. Among the insecticides, several studies found evidence supporting an association with organochlorine pesticides. A review of the toxicology literature also found evidence supporting the role of certain active substances or pesticide families in various mechanisms involved in the etiology of Parkinson's disease (oxidative stress and mitochondrial dysfunction, activation of dopamine metabolism, formation of cytoplasmic aggregates of α-synuclein, and apoptosis).

Several reviews and meta-analyses have been published since the previous collective expert review. Overall, all the meta-analyses confirm the existence of an association between pesticide exposure (primarily occupational) and risk of Parkinson's disease, and do not provide any new information compared to the meta-analyses discussed in the 2013 report. A few new studies, including three in France (two cohort studies and one case-control study), found an increase in the frequency of Parkinson's disease among farmers and an association with occupational pesticide exposure. Some of these studies demonstrate a dose-response relationship and show that, in addition to duration, the intensity of exposure is an important consideration. With regard to analyses by pesticide family or active substance, two meta-analyses on paraquat found significant associations, in line with the findings in 2013. The AGRICAN cohort study explored the link with 14 pesticides (11 dithiocarbamate fungicides, paraquat, diquat and rotenone). The analyses found an association for all of these substances, but after adjusting for exposure to at least one other pesticide, only the association for

ziram and zineb remained significant, with the association for mancopper at the threshold of significance. In analyses that took into account the duration of exposure, there was a significant trend for 7 of the 14 active ingredients; when the analyses were adjusted for exposure to at least one other pesticide (without distinction), the trend was significant for mancopper ($p = 0.04$), but there was no trend for zineb and ziram. One Dutch cohort study notes an increased risk for benomyl but these results are not corroborated by the AHS cohort study.

Presumption of a link between exposure to pesticides and Parkinson's disease

Exposure	Populations affected by excess risk	Presumption of a link
Pesticides (without distinction)	Occupational users	++
Herbicides (without distinction)		++
Insecticides (without distinction)		++
Pesticides (without distinction)	General population or local residents of treated areas	±

++ based on the results of the most recent meta-analysis in 2013; several additional meta-analyses do not alter the conclusion.
± based on the results of a 2013 case-control study and recent ecologic studies New data

The 2013 collective expert review highlighted the lack of studies on the role of environmental exposure to pesticides. Only case-control studies based on the California pesticide use reporting system were available at that time. Environmental exposure to pesticides was assessed by combining places of residence and work with pesticide use reports, using a geographic information system. An association was found between environmental exposure to certain tracer pesticides and Parkinson's disease. Several studies, carried out in France and other countries with different methodologies, have since been published and provide additional information. These found evidence supporting an increased risk of Parkinson's disease in relation to environmental pesticide exposure and proximity of residence to treated agricultural land. The studies report associations for a few active ingredients (mancozeb and

maneb), but as many are ecologic in design and can only provide imprecise indicators of exposure, further research, ideally based on individual data, is still required.

For both occupational and environmental exposure to pesticides, it remains difficult to isolate the role of specific products or families of products. The studies available often look at different products, and therefore only partially overlap, and the statistical analyses do not always take into account the question of exposure correlated to several products. However, in addition to the substances previously identified in 2013 (paraquat, rotenone and organochlorine insecticides, in particular dieldrin), two new recent meta-analyses confirm the link with paraquat (+), but the results for dieldrin are unchanged and the degree of presumption of a link remains weak (±) and is not shown in the table. The new studies point to associations with the following families or active substances: organophosphate insecticides, dithiocarbamate fungicides (mancozeb, maneb, zineb, ziram, and mancopper) and carbamate fungicides (benomyl). Some of these results are based on ecologic studies, are at the threshold of statistical significance, or raise the question of correlations between products, and have not been included in the table (organophosphates, mancozeb, maneb, benomyl) and require confirmation by further studies.

Finally, none of the studies address the role of early exposure to pesticides, either during pregnancy or childhood.

Families and active substances associated with excess risk of Parkinson's disease

Family Active substances	Population	Presumption of a link
Organochlorines		
Insecticides	Occupational users	++
Dithiocarbamates (fungicides)		
Mancopper	Farmers	±
Zineb	Farmers	±
Ziram	Farmers	±

Other		
Paraquat	Farmers	+ [a]
Rotenone	Farmers	+ [b]

++ based on the results of several cohort studies
+ [a] based on the results of a cohort study in 2013 and two meta-analyses (mainly including studies analyzed in 2013); the new studies do not alter the degree of presumption; + [b] based on the results of a cohort study in 2013; ± based on the results of a cohort study (AGRICAN) New data

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that causes muscle weakness combined with stiffness that gradually spreads and results in death due to respiratory insufficiency and difficulties swallowing. It occurs secondary to degeneration of motor neurons in the spinal cord (anterior grey column), brain stem and cerebral cortex. The median clinical course is 30 months on average from the initial symptoms, and 19 months from diagnosis.

ALS is the most common motor neuron disease, and nearly 2,200 people are estimated to have developed motor neuron disease each year in France over the period 2012-2014. Several studies suggest that ALS mortality and incidence have increased in recent decades, but the reasons for this change remain poorly understood. Several genetic and environmental factors are likely to be involved in the etiology of ALS. Among the environmental risk factors, smoking appears to be associated with an increased risk of ALS, along with exposure to lead, while the role of physical activity and trauma, including head injuries, is still uncertain.

The 2013 Inserm collective expert review identified a dozen studies on the relationship between ALS and occupational exposure to pesticides. Two meta-analyses supported an association, but the studies on which these were based were heterogeneous, particularly in terms of the methods used to assess exposure. Publication bias was also difficult to assess given the small number of studies available. The collective expert review

concluded that there was a need for large-scale studies using more precise methods of assessing exposure (including product types and duration of exposure) in order to better characterize the relationship between occupational exposure to pesticides and ALS.

Since the previous expert review, two meta-analyses have been published supporting an association between pesticide exposure (primarily occupational) and risk of ALS. These are based on studies published in 2012 or earlier, most of which were already included in the previous meta-analyses. The association was similar in the case-control and cohort studies. It was however higher for men than women, and in studies where pesticide exposure was assessed by experts compared to those based on self-reporting. There was no statistical evidence of publication bias.

Four original studies have been published on the subject since the previous collective expert review. Some of these provide evidence supporting an association between occupational exposure to pesticides and ALS, but they are heterogeneous, particularly in relation to the evaluation of exposure and consideration of confounding factors. Two cohort studies have been published, in the Netherlands and France: the first, based on a small number of exposed cases, found no association, whereas the second did not look at pesticide exposure, but found an increasing trend in the incidence of ALS among French farmers compared to the general population. Only two studies considered the role of environmental exposure, and they do not allow conclusions to be drawn due to conflicting results.

These new studies do not significantly alter the conclusions of the 2013 collective expert review. Large studies using more precise methods of evaluating exposure (including product types and the duration of exposure) remain necessary in order to better characterize the relationship between occupational exposure to pesticides and ALS, and to determine whether environmental exposure plays a role.

Presumption of a link between exposure to pesticides and amyotrophic lateral sclerosis

Exposure	Populations affected by excess risk	Presumption of a link
Pesticides (without distinction)	Farmers	±

± based on the results of two meta-analyses in 2013, two recent meta-analyses (which included studies analyzed in 2013), two cohort studies (Netherlands and France) and several hospital-based case-control studies; no new studies providing evidence to alter the degree of presumption

Cancers

Some cancers were previously analyzed in the 2013 expert review, and the data have been updated for childhood cancer, central nervous system (CNS) tumors, hematologic malignancies, and prostate cancer. Other types of cancer are considered in this expert review for the first time, including breast cancer, kidney and bladder cancers, and soft tissue and visceral sarcomas.

Childhood cancer

In France, approximately 1,700 new cases of cancer are diagnosed each year in children under 15 years of age. This number corresponds to an age-standardized incidence rate of around 15.6 cases per 100,000 children per year, comparable to the incidence rates observed overall in Europe and North America, although differences between countries persist for certain types of cancer. The incidence rate of childhood cancer in France has also remained fairly stable since 2000. Worldwide, cancer is one of the leading causes of death in children. In France in particular, it is the second leading cause of death among children aged 1-14 years, after accidents.

The main types of cancer diagnosed in children are acute leukemia (approximately 30% of new cases), central nervous system tumors (approximately 25%), lymphoma (approximately 10%),

and embryonal tumors (approximately 20%, comprising neuroblastoma, nephroblastoma, rhabdomyosarcoma, retinoblastoma, and hepatoblastoma).

Different etiologies are suspected for the various types of childhood cancer, but these are still poorly understood. The established risk factors for the main diagnostic groups are high-dose ionizing radiation and some rare genetic syndromes. The risk factors strongly suspected of playing a role in the onset of childhood cancers include genetic predisposition, infections, and exposure to environmental contaminants, in particular traffic-related pollution and pesticides.

Based on the results of several meta-analyses published prior to 2013, the previous Inserm collective expert review concluded there was a strong presumption of a link (++) between maternal occupational and domestic exposure to pesticides (insecticides and herbicides, without distinction) during pregnancy and the risk of leukemia in children. Similarly, there was a strong presumption of a link (++) between domestic exposure to pesticides use during childhood and the risk of leukemia.

Since then, four meta-analyses have been published: three exploring exposure linked to domestic pesticide use by parents (or by professionals), and one on occupational exposure.

These recent meta-analyses confirm the increased risk of acute leukemia in children from maternal exposure to pesticides due to domestic use during pregnancy and from childhood exposure. The first, a pooled analysis of individual data from the Childhood Leukemia International Consortium (CLIC), found a 43% increase in the risk of acute lymphoblastic leukemia (ALL) in children whose mothers were exposed to pesticides through domestic use during pregnancy (9 studies) and a 55% increase in the risk of acute myeloid leukemia (AML; 7 studies). An association was also reported between children's exposure to pesticides through domestic use after birth and the risk of ALL, but not AML, regardless of the categories of pesticides used (insecticides, herbicides, fungicides or rodenticides). The second

meta-analysis confirmed that exposure to pesticides through domestic use in the pre- and post-natal periods was associated overall with an increased risk of ALL (8 studies) and AML (5 studies), with similar increases in risk to those found in the first meta-analysis. The third meta-analysis also reports a link between pesticide exposure during pregnancy and the risk of leukemia. We note that the results of these meta-analyses are not independent as all three include the CLIC studies, which are assigned significant weight in the analyses.

The positive association previously observed between maternal occupational exposure during pregnancy and the risk of AML in children was confirmed by a meta-analysis based on 13 CLIC studies, along with early studies from outside the consortium and other recent studies. This research also found a three-fold increase in the risk of AML in children whose mothers were most exposed to pesticides in an occupational setting during pregnancy (9 studies). An increased risk of ALL was also suggested, particularly by the pooled analysis of the CLIC studies (over 8,000 cases of acute leukemia and 14,000 controls) in cases of paternal occupational exposure to pesticides in the preconception period. However, the results of the studies included in the analysis were highly heterogeneous.

A meta-analysis of childhood cancers and several small case-control studies also suggests an association between exposure from domestic pesticide use and the risk of non-Hodgkin lymphoma in children (weak presumption of a link).

Presumption of a link between exposure to pesticides and hematologic malignancies in children

Exposure	Effects	Presumption of a link
Maternal occupational exposure to pesticides (without distinction) during pregnancy	Leukemia (AML)	++ [a]
Paternal occupational exposure to pesticides (without distinction) in the preconception period	Leukemia (ALL)	+

Domestic exposure (home use) to pesticides (without distinction) during pregnancy or in the child's home	Leukemia (ALL and AML)	++ [b]
Domestic exposure to pesticides (without distinction) during pregnancy or in the child's home	Non-Hodgkin lymphoma	±

++ [a] based on the results of two meta-analyses in 2013 and an additional meta-analysis; strengthens the 2013 results
+ based on a meta-analysis (with between-study heterogeneity) and a case-control study New data
++ [b] based on the results of two meta-analyses in 2013, and three additional meta-analyses; strengthens the 2013 results
± based on the results of a meta-analysis of three studies and the results of several small studies New data
ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia

The 2013 Inserm collective expert review also concluded that there was a strong presumption of a link between paternal and maternal occupational exposure to pesticides during the prenatal period and the risk of CNS tumors in children. Only a few recent studies have examined the link between pesticide exposure and the risk of CNS tumors in children, and these have mainly focused on exposure related to domestic pesticide use (insecticides and herbicides) during pregnancy and childhood.

Two meta-analyses have been published, one including 18 studies published between 1979 and 2016, and the other including only some of these studies. The authors of the first meta-analysis reported a positive association between pesticide exposure through domestic use and the risk of CNS tumors in children, with a 26% increase in risk. The analyses found a positive association of a similar scale by pesticide category (insecticides and herbicides) and suggested an association with the risk of glioma.

Recently, a case-control study, pooling data from two French studies (ESCALE and ESTELLE) conducted in the general population, found a positive association between maternal domestic use of pesticides (mainly insecticides) during pregnancy and the risk of CNS tumors in children, with a 40% increase in risk, observed overall and for the main types of CNS tumors (ependymomas, embryonal tumors, and gliomas).

An increased risk of CNS tumors in children has thus consistently been reported. The findings apply to CNS tumors as a whole, as the studies do not enable firm conclusions to be made in relation to the various subtypes.

At present, there are still few geographic studies focusing on childhood cancers (mainly leukemia and CNS tumors) related to the presence of crops or the use of agricultural pesticides near the home. The results are heterogeneous and do not provide a basis for firm conclusions regarding the presumption of a link.

Positive associations with exposure to pesticides have been suggested for other types of childhood cancer (in particular embryonal tumors), but definitive conclusions are not possible given the current state of scientific evidence.

Presumption of a link between exposure to pesticides and central nervous system tumors in children

Exposure	Effects	Presumption of a link
Parental occupational exposure to pesticides (without distinction) during the prenatal period	Central nervous system tumors	++ [a]
Domestic exposure (home use) to pesticides (without distinction) during pregnancy or in the child's home	Central nervous system tumors	++ [b]

++ [a] based on the results of a meta-analysis in 2013
++ [b] based on the results of two meta-analyses and a case-control study New data

Central nervous system tumors in adults

Primary central nervous system tumors are a diverse group of tumors that develop from specialized cells. They include numerous histologic types, which are classified based on their origin into several groups: primarily neuroepithelial tumors (largely represented by gliomas), tumors of the meninges, tumors of the cranial nerves, and primary CNS lymphoma. Neuroepithelial tumors represent almost half of CNS tumors. They originate either from neurons or from glial cells surrounding the neurons.

Central nervous system tumors are rare, and malignant forms account for 1.5% of all forms of cancer in France. The incidence rate of malignant forms is approximately 11 cases per 100,000 person-years. Combined with 'benign' tumors (in particular meningiomas), which can also have a poor prognosis, the incidence rate is 20 per 100,000 person-years according to the Gironde registry. Other than ionizing radiation and certain specific genetic syndromes, no etiological factors have been established for central nervous system tumors, regardless of histologic type.

The 2013 collective expert review included around twenty studies on the link between brain tumors and pesticides, not including historic cohort studies and occupational case-control studies (based on job titles) that assessed pesticide exposure rather poorly, or involved a very small number of cases.

Based on these data, the 2013 collective expert review concluded that there was a weak presumption of a link between exposure to pesticides in agricultural populations and brain tumors (glioma and meningioma) but was unable to draw conclusions regarding specific active substances. Only one result regarding an active substance is reported: a significant increase in the risk of incidence of brain tumors in the Agricultural Health Study (AHS) cohort in individuals with the highest level of exposure to chlorpyrifos.

Since then, 12 new studies have been conducted, including 1 meta-analysis, 7 cohort analyses (4 of the AHS and 3 of AGRICAN) and 4 case-control studies.

While previous meta-analyses largely focused on risk of brain tumors in the agricultural setting, without distinction by tumor type or study design and without considering exposure to pesticides, the new meta-analysis was based on 11 case-control studies that estimated the risk of glioma in adults in relation to exposure to pesticides. It concluded that there was a non-statistically significant 15% increase in risk, but highlighted the small number of studies and between-study heterogeneity.

The four new case-control studies were conducted in Italy (two studies), France and India. In Italy, the two hospital-based case-control studies, conducted in two different regions, found increases in risk among farmers: one found a two-fold increase, and the other a three-fold increase. In France, the CERENAT study included around 600 cases and 1,200 controls in Gironde, Calvados, Manche, and Hérault. Based on a lifetime residential history, the analysis took into account exposure related to residential proximity to agricultural areas. Trends toward increased risk of meningioma were observed for individuals who had lived in areas with field crops, vines, orchards. This increase became statistically significant for the highest scores of exposure near field crops. In India, in a fruit-growing region, decreased levels of acetylcholinesterase were observed in individuals with primary brain tumors. As such, the four new case-control studies suggest an increase in risk in an agricultural setting but do not provide sufficient evidence to determine the strength of the association or the substances potentially involved.

New results have also been obtained from the two large prospective cohort studies: AHS in the United States and AGRICAN in France. In the AHS cohort, analyses of pesticide applicators did not find any association with alachlor and metolachlor. However, among the spouses of applicators, an increase in the risk of glioma was observed in relation to the use of organochlorines, particularly for those who had used lindane. Among the same spouses, no significant association was found with organophosphates. A follow-up analysis of the AGRICAN cohort through 2011 has also produced new data on central nervous system tumors. Individuals who had worked with at least one crop or form of livestock had an increased risk of tumors (both meningiomas and gliomas). The risks were higher for certain crops: forage peas, beet, and potatoes. Pesticide users were also twice as likely to develop a central nervous system tumor compared to other cohort participants. Specific analyses were conducted for carbamate pesticides (insecticides, fungicides and herbicides). Exposure to these substances increased

the risk of glioma and meningioma, particularly in the context of lengthy exposure, and the risk was greater for certain substances, with up to a three-fold or four-fold increase in risk.

Data from mechanistic studies of lindane, chlorpyrifos and some carbamates in neuronal models strengthen the plausibility of an association with central nervous system tumors. Lindane, a proven carcinogen, disrupts protein synthesis and transport. Several potential avenues may explain a carcinogenic effect from chlorpyrifos or its metabolites: *i*) blocking differentiation and maintenance in a proliferative state due to decreased levels of cAMP or production of reactive oxygen species; and *ii*) cell survival promoted by an increase in transglutaminase 2 activity. Mutagenic and genotoxic effects have been shown for carbamates, but at relatively high doses. Two members of this family, maneb and ziram, have been specifically studied in relation to Parkinson's disease, and their effects thought to contribute to this disease (protein aggregation and pro-oxidant activity) may also explain certain carcinogenic processes. Other potential mechanisms have also been highlighted, including endocrine or metabolic disruption, mitochondrial toxicity, immunomodulatory effects, and modification of the distribution of other contaminants. These effects require validation in other experimental models (such as co-cultures, 3D systems, and "brain organoids") and through studies of these pesticides in combination or in the presence of other carcinogens.

Presumption of a link between exposure to pesticides and central nervous system tumors (glioma and meningioma)

Exposure	Populations affected by excess risk	Presumption of a link
Pesticides (without distinction)	Agricultural populations	+

+ based on the results of three meta-analyses, cohort studies and cross-sectional studies in 2013, and the results of two cohort studies (AHS and AGRICAN) and four case-control studies
Degree of presumption raised from weak to moderate

Hematologic malignancies in adults

Hematologic malignancies are tumors of hematopoietic tissues, such as bone marrow or lymphoid tissue (for example lymph nodes and spleen). They are characterized by monoclonal proliferation of blood or immune cells at various stages of maturation. Advances in the understanding of hematologic malignancies have led to many changes in the way in which these diseases are classified, diagnosed and treated. Since 2001, the World Health Organization (WHO) has produced a new consensus-based classification that defines hematologic malignancies according to their cellular lineage, genetic abnormalities, and clinical characteristics. This was updated in 2008 and 2016, and is incorporated into the International Classification of Diseases for Oncology (ICD-O-3). Leukemias are "liquid" tumors that originate from the transformation of hematopoietic precursor cells in the bone marrow or mature hematopoietic cells in the blood. Leukemias can be lymphoid or myeloid, and acute or chronic. In lymphoma, the transformation of lymphocytes in secondary lymphoid tissues usually results in a disease that presents clinically as a solid tumor. Lymphomas are classified as either Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL), and numerous subtypes exist.

Distinguishing between disease entities on the basis of morphologic, phenotypic, genotypic, and clinical characteristics reflects a paradigm shift in the approach to classifying hematologic malignancies. While maintaining original classifications is useful for historic comparisons, contemporary descriptive statistics, at least in Western countries, produce detailed epidemiologic data by subtype, to reflect the current state of knowledge. With a view to clarity, we have decided to maintain the four groups used in the 2013 Inserm collective expert review (non-Hodgkin lymphoma, multiple myeloma, Hodgkin lymphoma, and leukemia). This enables readers to identify and compare the new epidemiologic data with the data included in the previous Inserm collective expert review.

Non-Hodgkin lymphoma

NHL are characterized by monoclonal proliferation of lymphocytes at different stages of their differentiation. In many respects, the different types of NHL appear to reflect the various steps of B or T cell differentiation, and to some extent, they can be classified according to the corresponding normal cell. However, this is not always necessarily the case and the normal counterpart of the tumor cell cannot be used as the sole basis for classification. The WHO classification distinguishes the types of NHL on the basis of morphologic and immunologic characteristics. The stage of differentiation, morphology, and phenotypic, genotypic, and clinical features are also used to distinguish between different subtypes of NHL. NHL therefore encompass a diverse spectrum of disease entities that differ in their pathophysiology, histologic diagnosis, biology, and prognosis.

NHL account for 60% of hematologic malignancies, with around 27,000 new cases in 2018 in mainland France. The incidence rates standardized to the world population are 25.5 and 16.1 per 100,000 person-years in men and women, respectively.

There was a 123% increase in the number of cases between 1990 and 2018 in men (7,000 to 15,500 incident cases) and a 109% increase in women (5,800 to 12,100 incident cases), half of which can be explained by population growth and aging. The other half of this increase corresponds to increased risk, whether linked to improved diagnosis, improved access to care, or risk factors with increasing prevalence. The average annual change in incidence rates standardized to the world population was 1% between 1990 and 2018 in men and women. The changes in incidence rates vary across the histologic subtypes of NHL, but most are following an increasing trend.

The main subtypes of NHL are diffuse large B-cell lymphoma (incidence rates of 4.7 and 3.2 per 100,000 person-years in men and women, respectively, in 2018 in France; 5,071 new cases estimated in 2018), follicular lymphoma (incidence rates of 2.9

and 2.0 per 100,000 person-years in men and women, respectively, in 2018 in France; 3,066 new cases in 2018), marginal zone lymphoma (incidence rates of 2.3 and 1.7 per 100,000 person-years in men and women, respectively, in 2018 in France; 2,790 new cases in 2018). The incidence of these three lymphoid malignancies has been increasing since the 1990s. It should be noted that multiple myeloma is one of the most common lymphoid malignancies. It is now grouped together with NHL but will be discussed in a separate section, as is chronic lymphocytic leukemia, which is now grouped together with small lymphocytic lymphoma in a single entity that will be discussed in the section on leukemia. These five diseases account for 80% of new cases of NHL diagnosed each year in France.

The 2013 Inserm collective expert review concluded that there was a strong presumption of a link between exposure to pesticides (without distinction between groups of chemicals or active substances) among farmers, pesticide applicators and individuals working in the pesticide production industry, and the risk of NHL.

The expert review also examined the association between NHL and specific pesticide families or active substances. The majority of these findings were derived from the American AHS cohort. The results of several studies (based on cohort, nested case-control, or case-control designs), show that occupational exposure to certain active substances is associated with a significant excess risk of NHL for farmers, applicators, livestock farmers, and individuals working in the production industry. Specific associations have been reported for lindane, dichlorodiphenyltrichloroethane (DDT), terbufos, diazinon, malathion, butylate, the phenoxy herbicide 2,4-D and glyphosate. The presumption of a link was qualified as weak "±" in several situations: for example, when it was based on a single case-control study, when other families or active substances were considered, or where the studies concerned occupational populations defined more broadly than farmers, or populations

exposed outside the profession. No analysis by histologic subtype was available.

Since the 2013 Inserm collective expert review, thirteen meta-analyses have been published (two addressing exposure to several families or active substances, ten focusing on a specific family or active substance, and the final one dealing with livestock farmers). All of these include analyses by subtype of NHL. Three cohort analyses have been published; two based on AHS data and one based on the Women's Health Initiative general population cohort. Finally, three case-control studies also present persuasive results. The first two meta-analyses are the most complete but differ in terms of their nature. The first provides an exhaustive review of the published case-control and cohort studies, then reports estimates of associations between NHL and 21 families of pesticides and 80 active substances, while the second is derived from the consortium of agricultural cohort studies (AGRICOH) and examines the role of exposure (14 families of pesticides and 33 active substances) in relation to the risk of developing NHL and its major subtypes.

The first meta-analysis found that several families of pesticides (phenoxy herbicides, carbamate insecticides, and organophosphate insecticides) were positively associated with the risk of NHL. Several active substances were also associated with the risk of NHL (lindane, dicamba, DDT, carbaryl, carbofuran, diazinon, malathion, and glyphosate). However, dose-response relationships were not evaluated in this study (yes/no analysis). The risk of B-cell lymphoma was associated with exposure to phenoxy herbicides (as was the risk of diffuse large B-cell lymphoma), glyphosate and DDT (as was the risk of follicular lymphoma). In the second meta-analysis, from the AGRICOH consortium, most of the combinations tested were not statistically significant, with the exception of terbufos and the risk of NHL, and glyphosate with the risk of diffuse large B-cell lymphoma, after adjusting for other pesticides. There was no evidence of between-study heterogeneity across the three cohorts.

Between 2013 and 2019, ten other meta-analyses investigated the relationship between a specific family of pesticides or active substance and the risk of NHL: two on organochlorines, one on organophosphates, one on carbamate and organophosphate insecticides, three on glyphosate, two on the phenoxy herbicide 2,4-D, and one on pentachlorophenol.

The first meta-analysis reported an increased risk of NHL with the organochlorine pesticides, and strong associations with dichlorodiphenyldichloroethylene (DDE), hexachlorocyclohexane (HCH), hexachlorobenzene (HCB), and chlordane. However, no association was observed with DDT. The recent North American Pooled Project study reported positive associations between several organochlorine active substances and various NHL subtypes, in particular for lindane, chlordane, and DDT: lindane with follicular lymphoma, diffuse large B-cell lymphoma and small lymphocytic lymphoma; chlordane with follicular lymphoma and small lymphocytic lymphoma; and DDT with diffuse large B-cell lymphoma and small lymphocytic lymphoma. This analysis suggests a possible etiological heterogeneity within NHL with respect to exposure to the active substances studied.

The meta-analysis on organophosphates found a statistically significant increased risk of NHL associated with exposure to one of three active substances: malathion, diazinon, and terbufos. This association was significant only for studies with case-control or case-control nested within a cohort designs. Some of these findings are supported by another meta-analysis focused on carbamate and organophosphate insecticides, in particular the risk found for malathion, which increased with the duration of exposure reported by farmers. These results were also observed for the diffuse large B-cell lymphoma and follicular lymphoma subtypes. An analysis considering the effect of combined exposure to all the organophosphate and carbamate insecticides examined found an association between the duration of exposure and the risk of NHL.

In the meta-analyses focusing on exposure to glyphosate, the risk of NHL was increased by 30 to 45% depending on whether the risk was assessed across all subjects (exposed versus non-exposed) or only in the most exposed groups. In a meta-analysis of case-control studies, adjustment for exposure to other pesticides decreased the risk, an effect not found in the meta-analysis based on data from the agricultural cohort studies.

With respect to 2,4-D, the authors looked at the highest level of exposure in each study and identified a statistically significant positive association with the risk of NHL. However, given the moderate level of between-study heterogeneity, a degree of caution is required when interpreting the results.

The most recent analysis of the AHS cohort considered 26 families of pesticides or active substances. A positive association with exposure to terbufos was found (without an exposure-response relationship). However, the risk of NHL associated with exposure to DDT or lindane increased with the total number of days of exposure, although no association was observed in a binary analysis (exposed/unexposed). A number of associations between active ingredients and certain subtypes of lymphoma were observed but these were based on a small number of exposed subjects: follicular lymphoma for lindane and diazinon.

The most recent analysis of the AHS cohort, focusing on glyphosate, found no increased risk of NHL or its major subtypes.

In the only published cohort study of women in the general population, those under 65 years of age who applied insecticides at least once had an increased risk of diffuse large B-cell lymphoma. The finding of a link between domestic exposure to insecticides and the risk of various subtypes of NHL merits further confirmation.

Along this same line, a case-control study provided information on the risk of NHL associated with exposure to an index of 27 correlated environmental chemicals, measured in household dust. The study found a positive association between exposure

and the risk of NHL and certain subtypes (follicular lymphoma and marginal zone lymphoma).

Finally, we note that recent research exploring the role of occupational agricultural exposure to pesticides on patient treatment outcomes found an association with treatment failure, event-free survival, and overall survival in patients with diffuse large B-cell lymphoma.

Taken together, the results strengthen the presumption of a link between NHL and exposure to pesticides, which remains qualified as "strong" as reported in the 2013 collective expert review.

Presumption of a link between exposure to pesticides and NHL

Exposure	Populations affected by excess risk	Presumption of a link
Pesticides (without distinction)	Farmers, applicators, production industry workers	++

++ based on the results of seven meta-analyses and one prospective cohort study (AHS) in 2013; the new studies do not alter the degree of presumption.

The conclusions on pesticide families and active substances associated with significant excess risk of NHL have been updated based on the results of the studies published since 2013, and for each case, the presumption of a link is classified as strong, moderate or weak. The links qualified as strong in 2013 remain unchanged (lindane, DDT, organophosphates and malathion), whereas the strength of the evidence for diazinon and chlordane is greater than in 2013, and the presumption of a link for diazinon is increased to strong. The presumption of a link between glyphosate and the risk of NHL in farmer populations is raised (from weak to moderate). A weak presumption of a link is reported for the first time with dicamba. The presumption of a link remains weak for the following active substances: aldrin, atrazine, carbaryl, carbofuran, coumaphos, chlorpyrifos, MCPA, mecoprop, and fonofos (not shown in the table).

Families and active substances associated with excess risk of NHL

Family Active substances	Populations affected by excess risk	Presumption of a link
Organochlorines		
Lindane (γ HCH isomer)	Applicators, farmers	++
HCH (mixture of isomers)	Livestock farmers	+
DDT	Farmers Occupational users	++ +
Chlordane*	Farmers	+
Dicamba	Farmers	±
Organophosphates		
Without distinction	Farmers Exposed individuals (occupationally or through domestic use)	++ +
Terbufos	Applicators	+
Diazinon*	Farmers	++
Malathion	Farmers	++
Carbamates / Dithiocarbamates		
Without distinction (carbamates)	Farmers	+
Butylate	Applicators	+
Triazines		
Without distinction	Production industry workers	+
Phenoxy herbicides not contaminated by dioxins		
2,4-D	Farmers	+
Aminophosphonate glycine		
Glyphosate*	Farmers, occupational users	+

++ at least one meta-analysis and at least one cohort study
+ at least one high-quality study (cohort study and/or several case-control studies)
± two positive case-control studies but a negative meta-analysis of three cohort studies New data
* Active ingredient for which the degree of presumption has been raised compared to 2013

New findings have been reported in special populations in which exposure to specific pesticide families or active substances has been shown to be associated with increased risk of NHL. These include farmers with a t(14;18) chromosome translocation, and those with a history of asthma or hematologic malignancy. For these populations, the conclusions remain unchanged compared to 2013 (table not shown). The approach that has emerged since 2013 of analysis by NHL subtype has, however, yielded interesting new results suggesting associations with certain pesticide active substances or pesticide families.

An entire chapter was devoted to the mechanisms of action of pesticides and hematologic cancers in the previous collective expert review. Only a few toxicological studies are discussed here in relation to the active substances for which analysis of the epidemiologic literature has revealed strong presumptions of a link: malathion, diazinon (organophosphates), DDT and lindane (organochlorines).

The previous collective expert review concluded that some organophosphates can be considered genotoxic and pro-oxidant in connection with the activation of certain signaling pathways involved in regulating cell proliferation and survival. Recent studies confirm that the mechanisms of action of malathion and diazinon consist primarily of production of reactive oxygen species, associated with an inflammatory state and genotoxicity. The potential immunosuppressive properties of malathion could also cause hematologic malignancies. Recent results also suggest that malathion has endocrine disruptor effects, and that diazinon alters DNA methylation profiles.

With respect to organochlorines, the 2013 collective expert review concluded, on the basis of studies conducted in several cell models and in particular in human lymphocytes, that DDT and its metabolite, DDE, could be considered pro-estrogenic and genotoxic, partly through production of oxidative stress. Immunomodulatory effects have also been observed with inhibition of natural killer (NK) cells, immune cells that induce lysis of tumor cells. This type of inhibition has also been described for lindane,

and a recent publication confirms its genotoxic effect. In addition, lindane may induce oxidative stress and activate pro-apoptotic processes in human lymphocytes, which is consistent with the immunosuppressive effects described for DDT.

The mechanistic effects of organochlorines (generation of oxidative stress, apoptosis and immunomodulation, genotoxicity) described in the literature to date support the plausibility of a relationship between chronic exposure to these compounds and the development of hematologic malignancies. Furthermore, while these compounds are potentially persistent, their ability to activate cytochrome P450 expression (perhaps by binding to xenobiotic receptors, which are also transcription factors), could alter the metabolism of various organs, including the lymphocyte compartment and promote a tumor phenotype. This intriguing hypothesis merits further investigation.

Multiple myeloma

Multiple myeloma (MM) is one of the most common hematologic malignancies in France. It is characterized by the presence of bone marrow infiltration by plasma cells, the presence of a non-IgM monoclonal protein (in serum and/or urine) and bone lesions (punched-out lesions or bone demineralization). There were an estimated 5,442 new cases of MM in mainland France in 2018. The incidence rates standardized to the world population are 4.2 and 2.9 per 100,000 person-years in men and women, respectively (male to female ratio of 1.4). The median age of MM patients at diagnosis is 70 years in men and 74 years in women. Incidence rates standardized to the world population increased during the study period in men and women, with an average annual change of +1.1% in men and +0.6% in women. Between 1995 and 2018, the number of MM cases increased from 1,440 to 2,822 among men and 1,510 to 2,620 among women. This 96% increase among men and 74% increase among women is attributable to demographic changes for 58% and 43% respectively, while 38% and 31%

of the increase is attributable to risk (partly related to improved diagnosis, improved access to care, or linked to risk factors).

Based on data from six meta-analyses and two cohort studies (the AHS and a North European cohort), the 2013 Inserm collective expert review concluded that there was a strong presumption of a link between exposure to pesticides, without distinction between chemical families or active substances, among farmers and pesticide applicators, and the risk of MM. The expert review was unable to come to a conclusion regarding the excess risk associated with exposure to specific active substances.

Since the previous expert review, five meta-analyses have been published; two based on data from three agricultural cohorts, one specifically focused on exposure to glyphosate, and two pooled analyses of case-control studies, including one looking at exposure to specific pesticides (carbaryl, captan, and DDT). The two meta-analyses based on data from three cohorts of agricultural workers found moderate associations with the use of certain active substances, but did not find a statistically significant association between exposure to most pesticide families or substances studied and the risk of MM. A significantly elevated risk was however observed for poultry and sheep farmers in the AHS cohort. The two pooled analyses from the InterLymph consortium, based on case-control studies conducted between the 1980s and 2000s in the general population, found that the profession of gardener/agricultural nursery worker was associated with the risk of developing MM, at the threshold of statistical significance (but not for the profession of farmer) and that the use of carbaryl, captan or DDT were all associated with a statistically significant increased risk of MM.

For glyphosate, a meta-analysis of case-control studies found a statistically significant elevated risk of MM in farmers exposed to glyphosate. This association was robust in several secondary analyses, and the analysis found no between-study heterogeneity or publication bias. However, the recent re-analysis of the AHS cohort did not find any association between glyphosate exposure and the risk of MM.

The most recent analysis of the AHS cohort found a statistically significant association between exposure to permethrin and risk of MM, that increased with exposure (p-trend = 0.002).

A study of the AGRICAN cohort found an elevated risk of MM among farmers, in particular those who started using pesticides on crops in the 1960s, on corn, and those who used insecticides on animals.

Finally, a Canadian case-control study reported positive trends indicating an increase in the risk of MM with the number of pesticides used, for fungicides, and with use of pesticides classified as probably carcinogenic by the International Agency for Research on Cancer (IARC). Men who reported using at least one carbamate pesticide, a phenoxy herbicide, or three or more organochlorines were at increased risk of MM. The herbicide mecoprop (when used on more than 2 days a year) was also significantly associated with the risk of MM.

Thus, the presumption of a link between occupational exposure to pesticides and MM remains strong, as it is based on several high-quality meta-analyses that have found significant associations.

Presumption of a link between exposure to pesticides and multiple myeloma

Exposure	Populations affected by excess risk	Presumption of a link
Pesticides (without distinction)	Farmers, applicators	++
	Livestock farmers	+

++ based on the results of six meta-analyses and two prospective cohort studies (AHS and North-European cohort) in 2013; the new studies do not alter the degree of presumption.

+ based on the results of a meta-analysis of three cohort studies New data

The evidence pointing to a role of specific active substances in MM remains weak, but it does allow a few to be identified, which was not the case in 2013. Exposure to permethrin was shown to be associated with an increased risk of MM in the AHS, with a significant exposure-response trend. This exposure

leads to alterations in blood parameters that may indicate disrupted hematopoiesis, which supports the biologic plausibility of the association observed between the use of permethrin and the risk of MM in pesticide applicators. A positive association was found for glyphosate in a meta-analysis of case-control studies, but not in a meta-analysis of the three agricultural cohort studies (US, France, Norway) or the most recent analysis of the AHS cohort. Associations were also found with carbaryl, captan and DDT, based solely on a well-conducted case-control study. For these substances, the presumption of a link is considered weak (±).

Families and active substances associated with excess risk of multiple myeloma

Family Active substances	Populations affected by excess risk	Presumption of a link
Organochlorines		
DDT	General population	±
Carbamates		
Carbaryl	General population	±
Pyrethroids		
Permethrin	Applicators	+
Aminophosphonate glycine		
Glyphosate	Farmers	± [a]
Other		
Captan	General population	±

+ based on the results of a cohort study in 2013, confirmed by follow-up (AHS) New data
± based on the results of a pooled analysis of three case-control studies New data
± [a] based on the results of a meta-analysis of three case-control studies and two overlapping analyses of the AHS cohort New data

Hodgkin lymphoma

Hodgkin lymphoma is a disease of the superficial or deep lymph nodes, with histology confirming the diagnosis of a monoclonal neoplasm of B cells composed of varying proportions of

mononuclear Hodgkin cells and multinucleated Reed-Sternberg cells, within a composite reactive infiltrate. Hodgkin lymphoma accounts for around 10% of lymphomas, with an estimated 2,130 new cases in France in 2018. The incidence rates standardized to the world population were 3.7 and 2.7 per 100,000 person-years in men and women, respectively, in mainland France in 2018 (male to female ratio of 1.4). The median age of onset of Hodgkin lymphoma is 33 years in women and 38 years in men. The incidence rates increased between 1990 and 2018 by an annual average of 1.2% in men and 1.7% in women. The majority of this upward trend is attributable to an increase in risk, while a small part is attributable to demographic changes.

Based on the data from four meta-analyses and a prospective cohort study, the 2013 Inserm collective expert review concluded that there was a weak presumption of a link between the risk of Hodgkin lymphoma and occupational exposure to pesticides in the agricultural sector, without distinction between chemical families or active substances. The expert review was unable to come to a conclusion regarding excess risk associated with exposure to specific active substances and the occurrence of the disease.

Only three new studies have been published in the scientific literature since 2013. A meta-analysis (based on two case-control studies) and an updated analysis of the AHS cohort, both focused on exposure to glyphosate and based on a low number of subjects, found no association with exposure to glyphosate. The third was a Canadian case-control study in the general population which found an association with chlorpyrifos, but that was also based on a small number of subjects. A second analysis of this study reported an elevated risk of Hodgkin lymphoma associated with the use of at least three pesticides classified by IARC as "probably carcinogenic" in humans. Finally, the risk in subjects under 40 years of age who reported using two acetylcholinesterase inhibitors was also significantly increased.

As a result, the presumption of a link between occupational pesticides exposure and Hodgkin lymphoma is unchanged compared to 2013.

Presumption of a link between exposure to pesticides and Hodgkin lymphoma

Exposure	Populations affected by excess risk	Presumption of a link
Pesticides (without distinction)	Agricultural sector professionals	±

± based on the results of four meta-analyses and one prospective cohort study (AHS) in 2013; and a recent meta-analysis (two case-control studies), the updated analysis of the AHS cohort and one Canadian case-control study; the new data do not alter the degree of presumption compared to 2013.

Leukemia

Leukemias are monoclonal proliferations of hematopoietic tissue cells (such as bone marrow), blocked at different stages of differentiation and circulating in the blood. The type of leukemia depends on the type of transformed blood cell (lymphoid/myeloid) and whether its growth is rapid or slow (acute or chronic leukemia). Within each group of leukemias (lymphoid or myeloid), numerous subtypes are identified on the basis of morphologic, immunophenotypic, genetic, and clinical characteristics.

Leukemia occurs most often in adults over 55 years of age, but is also the most common cancer in children under 15 years of age (see the chapter "Childhood cancer"). The two most common types of leukemia are chronic lymphocytic leukemia, now grouped with small lymphocytic lymphoma (CLL/SLL) into a single entity (incidence rates standardized to the world population in France in 2018 of 4 and 2 per 100,000 person-years in men and women, respectively; 4,700 new cases in 2018) and acute myeloid leukemia (3 and 2 per 100,000 person-years in men and women, respectively, in France in 2018; 3,450 new cases in 2018). Other forms are rarer, such as precursor cell lymphoblastic leukemia-lymphoma (900 new cases in France in 2018), chronic myeloid leukemia (870 new cases in 2018), and hairy cell leukemia (300 new cases in 2018). The trends in incidence are increasing for acute myeloid leukemia (mean annual change of approximately 1% in both sexes) and hairy cell leukemia in men (this rare leukemia is 5 times more common in men than in women).

Based on the data from seven meta-analyses and a prospective cohort study, the 2013 Inserm collective expert review concluded that there was a moderate presumption of a link between exposure to pesticides, without distinction between chemical groups or active substances, among farmers, applicators and production industry workers, and the risk of leukemia. An analysis by chemical groups identified active substances potentially involved, mainly organochlorines and organophosphates (see table below). Since 2013, three meta-analyses have been published: two based on combined data from three agricultural cohort studies (AHS, AGRICAN, and CNAP), and the third focusing specifically on glyphosate exposure (three case-control studies). Two updated analyses of the AHS cohort have been published, one looking at a large panel of active ingredients, and the other focusing on occupational exposure to glyphosate. Finally, pooled analyses conducted on data from the InterLymph consortium have examined the main risk factors for lymphoid leukemias (chronic lymphocytic leukemia, acute lymphoblastic leukemia, and hairy cell leukemia) analyzed collectively, including the farming profession.

In view of the results of these studies, all of which report associations between the farming profession and/or the use of specific substances and the risk of leukemia, the presumption of a link between occupational exposure to pesticides and leukemia remains moderate.

Presumption of a link between exposure to pesticides and leukemia

Exposure	Populations affected by excess risk	Presumption of a link
Pesticides (without distinction)	Farmers, applicators, production industry workers	+

+ based on the results of seven meta-analyses and one prospective cohort study (AHS) in 2013, and two additional meta-analyses; the new data do not alter the degree of presumption compared to 2013.

Families and active substances associated with excess risk of leukemia

Family Active substances	Populations affected by excess risk	Presumption of a link
Organochlorines		
Organochlorines (without distinction)	Applicators	+
Lindane	Applicators	+
DDT	Applicators	+
Heptachlor	Applicators	+
Chlordane + heptachlor	Applicators	+
Toxaphene	Farmers	+
Organophosphates		
Chlorpyrifos	Applicators	+
Diazinon	Applicators	+
Fonofos	Applicators	+
Malathion	Female farmers	+
Terbufos	Applicators	+
Carbamates/ Thiocarbamates/Dithiocarbamates		
S-Ethyl dipropylthiocarbamate (EPTC)	Applicators	+
Mancozeb	Farmers	+
Pyrethroids		
Deltamethrin	Farmers	+ [a]
Chloroacetanilides		
Alachlor	Production industry workers	+
Aminophosphonate glycine		
Glyphosate	Applicators	±

+ based on the results of a cohort study or nested case-control study
+ [a] based on the results of the meta-analysis of three agricultural cohorts (AGRICOH) New data
± based on the results of a cohort study (AHS) New data

All of the studies published since 2013 distinguish the type of leukemia studied, and focus primarily on the most common of these (CLL/SLL and acute lymphoblastic leukemia) but also long studied rarer subtypes, such as hairy cell leukemia. New findings have been made for CLL/SLL. These include: *i*) an association with occupational exposure to deltamethrin based on a meta-analysis of three cohort studies (without information on a dose-response relationship); *ii*) an association with terbufos with an exposure-response relationship (total number of days of exposure; AHS cohort); and *iii*) an association with DDT in the most highly exposed individuals (AHS cohort). The majority of associations identified are based on a small number of exposed individuals. No association was observed with glyphosate or with most of the other substances assessed. Regarding the risk of acute myeloid leukemia, a positive association with the use of glyphosate has been suggested (AHS cohort). Despite the low number of subjects due to the rarity of hairy cell leukemia, the risk of this type of leukemia is increased in farmers and among individuals exposed to glyphosate, but without reaching statistical significance (weak degree of presumption).

Prostate cancer

Like many other organs, the prostate gland is prone to cancerous transformation. In most of the cases, this consists of an adenocarcinoma resulting from the cancerous transformation of glandular epithelial cells.

Prostate cancer is now the most common non-skin cancer in developed countries in men. Its incidence rate has increased steadily in recent decades across these countries. In recent years, in some countries and regions where the incidence had most increased, there has been a smaller increase or even stabilization or a reduction in incidence (-3.5% per year between 2010 and 2015 in France). These changes may correspond to the combination of two phenomena: the fact that the majority of advanced cancers have already been diagnosed after several years of screening, and a greater focus on wait-and-see strategies on the part of caregivers and the

population in relation to screening, with awareness of a risk of "overdiagnosis".

The etiology of prostate cancer is largely unknown. A number of risk factors are however well established. These consist of age, a family history of prostate cancer, and ethnogeographic origin.

The 2013 Inserm collective expert review concluded that there was a strong presumption of a link between occupational exposure to pesticides, without distinction between chemical groups or active substances, among farmers, pesticide applicators, and individuals working in the pesticide production industry, and an increased risk of prostate cancer.

New research published since 2013 confirms that populations working in the agricultural sector are at higher risk of developing prostate cancer than the general population.

This recent epidemiological research thus strengthens the 2013 conclusions without enabling any further conclusions regarding the categories of pesticides associated on the basis of their targets (insecticides, fungicides, herbicides, etc.) or the chemical groups to which they belong.

Presumption of a link between exposure to pesticides and prostate cancer

Exposure	Populations affected by excess risk	Presumption of a link
Pesticides (without distinction)	Farmers, applicators, production industry workers	++

++ based on the results of six meta-analyses and one prospective cohort study (AHS) in 2013; the new studies do not alter the degree of presumption.

Regarding active substances from the organophosphate family, the AHS cohort study strengthens the evidence of a role, previously suggested in the 2013 Inserm collective expert review, of the insecticide fonofos in the development of prostate cancer in farmers (positive associations only in subjects reporting a family history of prostate cancer and in subjects with an aggressive form of the disease at diagnosis). Other insecticides from this family, terbufos and malathion, have recently been associated among farmers with an

increased risk of developing prostate cancer, but only for subjects with an aggressive form of the disease at the time of diagnosis. No new articles have been published regarding other organophosphates potentially associated in 2013 with the development of prostate cancer in farmers or in the general population.

In relation to active substances from the organochlorine family, in 2013, studies of exposure to the insecticide DDT (or DDE, its main metabolite) and the risk of developing prostate cancer presented conflicting results. A new case-control study in the general population conducted in Guadeloupe, coupled with measurement of exposure by analyzing levels of the substance in the blood, found that it was positively associated with the risk of developing prostate cancer, with a significant dose-response relationship. Another study has also suggested the role of *trans*-nonachlor, a minor component of the insecticide chlordane, in the general population. Along with the three organophosphates (fonofos, terbufos, and malathion), aldrin was associated among farmers with an increased risk of developing prostate cancer, but only in subjects with an aggressive form of disease at the time of diagnosis. No new data have been identified for dieldrin, β-HCH, or chlordane, for which the degree of presumption remains weak (±, not included in the table). Finally, we note that the potential association between prostate cancer and numerous active ingredients, notably fungicides, has not yet been studied epidemiologically.

Families and active substances associated with excess risk of prostate cancer

Family Active substances	Populations affected by excess risk	Presumption of a link
Organochlorines		
Aldrin	Farmers with aggressive disease	+ [a]
Chlordecone*	General population	++
DDE	General population	+ [b]

Organophosphates		
Coumaphos	Farmers with a family history of prostate cancer	+ [c]
Fonofos	Farmers with a family history of prostate cancer	+ [c]
	Farmers with aggressive disease	+ [a]
Malathion	Farmers with aggressive disease	+ [a]
Terbufos	Farmers with aggressive disease	+ [a]
Carbamates/ Thiocarbamates/ Dithiocarbamates		
Butylate	Farmers	+ [c]
Carbofuran	Farmers with a family history of prostate cancer	+ [c]
Pyrethroids		
Permethrin	Farmers with a family history of prostate cancer	+ [c]

++ based on the results of a case-control study with characterization by biologic markers of exposure in 2013 and a prospective study; strengthens the 2013 result
+ [a] based on the results of the AHS cohort study New data; + [b] based on the results of conflicting case-control studies in 2013, and a case-control study with characterization by biologic markers of exposure New data; + [c] based on the results of a case-control study nested in the AHS cohort in 2013
* see "Focus on chlordecone" below

From a mechanistic point of view, the vast majority of studies were conducted on organochlorine insecticides, most of which have been withdrawn from the market in France but still persist in the environment. These studies show that β-HCH and DDT/DDE are able to interact with hormonal regulation of the prostate, making the associations observed in epidemiological studies in relation to prostate cancer biologically plausible.

For some less persistent active substances (paraquat, glyphosate, cypermethrin, 2,4-D, atrazine, benomyl, vinclozolin, prochloraz, chlorpyrifos-methyl, and the fungicides cyprodinil, fenhexamid, and fludioxonil), for which epidemiological studies have not found any association with prostate cancer or which have not yet been studied

epidemiologically, mechanistic data exist that are consistent with or suggest an association with the development of prostate cancer.

Focus on chlordecone

Chlordecone was used in the French West Indies to control banana root borers from 1973 to 1993, while globally its use was stopped in 1976 when the production plant in the United States closed. The quantity used and spread in the French West Indies is estimated to be around 6,000 tons of commercial formulation (300 tons of the active substance). The use of chlordecone in the French West Indies has resulted in persistent soil pollution, and research by INRA has shown particularly high contamination with chlordecone (up to tens of mg per kg body weight) across all the animal species studied. It is estimated that at least a third of agricultural land (20,000 hectares) and almost half of freshwater resources and the marine coast are polluted by chlordecone. The polluted agricultural areas mainly correspond to banana plantations cultivated over the period 1973-1993.

The contamination of populations living in the French West Indies has been documented, confirming the strong ability of chlordecone to bioaccumulate throughout the food chain. Chlordecone analyses have detected the substance in various matrices (blood, fat, and milk). Detection rates in the blood were up to 90%, with concentrations of up to tens of µg/L. Exposure was primarily associated with the consumption of locally produced foods that were themselves contaminated (mainly root vegetables, meat, and fish).

In Guadeloupe and Martinique, the incidence rates of prostate cancer (age-standardized rate adjusted to the world population) were 173 and 164 per 100,000 person-years, respectively, over the period 2007-2014. This incidence rate in the French West Indies is nearly double the estimated incidence rate in mainland France over the same period (88.8 per 100,000 person-years) which can be explained by the sub-Saharan origins of the population, an ethnogeographic group with a higher risk of developing the disease.

Due to the frequency of prostate cancer in the French West Indies and the neurotoxic, reprotoxic, carcinogenic, and endocrine disrupting effects of chlordecone, epidemiological studies have been conducted in the region in recent years to identify health risks.

The 2013 collective expert review considered that there was a strong presumption of a link between exposure to chlordecone and the risk of developing prostate cancer. This assessment was based on the Karuprostate case-control study conducted in Guadeloupe over the period 2004 to 2007, which found an excess risk of prostate cancer with a dose-response relationship, but also on the main studies of the substance's biologic modes of action. A new study published in 2019, derived from the same incident case population used for the Karuprostate case-control study and prospectively looking at health events other than cancers, found that exposure to chlordecone was associated with excess risk of biologic recurrence of the disease after treatment with radical prostatectomy, with a dose-response relationship.

A detailed analysis was conducted of all existing toxicological and mechanistic data on chlordecone and its relationship with mechanisms of carcinogenesis, particularly in relation to the prostate. This supports the role of chlordecone as a tumor promoter and its ability to play a role in processes that promote tumor development and progression. This makes the associations observed between chlordecone and prostate cancer biologically plausible. In line with the conclusions of the 2013 collective expert review, and based upon a consideration of all epidemiological and toxicological data available, the experts conclude there is convincing evidence of a causal relationship between exposure to chlordecone and the risk of developing prostate cancer.

Breast cancer

The vast majority of breast cancers are adenocarcinomas that develop from the epithelial cells lining the ducts of the mammary gland. The incidence rate of this cancer among women in France

is around 100 cases per 100,000 person-years (58,459 new cases in 2018), and varies by age, with a peak between 70 and 74 years. While breast cancer is one of the leading causes of cancer deaths among women, there was a mean annual decrease of 1.3% in mortality rates between 1990 and 2018, which may be explained by improved treatment and screening leading to diagnosis at an earlier and thus curable stage. Its etiology is still largely unknown. A number of risk factors have however been identified: hormonal and reproductive factors (such as taking certain hormone therapies, age of first menstrual period, first pregnancy and menopause), alcohol and tobacco consumption, being overweight, and a sedentary lifestyle. A family history of cancer, particularly "hormone-dependent" (breast or ovarian) cancer, is also a risk factor.

The first epidemiological studies looking at exposure to pesticides and the risk of breast cancer date back to the 1990s and concerned the organochlorine insecticide DDT and its main metabolite, DDE. The involvement of these compounds, generally considered to be non-genotoxic, in the carcinogenic process, prompted numerous studies of exposure to pesticides in the development of breast cancer. Studies of occupational exposure among women working in the agricultural sector found either an increase or a reduction in risk compared to the general population. Others examined environmental exposure related to residential proximity to agricultural areas, including exposure to organochlorine insecticides. While one cohort study found an increased risk associated with exposure to DDT before the age of 20 years (at a time when global use of this substance was at its peak), two meta-analyses of around fifty articles published up to 2013, mainly using DDE as an indicator of exposure, found no significant excess risk of breast cancer related to environmental exposure to DDT.

The data available in 2013, which were analyzed in the previous Inserm collective expert review,[10] did not enable any conclusions to be drawn regarding the possible link between occupational or

10. See the chapter on breast cancer in the "Communications" section of the Inserm collective expert report entitled "*Pesticides: Effets sur la santé*" published in 2013 [report in French].

environmental exposure to pesticides and the risk of developing breast cancer. The scientific literature has since grown substantially, and it was important to re-examine this issue in this collective expert review.

Regarding occupational exposure, a series of three articles based on the US Agricultural Health Study (AHS) cohort examined the risk of developing breast cancer among around 30,000 spouses of farmers or pesticide users. No association was found in relation to the use of organochlorine pesticides (7 in total), except for dieldrin in patients with estrogen and progesterone receptor negative tumors (ER-PR-). A second article, on the use of organophosphate insecticides, found an increased risk of breast cancer. Of the 8 active substances analyzed, only chlorpyrifos was associated with an increased risk, at the threshold of statistical significance and particularly elevated in ER-PR- tumors. Subsequent follow-up of over a thousand incident cases of breast cancer in the AHS cohort confirmed an association with chlorpyrifos and also found a similar association with terbufos.

Other studies have looked at the risk of breast cancer in relation to environmental exposure to pesticides. Four publications have found statistically significant increases in risk (OR between 1.4 and 3.2) among women living within 2 km of an area of agricultural or industrial activity using pesticides. It should be noted that these studies do not provide any information on the active substances concerned (except for chlorpyrifos, in one study) and are based on imprecise assessments of exposure.

Around ten case-control studies investigated the risk of breast cancer in relation to blood levels of organochlorine pesticides. The majority of these studies, involving small sample sizes, reported conflicting results or results at the threshold of statistical significance. Two studies are however interesting as they show that environmental exposure to DDE or DDT appears to influence breast cancer survival. These studies, which included 633 and 748 incident cases, respectively, found excess deaths specific to breast cancer at 5 years for the highest tercile of exposure to DDT, and at 20 years

for the highest quartile of exposure to DDE. In the latter study, the risk was even higher in ER- tumors.

The majority of epidemiological studies conducted to date have looked at periods of exposure in adulthood, and with measurements of exposure conducted after DDT was banned (1972 in the United States). The period of exposure to pesticides in relation to the risk of breast cancer has been investigated by several new publications in the United States, focusing on exposure at a younger age (less than 20 years), particularly for the insecticide DDT. One study found an excess risk of breast cancer during the perimenopausal period (50 to 54 years) in women directly exposed to DDT (before 1972) who were over 14 years of age in 1945 (start date of DDT use). Another study, including over 2,000 women with breast cancer, found no association between cancer and exposure to pesticides during childhood and adolescence (before 14 years of age), regardless of tumor hormone status. An excess risk was however found in women who were under 18 years of age in 1972. Finally, maternal exposure to DDT before 1972 during pregnancy was associated with an excess risk of breast cancer in girls (OR = 3.7) for the highest quartile of exposure after adjustment for the other organochlorine compounds. Recent data have consistently shown the influence of exposure during pregnancy or around puberty on the development of breast cancer prior to menopause or during the premenopausal period. It should be noted that in these studies, the age periods of exposure coincide with the years in which global use of DDT was very high. Two questions thus remain unanswered: Are these critical periods of exposure still pertinent in the present day, when levels of exposure to DDT (or its metabolites, such as DDE) have significantly decreased? Do these critical periods of exposure also apply to other pesticides? Unfortunately, the lack of research means that these questions remain unresolved.

Epidemiological studies published in recent years, taken as a whole, do not provide any additional information to alter the conclusions of the previous Inserm collective expert review,

which was unable to establish any persuasive links between occupational or environmental exposure to pesticides and breast cancer. New research based on the AHS cohort has however shown that occupational exposure to organophosphate insecticides, including chlorpyrifos, and to a lesser extent terbufos and coumaphos, might be associated with an increased risk of breast cancer. These associations, at the threshold of statistical significance, require confirmation with additional studies. This critical analysis of the literature was extended to male breast cancer, but no association was found in relation to occupational exposure to pesticides in the small number of epidemiological studies addressing this issue.

Furthermore, the estrogenic potential of DDT and most organochlorines has been demonstrated through experimental mechanistic studies, and proliferation of breast cancer cells expressing estrogen receptor alpha is stimulated when antagonists bind to this protein. Mechanisms other than those involving estrogen receptors have also been described for organochlorines in breast cells (such as impaired cell communication, and resistance to apoptosis). This establishes a certain level of biologic plausibility for epidemiological studies of DDT for periods when this pesticide was in use and the population was significantly exposed.

For organophosphate insecticides, including chlorpyrifos, the mechanistic studies vary depending on the doses used. At high doses, minor or even null estrogenic effects are observed. Conversely, at low doses pro-estrogenic effects are observed through mechanisms involving stimulation of ERα but without direct binding to the receptor, instead involving post-translational modifications. This evidence, which may support the biologic plausibility of the associations observed in the small number of epidemiological studies of chlorpyrifos, is still limited and requires further detailed investigation.

Families and active substances associated with an excess risk of breast cancer

Family Active substances	Populations	Presumption of a link
Organochlorines		
DDT	General population, exposure during the prenatal period or before 18 years of age*	+
Organophosphates		
Chlorpyrifos	Professionals exposed in an agricultural setting	± [a]
Terbufos	Professionals exposed in an agricultural setting	± [b]

+ based on the results of two cohort studies New data
± [a] based on the results of a cohort (AHS) with confirmation in a follow-up New data
± [b] based on the results of a cohort study (AHS) New data
* before DDT was banned

Bladder and kidney cancer

Bladder and kidney cancers account for around 16,000 and 15,000 new cases per year, respectively, making these organs the fifth and sixth most common cancer sites. Twenty to thirty percent of bladder cancers are invasive, while one-third of cases of kidney cancer present with metastases at diagnosis. The 5-year survival rate of these cancers is around 75%. They are both more common in men, with male to female sex ratios of 6:1 for bladder cancer and 2:1 for kidney cancer.

Both cancers are strongly linked to smoking and ionizing radiation. Bladder cancer has been associated with certain occupational sectors, including the production of dyes, aluminum, rubber, and industrial paint. Many substances used in these occupational sectors, such as aromatic amines and polycyclic aromatic hydrocarbons, have been associated with this cancer with a high level of supporting evidence. Kidney cancer has been associated with a high body mass index, hypertension, and trichloroethylene.

Bladder cancer is thought to develop from the contact of reactive substances (for example pesticides or their metabolites) with the bladder mucosa, that can bind covalently to DNA and lead to the formation of adducts, a process that is a recognized stage in carcinogenesis. Interindividual genetic susceptibility based on differences in the expression, inducibility or activity of enzymes involved in bioactivation or detoxification is also thought to partly explain the occurrence of this cancer. Numerous genetic alterations, mainly related to cell proliferation or genome instability, and epigenetics, have also been associated with the formation of bladder tumors, with different processes for superficial and invasive tumors. The mechanisms resulting in kidney cancer, particularly clear cell renal cell carcinoma – the most common form – appear to be more epigenetic in nature rather than mutational. These involve, in particular, pathways implicated in signaling and in epithelial-mesenchymal transition, but also potentially environmental changes such as hypoxia. Clear cell renal cell carcinoma is characterized by inactivation of the *VHL* tumor suppressor gene, which regulates adaptive responses to hypoxia. The stages of carcinogenesis are based, among others, on angiogenesis, extracellular matrix assembly, ciliogenesis, microtubule stabilization, senescence, and DNA repair. However, current data suggest that *VHL* inactivation is not sufficient to initiate kidney cancer on its own. Mutation of the *PBRM1* gene, a component of the chromatin remodeling SWI/SNF complex, is also thought to be involved in carcinogenesis.

Studies of the occurrence of bladder cancer in agricultural settings, conducted as early as the 1980s, generally found lower incidence and lower mortality than in the general population. The reductions in risk were around 15 to 20%. Kidney cancer, meanwhile, was only rarely studied, and the results were not consistent between studies. However, these mostly retrospective studies often did not take tobacco use into account, and were based on imprecise estimates of exposure to pesticides. Given the strength of the link between smoking and bladder cancer,

the negative association observed between the farming profession and bladder cancer could therefore be explained, at least in part, by the lower smoking rate repeatedly found in the agricultural population, particularly in studies involving farm owners. However, as with lung cancer, these results did not rule out the existence of risk factors for urinary tract cancers in agriculture, and in particular the potential role of pesticides.

A meta-analysis was published in 2016 on the effects of pesticides on the risk of bladder cancer. It included 9 articles, including 7 case-control studies and 2 ecological studies conducted between 1977 and 2011, and calculated a combined risk of 1.65; 95% CI [1.22-2.22], but with significant between-study heterogeneity. This meta-analysis was not however exhaustive: over twenty studies have been conducted in total, including two prospective cohort studies, two retrospective cohort studies and around fifteen case-control studies, 8 of which concerned occupational exposure.

In addition to the studies included in this meta-analysis, two prospective cohort studies, the Agricultural Health Study and AGRICAN, have contributed to our knowledge regarding bladder cancer. The US cohort study, based on 321 incident cases, found significant positive associations with several herbicides (bentazon, bromoxynil, chloramben, diclofop-methyl, imazaquin, 2,4,5-T, and imazethapyr) and some insecticides (DDT, aldicarb, carbofuran, chlordane, toxaphene, fonofos, and permethrin), and trends with other substances (2,4-D and glyphosate). The link between bladder cancer and exposure to pesticides as assessed by type of agricultural activity was examined in the French cohort study based on 179 incident cases. The risk appeared to be significantly elevated among crop farmers, in relation to the duration of lifetime activity involving crops, approaching a four-fold increase in risk for female crop farmers, and a three-fold increase in non-smoking male crop farmers. Working in greenhouses and pea crops tended to increase the risk, particularly when individuals reported using pesticides, along with re-entry tasks in vineyards.

The first retrospective cohort study, conducted in British Columbia (Canada), looked at sawmill workers and analyzed the link between developing cancer and exposure to pentachlorophenol and tetrachlorophenol-based wood treatments over the period 1950-1995. There was no clear association between such exposure and bladder cancer. A retrospective cohort study of Icelandic sheep farmers also observed an inverse association with exposure to dipping sheep with lindane. These two retrospective cohort studies did not however take the participants' smoking status into account.

Seven of the eight case-control studies exploring occupational exposure to pesticides, three of them in Egypt, two in Italy, one in Turkey, and two in the United States, found increased risks of bladder cancer. These were conducted across a range of occupational settings (pesticide industry, livestock farming, general agriculture) and included also one study of women in Egypt examining nonoccupational exposure to agricultural work (defined as living with an agricultural worker). The levels of risk were sometimes elevated, exceeding 2 in 5 studies (and exceeding 4 in 3 studies), particularly for periods of exposure longer than 10 years. In addition, seven case-control studies investigated exposure of the general population (by measurement of plasma organochlorine levels, or examining contamination of water by arsenic derivatives used in agriculture in the United States, or proximity to agricultural areas in the United States and Belgium) and found no significant association with bladder cancer, although trends were observed in three of them. Three ecological studies have demonstrated moderate increases in the risk of bladder cancer in the general population, including one conducted in France and based on agricultural winegrowing areas over the period 1986-1989.

Some studies have looked at the role of genetic polymorphism in the association between pesticides and bladder cancer. In particular, these have focused on genes coding for enzymes involved in xenobiotic metabolism such as S-transferase glutathione, N-acetyltransferases and cytochromes P450. The

findings suggest the existence of individual susceptibilities that could play a role in the development of this cancer in relation to exposure to pesticides.

Presumption of a link between exposure to pesticides and bladder cancer

Exposure	Populations affected by excess risk	Presumption of a link
Pesticides (without distinction)	Occupational users	+
Pesticides at home (proximity, domestic use)	General population	±

+ based on the results of two prospective cohort studies and eight case-control studies New data
± based on the results of seven case-control studies and three ecologic studies New data

A meta-analysis published in 2016 included 11 studies (7 cohort study analyses and 4 case-control studies) looking at the link between exposure to pesticides and kidney cancer. It found a statistically significant increase in risk of 10 to 30% but with substantial between-study heterogeneity.

Due to the small number of incident cases, the US cohort study has not yet specifically analyzed kidney cancer in relation to the 50 substances included in the enrollment questionnaire. It has however produced data from several analyses regarding specific substances (trifluralin, imazethapyr, and diazinon), without demonstrating a statistically significant association. To date, kidney cancer has not yet been specifically analyzed in the French cohort study. The retrospective cohort study conducted in sawmill workers found a two-fold increase in the risk of kidney cancer in those exposed to pentachlorophenol. This compound has not been associated with risk of kidney cancer in toxicology studies, but since 2016 it has been classified by IARC as carcinogenic based on evidence that it causes hematopoietic tumors. An inverse relationship was observed between lindane and kidney cancer in the retrospective cohort study of Icelandic sheep farmers.

Four case-control studies, two of which included over 1,000 cases, have explored the link between occupational exposure to

pesticides and kidney cancer. All found increases in risk, but this was not significant in the smallest study (39 cases). A four-fold increase in risk was thus observed for exposure with a duration greater than 20 years to herbicides or insecticides, a two-fold increase in risk in Canada for use of pesticides or herbicides, and a risk greater than 2 in Central and Eastern Europe for exposure to pesticides for over 8 years. No case-control studies have explored the link between non-occupational exposure to pesticides and kidney cancer, and a single ecological study in Costa Rica did not find a link.

Epidemiological data report an association between exposure to arsenic (IARC Group 1), which is produced during the manufacture of pesticides, and the development of kidney and bladder cancers. The underlying mechanism is partly based on induction of reactive oxygen species that cause single- and double-strand DNA breaks. This damage causes chromosomal rearrangements that are associated with tumorigenesis.

Presumption of a link between exposure to pesticides and kidney cancer

Exposure	Populations affected by excess risk	Presumption of a link
Pesticides (without distinction)	Occupational users	+

+ based on the results of four case-control studies New data

Associations between pesticides with a structure similar to aromatic amines (imazethapyr and imazaquin) and bladder cancer have been observed in the AHS cohort study, but links have also been demonstrated with other herbicides. However, a study of rodents exposed to imazethapyr or imazaquin concluded that there was no carcinogenic effect, and the results are negative for genotoxic or mutagenic effects in various *in vitro* and *in vivo* tests.

In relation to organochlorines, an association with some active substances has been reported by epidemiological studies.

Chlorothalonil (a fungicide) is classified by IARC as a Group 2B agent (possibly carcinogenic) due to its disruption of mitochondrial respiration and endocrine disruptor effect with weak antagonist activity toward the androgen receptor. This carcinogenic activity has not been observed in humans. Pentachlorophenol (PCP) was classified by IARC as carcinogenic (Group 1) in 2019. Experimental carcinogenicity data *in vivo* indicate a weak but significant carcinogenic effect in rodents. Data from mutagenesis and genotoxicity tests for PCP show a positive overall effect, and tests performed with the major metabolite tetrachlorohydroquinone also produce positive results (DNA adducts or oxidative damage).

Some epidemiological studies have found an association between bladder cancer and the chlorophenoxy derivatives 2,4-D and 2,4,5-T. These derivatives are classified by IARC as Group 2B agents, by the US Environmental Protection Agency (EPA) as Group D agents (not classifiable as to human carcinogenicity), and are not classified by the European Chemicals Agency (ECHA). These compounds are contaminants in drinking water, and are generally highly toxic to the environment. For some of them, an endocrine disruptor effect has been suggested.

Carcinogenicity experiments for certain chlorophenoxy derivatives in rodents have produced positive results, in particular for 2,4-D or 2,4,5-T but these have been challenged by manufacturers on the basis of contamination with dioxin/furan impurities classified as carcinogenic, or the poorly conducted nature of the studies. The results of *in vitro* genotoxicity and mutagenicity tests involving these pesticides are generally negative, though some experiments point to a genotoxic effect in relation to the induction of oxidative stress.

Of the organophosphates, only malathion has been identified as promoting the development of precancerous renal abnormalities in rats, in the context of co-exposure to 17β-estradiol, but this was not observed in epidemiological studies.

Further research is required to better define how pesticides contribute to the molecular alterations that cause bladder and kidney cancer. Analysis of the most recent scientific literature has highlighted several priority areas for toxicology studies: *i*) investigation of mechanisms of carcinogenesis other than genotoxic effect, in relation to pesticides that are structurally similar to aromatic amines; *ii*) studies of gene-environment interactions (polymorphisms of metabolic enzymes or detoxification by antioxidant enzymes); and *iii*) investigation of carcinogenic effects in the context of co-exposure to other environmental agents (smoking).

Soft tissue and visceral sarcomas

Soft tissue and visceral sarcomas are rare malignancies, accounting for less than 1% of all cancers in adults. They develop in the supporting tissues of the body: adipose tissue, fibrous tissues such as the tendons and ligaments, striated and smooth muscle, blood and lymphatic vessels, and the dermis. They also occur in viscera, such as the wall of the digestive tract (stomach, intestines, and colon). Their prognosis is determined by the presence of metastases, predominantly in the lungs and present in approximately 10% of cases, and by tumor size, grade and stage, and location. Over 50 histologic types have been identified, and their nature and classification continue to evolve with advances in molecular biology and the discovery of new entities.

The latest estimates from the FRANCIM network report 2,658 new annual cases of such tumors in men and 2,636 in women in France, equivalent to incidence rates of around 5 cases per 100,000 person-years. According to European and US registries, the 5-year survival rate for this cancer, all forms combined, is around 60 to 65%.

The etiology of these tumors is poorly understood. Most cases are sporadic, but associations with certain genetic syndromes such as neurofibromatosis type I, Li-Fraumeni syndrome, Werner syndrome, and retinoblastoma are now established. Some

sarcomas develop in relation to diseases of the immune system (such as Kaposi's sarcoma in AIDS). Risk factors related to the general or occupational environment are also suspected, such as ionizing radiation, dioxins, vinyl chloride (for hepatic angiosarcoma), arsenic, and pesticides.

The potential role of pesticides in the development of soft tissue and visceral sarcomas emerged in the late 1970s following clinical observations in Sweden, much earlier than the onset of the general debates about the health effects of pesticides. The number of patients with these cancers who had handled phenoxy herbicides appeared abnormally high to Swedish oncologists. An increasing number of epidemiological studies in the 1970s and 1980s sought to clarify the specific role of phenoxy herbicides as well as chlorophenols, in the occurrence of sarcomas. This gave rise to a number of review articles examining the role of pesticides in the development of soft tissue and visceral sarcomas, but none address agricultural use of pesticides as the main theme. They focus instead on the specific question of the carcinogenic potential of phenoxy herbicides (including 2,4-D) or chlorophenols. The latest review of the subject included all studies published up to 2014 regarding the role of phenoxy herbicides in the development of soft tissue sarcomas, totaling 10 case-control studies and 10 cohort studies. The authors did not calculate a combined risk on the basis of these studies and, as in previous reviews, concluded that it was not possible to draw definitive conclusions regarding the existence of a risk associated with these substances, based on the existing data.

Due to the low incidence of these cancers, the prospective AHS and AGRICAN cohort studies have not yet produced data on the risk of sarcoma in relation to agricultural exposure. The expertise identified nine analyses of retrospective cohort studies, conducted between 1979 and 1986, exploring the hypothesis of a link with chlorophenols or phenoxy herbicides in both industrial and agricultural contexts. Some of these studies were then pursued as prospective cohorts into the 1990s. Four of them

included fewer than 500 workers from production sites and provided limited information because the number of cases remained low and generally did not enable conclusions to be drawn, even if trends toward excess sarcomas were observed. A project by the IARC combined data from 24 international cohorts, bringing together 26,615 workers, and looking at exposure to phenoxy herbicides and chlorophenols over the period 1939-1992, taking into account exposure to dioxins. Based on the occurrence of 9 cases of sarcoma, exposure to phenoxy herbicides and chlorophenols was associated with a two-fold increase in the risk of sarcoma, at the threshold of statistical significance (OR = 2.0; 95% CI [0.91-3.79]). This analysis was supplemented by a nested case-control study, enabling an in-depth estimation of exposure to phenoxy herbicides and chlorophenols, taking into account the duration and cumulative score of exposure (based on the sector, work, protective equipment, etc.). There was a 10-fold increase in risk from exposure to phenoxy herbicides overall, and the risks were elevated for 2,4-D, 2,4,5-T and MCPA, but the results were not statistically significant due to small sample size. There was however no evidence of an increased risk associated with chlorophenols.

In addition, 3 retrospective cohort studies have been conducted in the agricultural setting. The first focused on the role of exposure to phenoxy herbicides in the occurrence of soft tissue sarcomas in a cohort of 350,000 agricultural and forestry workers in Sweden. After classifying exposure into subcategories based on job titles, no increase was observed in the risk of sarcoma overall or in each of the occupational categories. The second study, in Finland, included nearly 2,000 herbicide applicators, but detected no cases of sarcoma over an 18-year follow-up period. Finally, a Danish cohort study including over 3,000 gardeners, conducted over the period 1975-2001, found a higher frequency of sarcomas among gardeners born before 1915, who were considered to be the most exposed to pesticides.

Around 15 case-control studies have investigated the role of pesticides in the occurrence of sarcomas. The first of these, a Swedish study including 52 cases and 208 controls, found a 5- to 6-fold increase in the risk of sarcoma in individuals exposed to either phenoxy herbicides or chlorophenols. This study was based on a national cancer registry with diagnoses confirmed by pathological examination, and self-reported estimates of exposure. The hypothesis of contamination of these pesticides by dioxins (manufacturing impurities) was highlighted by the authors. A second study was conducted in the same country and using an identical protocol, but in a different region. It found similar results from 110 cases and 220 controls, for a period when 2,4,5-TP, the phenoxy herbicide most frequently contaminated by dioxin derivatives, was banned. In this second study, increased risks were also observed for phenoxy herbicides (2,4-D and MCPA), in theory uncontaminated or less contaminated by dioxins.

Just after these two Swedish studies showing an elevated risk, numerous case-control studies were conducted in various countries: the United Kingdom, New Zealand, Italy, the United States (Kansas, Washington State, and other states), Sweden, and Australia. These studies, conducted between the 1970s and 1990s, produced conflicting results regarding the role of phenoxy herbicides and chlorophenols, with some finding elevated risks, sometimes statistically significant, and others not, among agricultural workers, timber workers, or gardeners.

Two studies focused on other occupational sectors. In the United States, one study found an increased risk among farmers who treated animals with insecticides. This was more marked in the earlier years, for spraying and dusting applications, and among individuals who did not wear protective equipment, and was primarily seen for fibrous and myomatous sarcomas. A Canadian study, that did not observe a link with phenoxy herbicides, found a trend toward increased risk with insecticides and fungicides and with potato seed treatment. It also reported a significant risk among chicken farmers and a trend among sheep and

small animal farmers. Analyses of specific active substances found links to aldrin and diazinon. This latter substance was particularly associated with undifferentiated sarcomas and with fibrous and myomatous sarcomas.

In total, around 10 cohort studies and fifteen case-control analyses have explored the link between pesticides and soft tissue and visceral sarcomas to date. They have specifically focused on two families of pesticides: phenoxy herbicides and chlorophenols, especially in the 1970s and 1980s, following case-control studies in Sweden showing particularly strong associations with these substances. The contamination of these pesticides with dioxins during certain manufacturing processes appeared to partly explain the results and the divergence among the studies in the different countries. These divergent results might also, however, be explained by methodological differences, notably the difficulties in characterizing cases (identified solely using international classification of disease codes, or precise histopathologic characterization, taking into account all sarcomas or subtypes), and in group selection (controls taken from the general population or from other cancer registry cases), and characterizing exposure (solely using job titles or with a detailed investigation of the nature, duration, and intensity of the exposure). Furthermore, the rare nature of these cancers means that estimates are uncertain, as they are based on very limited numbers of cases, particularly in cohort studies. Finally, though the role of dioxins was plausible in studies of populations significantly exposed to 2,4,5-T, the specific role of phenoxy herbicides and chlorophenols, or indeed other pesticides, in the occurrence of these tumors has not been definitively ruled out. In the 1990s, new studies thus suggested links to insecticides, particularly in relation to treatment of farm animals, as well as increased risks in other occupational contexts such as the wood industry.

Presumption of a link between exposure to pesticides and soft tissue and visceral sarcomas

Exposure	Populations affected by excess risk	Presumption of a link
Pesticides*	Agricultural workers, wood industry workers, gardeners, livestock farmers	+

* primarily phenoxy herbicides and chlorophenols
+ based on the results of a cohort study and several case-control studies New data

Other health events

Respiratory problems, thyroid disorders, and endometriosis were not analyzed in the 2013 expert review. In this section we analyze the epidemiological and toxicological studies for these health events.

Respiratory health

Asthma and chronic obstructive pulmonary disease (COPD) are common chronic respiratory diseases whose prevalence has increased in recent decades. Asthma is the most common chronic disease in children, with a prevalence in France of 11%, while the prevalence of COPD is 5 to 10% among the population aged over 45 years in France. Asthma is not simply one disease but a respiratory syndrome that often begins in childhood and manifests in attacks of varying duration and intensity, during which the patient has difficulty breathing, wheezing, coughing, and a tight chest. COPD, which generally develops from the age of 40-50 years, is defined according to the latest international guidelines by the concomitant existence of respiratory symptoms and airflow limitation. In epidemiological studies, asthma is often assessed using questionnaires, generally on the basis of a question about the existence of an asthma diagnosis – a very specific definition – but also by the presence of respiratory symptoms suggestive of asthma, particularly wheezing

in the past 12 months, which is generally a more sensitive definition, but with less specificity (although this remains high). Self-reported diagnosis of COPD is a specific definition but has very little sensitivity; this definition is therefore not appropriate to define the prevalence of the disease, but remains useful in the context of etiologic studies in which a highly specific definition of the disease is preferable. Of course, where possible, a definition based on post-bronchodilator spirometry data remains the gold standard for evaluating COPD in epidemiology.

The etiology of these chronic respiratory diseases remains poorly understood. Asthma and COPD have a genetic component, but their rapid rise in developed countries highlights the major impact of the environment more broadly. Several environmental factors have been proposed as being potentially involved in the development of asthma. Some have protective effects (such as living on a farm, and contact with infectious agents in early childhood), whereas others are risk factors (such as smoking, air pollution, and certain occupational forms of exposure). Tobacco consumption is the main risk factor for COPD, with 80% of cases attributable to active or passive smoking. Other environmental factors have however been identified, such as air pollution and occupational exposure to certain chemicals (including coal dust, silica, and organic dust), or are suspected, such as exposure to pesticides.

The literature on the impact of pesticides on respiratory health is significant, totaling around a hundred articles, two-thirds of which concern occupational exposure: 67 articles on occupational exposure, including 28 articles since 2014 (date of the last literature review), and 34 articles on environmental exposure, including 14 since 2014. A literature review published in 2015 on the potential role of occupational exposure to pesticides in the occurrence of respiratory symptoms and diseases (asthma, COPD, and chronic bronchitis) concluded that occupational exposure to pesticides posed a risk to respiratory health. It went on to highlight the need for further research, in particular via cohort studies with detailed characterization of

exposure, in order to document dose-response relationships and specific forms of exposure to pesticides, and using objective respiratory health measures, notably spirometry to assess airflow obstruction. With regard to environmental exposure, the 2015 literature review concluded that further studies were needed to assess the role of environmental exposure to pesticides in respiratory disease among children and adults. There is a high level of variability in estimates of exposure and the definition of health events; as a result, only two meta-analyses, one focusing on occupational pesticide exposure and the risk of COPD/chronic bronchitis in adults, and the other on the association between prenatal exposure to DDE and respiratory health in children, have been published.

Regarding occupational exposure, the recent meta-analysis based on 9 cohort studies concluded that COPD and chronic bronchitis were significantly increased with exposure to pesticides (OR = 1.33; 95% CI [1.21-1.47]). In addition, the results of recent cohort studies in the general population, whose exposure was based on the ALOHA job-exposure matrix, and farmer cohorts, have provided evidence in support of the association between pesticide exposure and both the level and decline in ventilatory function, as well as the incidence of COPD. The results of exposed-unexposed studies and cross-sectional studies conducted in different regions of the world all point to a harmful effect from occupational exposure to pesticides on respiratory health, and more specifically respiratory symptoms, asthma, and respiratory function, although most of these studies were conducted on small to medium-sized samples (<300 people).

Presumption of a link between exposure to pesticides and impaired respiratory health

Exposure/populations	Effects	Presumption of a link
Occupational exposure to pesticides (without distinction)	Respiratory function Asthma, wheezing COPD, chronic bronchitis	+ + ++
Environmental exposure to pesticides at home (proximity, household use)	Respiratory function Asthma, wheezing	± +

++ based on the results of a high-quality meta-analysis and consistency with the results of studies published since the meta-analysis New data
+ based on the results of several studies, including at least one large cohort study New data
± based on the results of several studies but no cohort studies New data

Around 10 studies have explored the role of specific pesticides on various respiratory health parameters. These studies, carried out in farmers and most notably on the AHS cohort (9 articles) including a large number of subjects (>20,000), identified candidate substances for respiratory disease (see table below).

With regard to environmental exposure, two recent cohort studies found no significant association between pre- or post-natal exposure to DDE and the respiratory health of school-age children (wheezing, asthma, or ventilatory function). A meta-analysis of 10 studies did however conclude that there was an effect – at the threshold of statistical significance – from prenatal exposure to DDE on symptoms of bronchitis and wheezing at 18 months (OR = 1.03 [1.00-1.07] for a two-fold increase in the concentration of p,p'-DDE in cord blood), but the study found no association with symptoms at 4 years of age. With regard to environmental exposure to organophosphate pesticides, some results from cohort studies based on biomarkers of exposure suggest a potential impact from these pesticides on the respiratory health of children, but further studies are required in order to draw definitive conclusions. Finally, for COPD and chronic bronchitis, no rigorous studies exist on which a presumption of a link might be established.

Families and active substances associated with excess risk of impaired respiratory health

Family Active substances	Populations	Presumption of a link		
		Respira-tory function	Asthma, wheezing	Chronic bronchitis, COPD
Organochlorines				
Organochlorines	General population	±		
DDT	Farmers		±	±
	General population	+	+	
Heptachlor	Farmers		±	±
Hexachlorocyclohexane (HCH)	Farmers		±	±
Organophosphates				
Organophosphates	General population		±	
Chlorpyrifos	Farmers	±	±	
Coumaphos	Farmers		±	±
Diazinon	Farmers		±	±
Dichlorvos	Farmers		±	±
Malathion	Farmers		±	±
Parathion	Farmers		±	±
Carbamates/Dithiocarbamates				
Carbamates/ Dithiocarbamates	Agricultural setting		±	
Carbaryl	Farmers		±	±
Pyrethroids				
Pyrethroids	General population	±		
Permethrin	Farmers		±	±
Triazines				
Atrazine	Farmers		±	
Phenoxy herbicides				
Phenoxy herbicides	Veterans/ Farmers		±	±
2,4-D	Farmers		±	
2,4,5-T	Farmers		±	±

Aminophosphonate glycine				
Glyphosate	Farmers		±	
Other				
Chlorimuron-ethyl	Farmers		±	±
Paraquat	Farmers	±	+	±

+ based on the results reported in at least two independent high-quality studies (two studies based on the same cohort study, such as the AHS, are not considered to be independent) New data

± based on the results reported in a single study (or several studies based on the same cohort study) New data

The expert group assessed the links between exposure to certain pesticides and respiratory health based on pathophysiological mechanisms analyzed in animal models and *in vitro* using cell lines. Three effects were investigated for the 17 pesticides identified from the epidemiological data (see table above); oxidative stress, mitochondrial toxicity, and immunomodulation of the inflammatory response. All three effects were found for chlorpyrifos and permethrin. The involvement of two factors (oxidative stress and mitochondrial toxicity) was found for malathion, HCH, DDT, atrazine, glyphosate and paraquat; and the involvement of oxidative stress and immunomodulation were found for diazinon, parathion, and 2,4-D. The association between exposure to 17 pesticides and respiratory health is thus supported by mechanistic data, for 11 of them, including chlorpyrifos and permethrin, which were associated with all 3 effects.

Of the 7 additional pesticides also considered with a less restrictive classification, 6 were associated with induction of oxidative stress. In addition to induction of oxidative stress, carbofuran causes mitochondrial toxicity, and cyfluthrin and chlorothalonil have an immunomodulatory effect. These mechanistic data, particularly when associated with an irritant effect (H317, H335) for chlorothalonil, require validation by epidemiological studies, but illustrate the value of combining research from epidemiology and molecular toxicology. Furthermore, on the basis of an immunomodulatory effect in the lungs, 6 pesticides not identified in the epidemiological data have been

considered: mancozeb, methoxychlor, deltamethrin, indoxacarb, imidacloprid and fipronil, along with PBO, a synergistic agent frequently combined with pyrethroids.

For organophosphate and carbamate insecticides, the toxic effect in the lungs results from inhibition of acetylcholinesterase (AChE), an enzyme that breaks down acetylcholine and is a target of these agents. Bronchoconstrictive effects have however been observed for pesticides at concentrations that do not inhibit AChE, and involve activation of muscarinic M3 receptors in the smooth muscle of the respiratory tract. The impact of pesticides on respiratory health has long been underexplored in toxicology, one of the major factors being the lack of research into this effect in rodent experimental models. The relevance of an approach that starts with identification of a toxic effect in mechanistic studies and that then searches for a potential link to human disease should be explored, for example on these compounds.

Thyroid disorders

The thyroid is an endocrine gland that synthesizes hormones involved in numerous physiologic processes such as cell metabolism, muscle energy, and body temperature. Its function is controlled by the hypothalamic-pituitary-thyroid axis, a pathway that involves thyrotropin-releasing hormone produced by the hypothalamus, which stimulates synthesis of thyroid-stimulating hormone (TSH) by the anterior pituitary gland. TSH acts on thyroid follicular cells to stimulate synthesis and secretion of the thyroid hormones triiodothyronine (T3) and thyroxine (T4). Hypothyroidism is characterized by insufficient secretion of thyroid hormones, and hyperthyroidism by their excess secretion. A distinction is made between overt forms, which are characterized by abnormal levels of TSH, T4, and T3, and subclinical forms in which only TSH levels are abnormal. Some cases are caused by abnormal pituitary activity (i.e. inappropriate secretion of TSH).

Iodine is essential for the production of thyroid hormones and must be supplied by the diet. In countries with sufficient iodine intake, the prevalence of overt hyperthyroidism is between 0.2% and 1.3%, while the prevalence of subclinical hyperthyroidism is between 1% and 5%. For overt hypothyroidism, the prevalence in the general population is estimated to be between 0.2% and 5.3% in Europe.

Risk factors include sex, autoimmune disease, family history of thyroid disease, certain drugs, age, and iodine deficiency. Pesticides are one of the suspected risk factors; the limited epidemiological data available were examined in the 2013 expert review, but did not provide sufficient evidence to draw conclusions regarding a potential link between exposure to pesticides and the occurrence of thyroid disease.[11] The literature has grown over the past few years and over 70 epidemiological studies were identified, with around 60 studies focusing on occupational or environmental exposure, in similar proportions, and around 10 looking at residents living in close proximity to agricultural or industrial areas. The majority of studies are cross-sectional, along with 15 cohort studies and 3 case-control studies (including 1 nested in a cohort study).

Regarding occupational risk, an association between exposure to organochlorine pesticides and an increased risk of hypothyroidism was found in three studies using data of the US Agricultural Health Study (AHS), a prospective cohort of pesticide applicators, while the results are less consistent for other pesticide families. In analyses by active substance, the risk of hypothyroidism was increased in participants who used certain organochlorine insecticides (chlordane, aldrin, heptachlor, and lindane), organophosphate insecticides (diazinon, dichlorvos, malathion, and coumaphos), and herbicides (dicamba, glyphosate, and 2,4-D). After adjusting for correlated pesticides, the associations remained significant for chlordane, heptachlor,

11. See the chapter entitled "*Pesticides et pathologies métaboliques: données épidémiologiques*" in the Inserm collective expert report "*Pesticides: Effets sur la santé*" published in 2013.

diazinon, and dicamba. Carbamate and pyrethroid insecticides, as well as the fungicides and fumigants studied, were not associated with the risk of hypothyroidism. These results were generally consistent with previous analyses of the same cohort based on prevalent cases or incident cases with shorter follow-up. A more detailed analysis of data from the AHS was conducted to explore the risk of subclinical hypothyroidism (defined by the authors as TSH >4.5 mIU/L). For the highest categories of exposure, an approximate 4.7-fold increase in risk was found in relation to lifetime cumulative exposure to aldrin (with an exposure-response relationship), and an approximate 2.8-fold increase in risk for the herbicide pendimethalin.

Based again on the AHS, a cross-sectional study of the spouses of pesticide applicators found an increased risk of hypothyroidism with exposure to chlordane, the fungicides benomyl and maneb/mancozeb, and the herbicide paraquat. A longitudinal study of this population confirmed the increased risk of hypothyroidism with exposure to benomyl and maneb/mancozeb, and found an association with use of metalaxyl. An increased risk of hypothyroidism was also found for pendimethalin, parathion and permethrin after adjusting for other correlated pesticides. It should be noted that a reduction in risk was observed for certain active substances (the insecticide phorate and the herbicides imazethapyr and metolachlor).

Regarding the risk of hyperthyroidism, cross-sectional and longitudinal analyses found an association with maneb/mancozeb among the spouses of pesticide applicators in the AHS cohort. In the longitudinal analysis, an association was also found for diazinon and metolachlor, while a reduction in risk was found for the herbicide trifluralin. However, in the subjects in the AHS cohort (mainly men), several pesticides were associated with a reduction in the risk of hyperthyroidism (malathion, maneb/mancozeb, dicamba, metolachlor, atrazine and chlorimuron-ethyl).

Numerous other studies, most cross-sectional in design, have looked at the associations between occupational exposure to pesticides and serum thyroid hormone and TSH levels in the

absence of a clinical diagnosis of thyroid disease. The results of these studies are heterogeneous and do not make it possible to draw conclusions regarding thyroid disease.

Presumption of a link between exposure to pesticides and thyroid disorders

Exposure/populations	Effects	Presumption of a link
Occupational exposure to pesticides (without distinction)	Overt or subclinical hypothyroidism	+
Occupational exposure to fungicides (without distinction)	Hypothyroidism	±

+ based on the results from the AHS cohort and cross-sectional studies New data
± based on the results from the AHS cohort New data

Around thirty studies in the general population were identified, three with large numbers of cases: the US NHANES (National Health and Nutrition Examination Survey) study, a Korean study and a Thai study. The results do not concern the same active substances and, in general, are inconsistent with regard to sex and age. The Korean study did however find that urinary concentrations of 3-phenoxybenzoic acid (3-PBA), a metabolite common to several pyrethroids (cypermethrin and deltamethrin, but not cyfluthrin) were negatively associated with total T4 and T3, especially in men. The NHANES study found an association between 3,5,6-trichloro-2-pyridinol (TCPy; a urinary metabolite of chlorpyrifos and chlorpyrifos-methyl), serum p,p'-DDE (a metabolite of the organochlorine pesticide DDT), and thyroid hormones, although the results varied between men and women and by age. The results of other general population studies with smaller numbers of cases support the above associations, notably for TCPy, dieldrin, hexachlorobenzene and DDT. However, the results of studies in the general population, taken as a whole, do not make it possible to draw definitive conclusions regarding an association between exposure to pesticides and consistent variations in circulating thyroid hormone levels.

Numerous studies have focused specifically on the association between pesticides and the risk of thyroid disorders in certain susceptible populations (pregnant women and neonates) or particularly exposed populations (residents living in proximity to agricultural or industrial areas).

Thyroid disease during pregnancy can have harmful effects on the health of the pregnant woman, but also on fetal development and growth, and the impact of pesticides on thyroid function during this sensitive period has been the subject of several studies. In the CHAMACOS cohort study, based in California, exposure to hexachlorobenzene was associated with a decrease in free and total T4, and in a cross-sectional study this pesticide was associated with a decrease in total T3. In two cross-sectional studies of Chinese pregnant women, urinary levels of organophosphate pesticide metabolites were associated with a reduction in TSH and an increase in free T4, while pyrethroids were associated with a decrease in free T3.

Several mother-child studies have explored the effect of prenatal exposure to pesticides on thyroid function in neonates. The most recent of these, conducted from a prospective cohort study in the Netherlands, found no relationship between exposure to organophosphate pesticides and thyroid hormone levels in maternal or cord blood, despite high levels of biomarkers. Exposure to pyrethroids (measured by the metabolite 3-PBA in urine) was analyzed in the 1st trimester of pregnancy in Japanese women and no association was found with TSH and T4 concentrations in both the mothers and neonates, while in another cohort study in South Africa, pyrethroids were positively associated with TSH in neonates. Some small cross-sectional mother-child studies have found that maternal levels of certain organochlorine pesticides were generally associated with decreased thyroid hormone and/or increased TSH levels in neonates.

A number of studies of populations living in proximity to agricultural or industrial areas were identified. In a Spanish study, individuals living in an intensive farming area where pesticides

were heavily used had a 49% increased risk of hypothyroidism and, to a lesser extent, other thyroid disorders (goiter, thyroiditis, and thyrotoxicosis). A Brazilian study of a population living in an industrial zone contaminated with organochlorine pesticides found a negative association between endosulfan II and total T3, and between DDT and free T4 in men, whereas these associations were positive in women. This study also found an increase in thyroid hormones related to α-chlordane, HCB, heptachlor, and methoxychlor in women, and a decrease in free T4 and an increase in TSH linked to β-HCH in men. Finally, in two studies of populations living near industrial areas, an increase in HCB levels was associated with a decrease in total T4.

For thyroid cancer, only one study found an increased risk associated with exposure to malathion, in the spouses of pesticide applicators in the AHS cohort. However, no increase in risk was observed in other populations with large numbers of cases (families of farmers, individuals living on a farm, individuals working in a pesticide production plant). Taken together, the results of these studies do not demonstrate a robust link between exposure to pesticides and the occurrence of thyroid cancer.

The results of experimental toxicology studies support the biological plausibility of some of the associations described above. Pesticides could disrupt thyroid function through mechanisms acting on numerous biological processes in the gland or in peripheral tissues. These include modification of thyroid hormone production (inhibition of thyroid peroxidase, deiodinases, and iodine transport), bioavailability (impaired uptake by transport proteins), or metabolism (stimulation or inhibition of the metabolism of phase II liver enzymes). Pesticides could also disrupt the production/inhibition of T3 through modification of deiodinase activity or interaction with genomic or non-genomic receptors.

Among the pesticide families identified in the studies described above, organochlorines, as a whole appear to be associated with a reduction in T4 (the results for free T3 are contradictory).

An increase in hepatic uridine diphosphate glucuronyltransferase (UGT) activity, which is observed with DDT and HCB, might be responsible for this effect. However, *in vitro* studies show that mechanisms involving other components of the hypothalamic-pituitary-thyroid axis, such as TSH receptor function, are possible. Other studies in experimental models confirm that some carbamate fungicides (mancozeb and thiram) reduce the production of thyroid hormones, an effect that may be linked to dysregulation of thyroid peroxidase activity. The results of *in vitro* and *in vivo* studies also point to a reduction in thyroid hormone levels linked to exposure to organophosphates (in some cases at environmental doses). At a mechanistic level, this effect can be attributed to a reduction in their synthesis. Experimental results for pyrethroids strongly suggest an effect on the hypothalamic-pituitary-thyroid axis. *In vitro* studies suggest a mechanism of action involving thyroid hormone receptors for permethrin, tetramethrin, and deltamethrin, particularly at low doses (around 10^{-8} M) but insufficient research has been conducted *in vivo* (except for permethrin, for which the *in vitro* and *in vivo* results are consistent).

Potential thyroid disrupting activity was also found for glyphosate, fipronil, and the neonicotinoid pesticide imidacloprid, for which the epidemiological data are limited or non-existent.

Rodents are the standard model used in regulatory toxicology to assess potential effects on thyroid function, despite limitations such as the lack of expression of serum thyroxine-binding globulin (TBG) and the importance of regulation of the hepatic conjugation of thyroid hormones. Models based on metamorphosis assays in fish or amphibians could be used instead of rodents after an *in vitro* screening stage. These rodent and amphibian models often reveal sexual dimorphism with respect to gene expression in different tissues, some of which may be co-regulated by the hypothalamic-pituitary-gonadal axis, with phenotypic or pathophysiologic consequences.

There are three particularly interesting avenues for further research: *i)* few experiments have evaluated pesticides as

potential immune system disruptors (for example in Graves' disease), which may represent an initial event amplified by interference with the targets of the hypothalamic-pituitary-thyroid axis; *ii)* few experiments have focused on non-genomic regulation (for example, by binding to $\alpha_v\beta_3$ integrin) of the hypothalamic-pituitary-thyroid axis following exposure to pesticides; and *iii)* few experiments have looked at combinations that evaluate the specific effects of different active substances compared to combinations typically found in agriculture and livestock farming.

Finally, pesticides found to have thyroid disrupting effects should be examined in epidemiological studies, and conversely, associations found in exposed populations should prompt research on mechanisms of action. Until only very recently, this area of toxicology lacked an AOP[12] approach, which would help overcome the ambiguities and controversies generated by the limitations of *in vivo* tests.

Families and active substances associated with excess risk of overt or subclinical hypothyroidism or an increase in levels of thyroid-stimulating hormone

Family Active substances	Populations	Presumption of a link
Organochlorines		
Organochlorines (without distinction)	Applicators, farmers	+
DDT/DDE	Applicators, farmers, other occupational users	±
	General population (pregnant women, children, and neonates)	+
Aldrin	Applicators	±
Heptachlor	Applicators/farmers	+
Lindane	Applicators	±

12. *Adverse outcome pathway*: a model that combines knowledge of the link between a molecular event and a harmful effect at a level relevant to a risk assessment.

Chlordane	Applicators/farmers	+
Hexachlorobenzene (HCB)	General population (pregnant women and neonates)	+
	Residents living in proximity to agricultural or industrial areas	±
Carbamates/Dithiocarbamates		
Benomyl	Applicators	±
Maneb/mancozeb*	Applicators, agricultural workers, production industry workers	+
Organophosphates		
Chlorpyrifos	General population	±
Diazinon*	Applicators	+
Malathion*	Applicators	+
Parathion	Applicators	±
Pyrethroids		
Pyrethroids	General population (adults and neonates)	±
Phenoxy herbicides		
2,4-D	Farmers	±
Other		
Paraquat	Applicators, farmers	±
Glyphosate	Applicators, farmers	±
Dicamba	Applicators	±
Pendimethalin	Applicators	±

+ based on the results reported in at least two independent high-quality studies (two studies based on the same cohort, such as the AHS, are not considered to be independent) New data
± based on the results reported in a single study (or several studies based on the same cohort) New data
* excess risk of hyperthyroidism with weak presumption of a link (±)

Endometriosis

The endometrium is a mucous membrane that covers the inner lining of the uterus. Its properties change over the course of the menstrual cycle: in the first phase, it thickens and becomes vascularized to receive the embryo during the second phase, but if fertilization does not take place, desquamation occurs, resulting in a period or menstruation. Chronic inflammation of this tissue, or endometriosis, is a disease characterized by the abnormal (ectopic) presence of endometrial cells outside the uterine cavity. It affects, according to some estimates, between 5% and 10% of women of childbearing age. In general, a distinction is made between ovarian (ovarian endometriomas), superficial peritoneal and subperitoneal forms of the disease. The latter can be further divided into retroperitoneal or deep (infiltrating the abdominal or pelvic viscera).

The etiology of the disease remains largely unknown. Various studies suggest non-exclusive genetic, nutritional, and hormonal factors. The factors most commonly associated with the risk of endometriosis include early age at menarche, a shorter menstrual cycle, low birth weight, lower lifetime body mass index (BMI), and having fewer children. Certain endocrine disruptors have been suggested as potentially contributing to its development and severity.

Few epidemiological studies have been published to date on the link between pesticides and the risk of endometriosis, and the existing research solely concerns non-occupational exposure. Most of the studies identified by this collective expert review examined organochlorine pesticides, while only one study looked at low persistence pesticides.

Two systematic reviews with meta-analyses, published in 2019, examined the role of exposure to persistent organic pollutants (POPs), including organochlorine pesticides, in the occurrence of the disease. In the first, exposure to organochlorine pesticides was associated with a statistically significant increase in the risk of endometriosis based on the results of a cohort study (with

concurrent measurement of exposure and diagnosis) and four case-control studies. According to the authors of the systematic review, this result should be interpreted with caution given the heterogeneity of the studies. The second meta-analysis also concluded that there was a statistically significant increase in risk based on 8 studies, including two cohort studies in the same population and 6 case-control studies.

The earliest hospital-based case-control studies, conducted in Canada and Japan and published in 1998 and 2005, found no association between the risk of endometriosis and exposure to a dozen organochlorine pesticides. The results of these studies are however difficult to interpret due to unquantified data and methodological uncertainties. Two other studies in the United States and Italy examined POPs and did not find a statistically significant increase in risk for hexachlorobenzene (HCB) and/or dichlorodiphenyldichloroethylene (DDE).

Two publications were identified that focused on the same population of 600 American women (organized into two subcohorts) and that involved measurement of pesticide exposure at the time of disease diagnosis. In the first study, serum levels of two isomers of the same pesticide (hexachlorocyclohexane, HCH) were found to be associated with an increased risk of the disease. Of the fifty POPs (including 11 organochlorine pesticides), only γ-HCH was associated with increased risk in the subcohort of women that had undergone laparoscopy or laparotomy for other indications, while β-HCH was the only associated substance in the second subcohort of women recruited from the general population and diagnosed by MRI. A study of these same subcohorts, published in 2020, measured urinary levels of around a dozen active substances (or their metabolites) from the organophosphate pesticide, pyrethroid insecticide, and phenoxy herbicide families. No significant differences were found in total pesticide concentrations between women with or without endometriosis, but the authors concluded that high levels of exposure to diazinon, chlorpyrifos or chlorpyrifos-methyl (organophosphate pesticides) might be associated with a risk of endometriosis based on observed trends.

The existence of a potential link between the disease and exposure to HCH and HCB has been suggested by three case-control studies. In a US study, serum levels of organochlorine pesticides were measured in 248 cases and 538 population controls. Two compounds, β-HCH and mirex, were positively associated with endometriosis (for the 3rd and 4th quartiles of exposure). The association with β-HCH was stronger when the analysis was restricted to ovarian endometriosis.

Another US study, based on a very low number of subjects (84 women, of whom 32 were diagnosed with endometriosis), measured serum levels of six organochlorine pesticides. HCB was associated with a statistically significant increase in risk for the highest tercile of exposure (a 5-fold increase), while trends were observed for aldrin, β-HCH and mirex, but interpretation of these results is limited by the small number of subjects with levels above the limit of detection. A hospital case-control study in France evaluated the association between exposure to POPs, including several organochlorine pesticides, and deep endometriosis with or without ovarian endometriosis in 55 cases and 44 controls. Positive associations were found for *trans*-nonachlor, dieldrin, β-HCH and HCB and *cis*-heptachlor epoxide (a 5-fold increase in risk).

Mechanistic analyses have shown that some pesticides have immunomodulatory effects that disrupt the cytotoxic activity of NK cells or macrophage function (associated with inflammation). This has been demonstrated through clinical and experimental studies for various pesticides, including members of the organochlorine and organophosphate families examined in the epidemiological studies above. These effects might promote endometrial cell migration and their maintenance at the site of endometriotic lesions. Estrogens appear to play a crucial role, but with a complexity that requires consideration of the timeline of action of pro- or anti-estrogenic pesticides (especially for deep forms). The role of epigenetics as a process that can influence the expression of key components in endometriosis (such as aromatase and estrogen receptors) remains insufficiently explored, and could help define susceptibility profiles for development of this disease.

Endometriosis is a complex disease that is likely to involve several pathophysiologic mechanisms that explain its different clinical forms. The involvement of several hormones, particularly estrogens, is suspected and it is therefore logical to hypothesize that environmental endocrine disruptors, and notably certain pesticides, might play a role as etiological agents.

The results of around ten epidemiological studies in this area, taken together, support a weak presumption of a link between exposure to organochlorine pesticides and the risk of endometriosis. Two active substances belonging to this family, β-HCH and HCB, appear to be involved, but the evidence is weak. One recent study has suggested a link with certain organophosphate pesticides, but this observation requires confirmation. Difficulties in accurately assessing the degree and timeline of exposure due to a lack of appropriate markers and variability in detection rates are major sources of uncertainty. High quality observational studies therefore appear necessary to confirm these links and to pursue further research on other endocrine disruptors.

Presumption of a link between exposure to pesticides and endometriosis

Exposure	Populations affected by excess risk	Presumption of a link
Organochlorine pesticides	General population	±

± based on the results of two meta-analyses published at the same time (including five studies and eight studies that partially overlap) New data

Families and active substances associated with excess risk of endometriosis

Family Active substances	Populations affected by excess risk	Presumption of a link
Organochlorines		
β-hexachlorohexane (β-HCH)	General population	± [a]
Hexachlorobenzene (HCB)	General population	± [b]

± [a] based on the results of one cohort study and two case-control studies New data
± [b] based on the results of one cohort study and one case-control study New data

Focus on active substances

While this collective expert report, like that on pesticides in 2013, takes a disease-based approach, it also focuses on three active substances: chlordecone and glyphosate were analyzed at the request of the commissioning bodies, to which was added succinate dehydrogenase inhibitor (SDHi) fungicides. Exposure to chlordecone, which is adressed only in association with prostate cancer, is analyzed in the section "Focus on chlordecone" in the chapter on prostate cancer. These three pesticides were examined because they are the subject of scientific and societal debate and reflect the complexity of the field of environmental health. Chlordecone is an active substance that was used in limited areas, primarily the French West Indies on bananas, and for which there exists toxicological data but only two epidemiological studies. Conversely, glyphosate is the most widely used herbicide in the world, and it has been the subject of extensive epidemiological and toxicological studies. However, these studies are difficult to interpret and sometimes conflicting, as exemplified by the difference in interpretation between IARC and EFSA following an analysis of the carcinogenic potential of glyphosate in 2015. Finally, for SDHi fungicides, very few studies are available and the risk assessment is currently based primarily on the mechanism of action of these pesticides.

Glyphosate and glyphosate-based formulations

The herbicidal properties of glyphosate were discovered by Monsanto in 1970 and the first commercial formulation containing glyphosate was marketed in 1974 as Roundup. Glyphosate is the most widely used herbicide in the world, with its consumption increasing from 56,000 tons in 1994 to over 820,000 tons in 2014, primarily in the agricultural sector. It is also the most widely used herbicide in France, with annual quantities sold of 6,421 tons (in 2009) and 10,070 tons (in 2014). A portion is sold in the form of commercial products authorized for use by

the general public (non-professionals): between 13.9% (2017) and 23.7% (2013).

Due to the methods and circumstances of application, dermal absorption is considered the main route of exposure among both professional and non-professional users. In addition, contamination of foodstuffs may also result in oral exposure of consumers. Glyphosate undergoes very little metabolism in the body (less than 1%) and is excreted in the urine unchanged. It does not have a high bioaccumulation potential, and its half-life in humans is estimated to be between 5 and 10 h.

Quantification of glyphosate in urine is the most appropriate method for estimating and monitoring population exposure over time. However, this requires rigorous analytical methods for extraction, separation and detection. The urinary concentrations frequently found in occupationally exposed populations or in the general population are in the μg/L range. These values are 100 to 1,000 times lower than those expected for chronic exposure corresponding to the acceptable daily intake (ADI) currently set by EFSA, that is 0.5 mg/kg/day. This reference value is, however, based on experimental data in laboratory animals and it does not enable one to rule out all risk to humans, particularly in cases of repeated and long-term exposure. Many epidemiological studies have therefore considered the public health impact of occupational exposure (and to a lesser extent residential exposure) to glyphosate-based formulations. These studies have investigated the occurrence of both cancers and non-cancer diseases.

In 2013, the Inserm collective expert report concluded that exposure to glyphosate was associated with an excess risk of non-Hodgkin lymphoma (NHL) with a moderate presumption of a link for occupationally exposed populations (considered as a whole without distinction of a specific employment categories) and a weak presumption of a link specifically with respect to farmers. New data have been acquired since 2013. A follow-up analysis of the AHS cohort in the United States found no increased risk of developing NHL or its major subtypes

among licensed pesticides applicators exposed to glyphosate. However, a meta-analysis published by the AGRICOH consortium, combining the AHS cohort with two other agricultural worker cohorts (AGRICAN in France and CNAP in Norway) and including over 300,000 subjects, with 2,430 cases of NHL, found a statistically significant association between the risk of diffuse large B-cell lymphoma and exposure to glyphosate. The presumption of a link between exposure to glyphosate and the risk of developing NHL is therefore considered by the Inserm expert group to be moderate regardless of the employment category (farmer or other).

Regarding multiple myeloma, the 2013 Inserm collective expert report did not conclude on the existence of a link between exposure to glyphosate and the risk of developing this disease, as the few French and North American case-control studies and the AHS cohort were based on a limited number of cases. Recently, a new follow-up analysis of the AHS cohort found no association with multiple myeloma. However, a meta-analysis of earlier case-control studies, as well as some data from the AHS cohort, found an increased risk among farmers exposed to glyphosate that was at the limit of statistical significance. Taking these new data into account, the presumption of a link with respect to the risk of multiple myeloma is considered to be weak (±). It is based on a low level of evidence: a risk that is elevated, but at the limit of statistical significance in a meta-analysis of three case-control studies and one cohort study.

Very little information was available on exposure to glyphosate and the occurrence of Hodgkin lymphoma at the time of the 2013 Inserm collective expert report. Little has been published in the scientific literature since then: three studies, including a meta-analysis (based on two previous case-control studies) and a follow-up analysis of the AHS cohort. No association was found between exposure to glyphosate and the occurrence of Hodgkin lymphoma. In view of these results, no presumption of a link can be established.

Only a single study looking at exposure to glyphosate and the risk of leukemia was available at the time of the 2013 Inserm collective expert report. This study, that focused on occupational exposure in the AHS cohort and did not include acute myeloid leukemia, suggested an increased risk in the second tertile of exposure to glyphosate. The evidence was thus insufficient to establish a link. Since 2013, two meta-analyses have been published based on data from the AGRICOH consortium, concluding that there is no association with the risk of developing chronic lymphocytic leukemia (CLL). A third analysis of three case-control studies also concluded that there was no association with CLL. Two of the three case-control studies evaluating the risk of developing hairy cell leukemia found an increased, though not statistically significant, risk associated with glyphosate exposure. A recent follow-up analysis of the AHS cohort did not confirm the trend for increased risk of CLL reported previously. Finally, this new follow-up analysis of the AHS cohort, based on a limited number of cases, identified for the first time a more than two-fold increase in the risk of acute myeloid leukemia among the most exposed subjects, which did not reach statistical significance. Taking into account in particular the latest results from the AHS cohort, the presumption of a link between exposure to glyphosate and the risk of developing leukemia is considered to be weak. This presumption is based on a single study (AHS cohort) that was well conducted but requires confirmation.

Prostate cancer and bladder cancer have been studied in relation to exposure to glyphosate in the AHS cohort. With regard to prostate cancer, the various follow-up analyses of the cohort over time have not shown any excess risk. For bladder cancer, an excess risk that was not statistically significant has been observed. At present, based on the available studies, it is not possible to establish a presumption of a link between exposure to glyphosate and prostate and bladder cancer.

Concerning non-cancer diseases, some studies, primarily within the AHS cohort, point to occupational exposure in the

agricultural sector to multiple pesticides, including glyphosate, being associated with an increased risk of wheeze (with or without an allergic component) in male farmers and industrial applicators and of allergic asthma in their pesticide-applying spouses. In view of the limited number of studies and the fact that the results are primarily based on a single cohort study (AHS), the presumption of a link to respiratory health is considered to be weak.

Other studies, all based on the AHS cohort, have reported an excess risk of hypothyroidism in male glyphosate applicators, without evidence of a dose-response relationship. Among their glyphosate-applying spouses, no association was found with the risk of hypothyroidism.

Finally, various studies have explored whether occupational or residential exposure to glyphosate might be linked to the occurrence of anxiety and depressive disorders, Parkinson's disease and chronic kidney disease of unknown etiology in adults, with birth defects and neurobehavioral disorders in young children, and with growth indicators in newborns (gestational length, birthweight). However, at present the ecological nature of some studies, imprecision in measuring exposure, low subject numbers and the inconsistency of the conclusions, make it impossible to reach definitive conclusions and thus establish a presumption of link.

And what about the biological plausibility of the epidemiological associations described above? Numerous experimental studies have been carried out, on both cancer and non-cancer diseases in relation to this issue.

In recent years, glyphosate has been thrust into the spotlight by a debate regarding its carcinogenicity. This stemmed from the divergence between the conclusions of IARC and the other national and international agencies responsible for the classification and regulation of chemicals. These divergent conclusions are largely due to the different approaches and criteria used.

For carcinogenicity testing in laboratory animals as well as mutagenicity studies, the level of evidence is relatively limited. However, many studies show genotoxic damage (DNA breaks or structural changes). These changes, if not faithfully repaired, can lead to the development of mutations and trigger carcinogenesis. Such effects are consistent with the direct or indirect induction of oxidative stress by glyphosate, observed in various species and cell systems, sometimes at exposure levels compatible with those that may be experienced by human populations.

In addition to glyphosate's ability to induce production of reactive oxygen species, other toxicological characteristics have been described. Glyphosate is used to block amino acid synthesis in plants. Its principal mode of action is the inhibition of an essential enzyme that is expressed by plants, but also by fungi and certain bacteria. Unlike these organisms, animals and humans do not have the gene coding this enzyme. However, experimental studies suggest deleterious effects related to mitochondrial toxicity (associated with behavioral disturbances in models such as zebrafish) and endocrine disruption, including impaired steroidogenesis and activation of estrogen pathways without binding to estradiol receptors. The results of studies published since 2013, that must be confirmed, also indicate dysregulation of the concentration of neurotransmitters (consistent with behavioral alterations), and also of the gut microbiota in several animal species including humans, that are a logical target of glyphosate as certain bacteria also express the enzyme targeted in plants. Such mechanisms merit further investigation and greater consideration during regulatory evaluation procedures.

Finally, although beyond the scope of this review, the expert group notes that the potential effects of glyphosate use on ecosystems and their regulation raise important questions surrounding the environment and its indirect impact on human health. These deserve to be addressed using an integrated and systemic (i.e. "One Health") approach and incorporated by policy makers in the decision making process on equal standing with social and economic considerations.

Succinate dehydrogenase inhibitor fungicides

Succinate dehydrogenase inhibitors (SDHi) are a family of fungicides, some of which, such as carboxin and flutolanil, have been used for over thirty years. Other, so-called second-generation SDHi, have been used for around a decade, for example boscalid, benzovindiflupyr, isopyrazam, penthiopyrad, and sedaxane. While use of the first generation of these pesticides in France has declined over the past ten years, the use of second-generation SDHi has increased and expanded to other spheres of activity (for example for control of nematodes in turf).

The French population is potentially exposed to SDHi *via* the air, food, water, and soil (use on stadium pitches or golf courses), or in an occupational setting through the handling and spreading of these products. In France, monitoring programs in the various environmental compartments focus on several SDHi, including boscalid (the most sold), which is monitored and detected in the air and in aquatic systems. Boscalid, along with flutolanil and carboxin, were included in the French 'Total Diet Studies' designed to assess the risk to consumer health, and are monitored in foodstuffs along with bixafen, fluopyram, fluxapyroxad, penthiopyrad and benzovindiflupyr. At the European level, SDHi fungicides were quantified in 2.2% of over 500,000 food samples analyzed in 2018. Of the sixteen SDHi measured, fluopyram and boscalid were by far the most commonly quantified, and boscalid was found at levels exceeding the maximum residue limit in 0.08% of the samples tested. As SDHi are not included in current human biomonitoring programs in France, very limited data are available on the levels of these substances among the general population. In France, a single academic study, involving 311 pregnant women in the ELFE cohort, quantified boscalid with a detection frequency of 63% in hair. No studies have been identified evaluating occupational exposure to SDHi.

The mechanism of action of SDHi fungicides is based on disruption of mitochondrial function through inhibition of the

activity of SDH, an enzyme complex involved in cell respiration (complex II) and that is essential to life. In humans, the consequences of genetic inactivation of SDH (mutation of one of the four genes coding for the enzyme subunits) are well documented, resulting in the development of neurologic diseases and cancers, particularly linked to accumulation of succinate, the substrate of SDH. High levels of this oncometabolite can lead to processes associated with tumorigenesis. These include dysregulation of metabolic homeostasis, oxidative stress leading to a state of cellular "pseudohypoxia", epigenetic changes, and promotion of epithelial-mesenchymal transition, a process involved in metastasis.

While mitochondrial dysfunction of genetic origin in humans creates a predisposition for many diseases, this does not ipso facto mean that partial or complete inhibition of SDH activity, for example in the case of chronic exposure to SDHi, leads to the same pathophysiologic effects. Nevertheless, the SDH complex is highly conserved between species. Crystallography and genetic studies have shown that the structure of SDH is conserved from one species to another, with homologous peptide sequences at the catalytic site. All of this raises legitimate questions about the deleterious effects of exposure to SDHi on human health and biodiversity. Despite conservation of the structure of SDH over the course of evolution, some studies suggest significant variability in the inhibition profile of its activity by different SDHi depending on the species. These studies are based on measurements of the median inhibitory concentration (IC_{50}), which, in this case, corresponds to the concentration of a given SDHi that results in 50% inhibition of SDH activity. The results of these studies are however difficult to compare due to differences in methodology, or in some cases missing methodological information. The currently available data do not therefore provide sufficient evidence to draw conclusions regarding the specificity of SDHi for fungal SDH and their safety for non-target species. This would require *in vitro* IC_{50} data obtained using homogeneous samples, and *in vivo*

experimental data from animal models that take into account the toxicokinetics, toxicodynamics, and biotransformation of SDHi in whole organisms.

Regarding the potential toxic effects of SDHi in different species, a series of studies in zebrafish, half of which have been published by the same research group, show that exposure to SDHi could lead to developmental abnormalities and numerous malformations as well as impaired metabolism, thyroid function, and reproduction. These effects suggest that SDHi fungicides could be considered, at least in this species, as endocrine disruptors.

Some studies have explored the effects of SDHi on ecosystems. Exposure of bees to boscalid alters the composition of the gut microbiota and has an impact on behavior. Other studies have shown deleterious effects on soil organisms (toxicity and effects on behavior in nematodes and earthworms) and aquatic organisms (toxicity in algae and teratogenic effects in amphibians). Further studies should be pursued to document the impacts of SDHi on biodiversity and potentially on the regulation of ecosystems, and their impact on human health.

The carcinogenicity data for SDHi, analyzed here, are derived solely from reports published by European health authorities as part of their evaluation of marketing authorization applications submitted by companies. According to the conclusions reached in these reports, the majority of SDHi do not show any genotoxicity. However, an increase in the incidence of adenomas and carcinomas has been demonstrated in rodent studies for the majority of SDHi, albeit with some sexual dimorphism. Various organs are involved; principally the liver, but also the thyroid, lungs, and uterus. Despite these observations, the vast majority of EU-approved SDHi are not classified by the regulatory authorities as substances that may cause cancer or are suspected of doing so. These conclusions were based on the mode of action reported by industry studies to account for the carcinogenic effects of SDHi in rodents, which involves activation of the nuclear receptor CAR (constitutive androstane receptor). This

mode of action is considered specific to rodents and was judged not to be relevant to humans by health authorities. Questions regarding the mode of action of SDHi and the experimental models used are the subject of debate within the scientific community and health agencies, and it is not currently possible to rule out mechanisms of action involved in cancerous transformation, other than that involving the CAR receptor, might be at play that are relevant to humans.

With regard to regulatory testing, the Organization for Economic Co-operation and Development (OECD) has examined how to assess the carcinogenic potential of substances not recognized as being genotoxic, such as SDHi. A consensus paper published by an OECD international expert group recognized the need to expand evaluation with *in vitro*/*ex vivo* tests, using an integrated approach based on an adverse outcome pathway framework, which consists of describing a logical sequence of causally linked events at different levels of biologic organization. Some mechanisms identified by the OECD are relevant to SDHi, including oxidative stress and epigenotoxicity, while others not mentioned might include mitochondrial toxicity and epithelial-mesenchymal transition. Carcinogenicity testing might also incorporate the notion of impact on tumor progression (promotion/metastasis) since the initiation process, which is the particular focus of genotoxicity and mutagenicity tests, is not the only one involved in cancer. However, making specific recommendations for improving assays and models used in regulatory toxicology would require an analysis of all the processes and tests, and is an undertaking far beyond the scope of this expert review.

Finally, as with all pesticides, regulatory toxicology evaluates active substances rather than formulations. In relation to SDHi, some formulations contain strobilurin fungicides that inhibit cell respiration at the level of respiratory complex III and might therefore potentiate effects on mitochondrial function. This underscores the importance of testing not only active substances but also formulations in toxicology studies.

At present, there are virtually no epidemiological data on the possible effects of SDHi active substances on the health of farmers or the general population. The only study to have examined this question, conducted on participants in the ELFE cohort, found no association between exposure to boscalid during pregnancy and intrauterine growth. Using an indirect estimate of exposure to SDHi, that is by considering agricultural tasks or activities that could expose workers to SDHi which have been on the market for several decades (consistent with the time to onset of disease such as cancers or degenerative diseases), the limited data available do not reveal any signals suggesting a specific excess risk in these agricultural populations. Very little data are therefore available in humans to assess the risks associated with use of SDHi. Several strategies could help clarify the potential consequences of occupational and environmental exposure to SDHi on human health; these include, in the short term, expansion of human biomonitoring programs and the exploitation of existing cohorts (such as AGRICAN and ELFE), and in the longer-term, initiation of new epidemiological studies.

Annex 1: Inserm Collective Expert Reviews: principles and methods

The aim of Inserm Collective Expert Reviews[13] is to summarize scientific knowledge on topics in the health sector through a critical analysis of the international literature. They are conducted at the request of institutions (ministries, health agencies or insurance bodies, etc.) who want up-to-date research data relevant to their public policy decisions.

Since their inception in 1994, over 80 collective expert reviews have been conducted on numerous subjects. Inserm is responsible for the conditions under which the expert reviews are performed (selection of source documents, constitution of expert groups based on the qualifications and independence of its members, transparency of the process, etc.) in accordance with its Charter of Expertise, which sets out its ethical principles.[14]

The Collective Expert Reports Unit of Inserm, which is part of its Public Health Thematic Institute, manages the scientific and technical coordination of the expert reviews following a defined procedure consisting of six main stages.

Commission of the collective expert review

The first stage involves *i*) working with the commissioning body to ensure the request is clearly defined, *ii*) verifying that sufficient scientific literature exists on the topic in question, and *iii*) drawing up an agreement outlining the scope and principal

13. Brand name registered by Inserm.
14. Inserm Charter of Expertise available from:
https://www.inserm.fr/wp-content/uploads/media/entity_documents/inserm-charteexpertise.pdf

topics of the expert review, as well as the project duration and budget. During this stage the commissioning body's request is translated into scientific questions that will be addressed by the experts.

Literature searching

A document base is assembled from articles identified through searches of international bibliographic databases, along with other documents identified from the gray literature (institutional reports, etc.) relevant to the scientific questions posed. This document base is provided to the experts, and updated during the expert review and is complemented by the experts according to their area of expertise.

Constitution of a multidisciplinary expert group

For each expert review, a group of 10 to 15 experts is formed whose composition is determined by the scientific fields required to analyze the literature and answer the questions asked, while also ensuring the complementarity of approaches and disciplines.

Experts are selected from across the French and international scientific community. The selection is based on scientific expertise as demonstrated by their publications in peer-reviewed journals and by peer recognition. The experts must be independent of the commissioning body and of recognized lobbying groups. Prior to the start of the expert review, all the experts are required to complete and sign a declaration of interests that is kept on file by Inserm. The composition of the expert group is approved by the executive management of the Inserm Public Health Thematic Institute.

The experts' work lasts from 12 to 18 months depending on the amount of literature analyzed and the complexity of the topic.

Critical analysis of the literature by the experts

Over a series of expert group meetings, each member presents their critical analysis of the literature on a given topic, which is then discussed by the group. This analysis leads to the drafting of the various chapters of the expert report, that is constructed through collective discussion to ensure its coherence and articulation.

Individuals outside the group of experts may be invited to participate in these meetings to provide a complementary approach or viewpoint. Depending on the topic, meetings with civil society organizations may also be arranged by the Collective Expert Report Unit in order to learn about their issues of concern and to identify other sources of data.

Summary and recommendations

A summary is produced that brings together the key points of the literature analysis and outlines the principal findings and overarching themes. Most collective expert reports include recommendations for action or research intended for decision-makers. These recommendations, formulated by the group of experts, are based on scientific arguments resulting from the analysis. The collective expert review procedure does not generally include an assessment of their feasibility and social acceptability. Such assessment may be subject to other types of expert review.

Publication of the collective expert report

After submission to the commissioning body, the collective expert report, consisting of the analysis, summary and recommendations, is published by Inserm. In agreement with the commissioning body, various communications strategies may be used, such as press releases, press conferences, or seminars open to various stakeholders including patient organizations, professionals, researchers, and institutions.

The expert reports are available from bookstores and can be accessed from the Inserm website.[15] The full collection is also available from iPubli,[16] which provides free access to Inserm publications.

15. https://www.inserm.fr/information-en-sante/expertises-collectives
16. http://www.ipubli.inserm.fr/handle/10608/1

Annex 2: Literature search strategy

Based on the specifications of the expert review and corresponding scientific questions, a literature research was conducted to identify studies on the health effects of pesticides and to compile the document base provided to the experts for analysis. A systematic search for potential interests was conducted on the bibliographic corpus and the links identified are reported in the list of references in each section.

Search strategy for potential interests

The strategy used was a search in all fields and the full text for the names of the following manufacturers: Monsanto, Bayer, Syngenta, Nufarm, Hedland, Dow, Agrosciences, Makhteshim, Scotts, Rhone Poulenc, Sumiagro, Agri-Guard, Cheminova, Agria, Ventura Agro, etc. The articles were analyzed and categorized into 4 categories: industry studies for regulatory evaluation dossiers, studies funded by an agrochemical company, studies with one or more authors affiliated to an agrochemical company, and studies with an identified declaration of interests.

Main sources and bibliographic databases

The literature searches were carried out using bibliographic databases (PubMed/Medline, Scopus, Cairn, etc.) and the MeSH thesaurus, and the keywords listed below. The database searches covered the years of publication 2012-2020. The articles were sorted for relevance to the subject of the expert review.

Main keywords used in searches and size of the document base

The first document base was completed in July 2018. It currently includes over 5,300 references. The literature search was based on the combination of keywords relating to the topic of the expert review and keywords relating to the various subtopics explored (background, epidemiology, determinants, consequences). An overview of the search parameters is provided below:

Search no. 1

"prospective studies"[MeSH Terms] OR "prospective studies"[All Fields]

OR "cohort studies"[MeSH Terms] OR "cohort"[All Fields] OR "cohorts" [All Fields]

OR "follow-up studies"[MeSH Terms] OR "follow-up"[All Fields]

OR "case-control studies"[MeSH Terms] OR "case-control"[All Fields]

OR "retrospective studies"[MeSH Terms] OR "retrospective studies"[All Fields]

OR "longitudinal studies"[MeSH Terms] OR "lonsgitudinal studies"[All Fields]

OR "cross-sectional studies"[MeSH Terms] OR "cross-sectional studies"[All Fields]

OR "prospective studies"[MeSH Terms] OR "prospective studies"[All Fields]

OR "pilot projects"[MeSH Terms] OR "pilot study"[All Fields] OR "pilot studies"[All Fields]

OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]

OR "risk factors"[MeSH Terms] OR "risk factors"[All Fields]

OR "multicenter study"[Publication Type] OR "meta-analysis"[Publication Type]

AND

"pesticides"[MeSH Terms] OR "pesticides"[All Fields]

OR "fungicides, industrial"[MeSH Terms] OR "fungicides"[All Fields]

OR "herbicides"[MeSH Terms] OR "herbicides"[All Fields]

OR "insecticides"[MeSH Terms] OR "insecticides"[All Fields]

OR "Agrochemicals" [MeSH Terms]

AND

[disease keywords]

Search no. 2

"agricultural workers' diseases"[MeSH Terms]

AND

[disease keywords]

Search no. 3

"occupational exposure"[MeSH Terms] OR "environmental exposure"[MeSH Terms] OR "environmental"[All Fields] AND "exposure"[All Fields]

AND

"pesticides"[MeSH Terms] OR "pesticides"[All Fields]

OR "fungicides, industrial"[MeSH Terms] OR "fungicides"[All Fields]

OR "herbicides"[MeSH Terms] OR "herbicides"[All Fields]

OR "insecticides"[MeSH Terms] OR "insecticides"[All Fields]

OR "agrochemicals" [MeSH Terms]

AND

[disease keywords]

Other keywords

"farmers", "farm residents", "gardeners", "pesticide applicators", "occupational pesticide exposure"

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Pesticides et effets sur la santé. Nouvelles données

Éditions EDP Sciences, juin 2021, 1 032 pages, 80 €
Collection Expertise collective
ISBN 978-2-7598-2629-2

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Achevé d'imprimer en février 2022 par Corlet Imprimeur
14110 Condé-en-Normandie
Dépôt légal : février 2022 - n° d'imprimeur : 21110843 - *Imprimé en France*

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ISBN 978-2-7598-2721-3
ISSN 1264-1782
DOI: 10.1051/978-2-7598-2721-3

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