

Inserm Collective Expert Report

The effects of pesticides on health: New data

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 "The effects of pesticides on health", 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 analysed 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's 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 tumors of the central nervous system.

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.