



Inserm

La science pour la santé
From science to health

**Pesticides and health: a
multidisciplinary INSERM expertise**

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Pesticides and health: a multidisciplinary INSERM expertise

The objectives were to study:

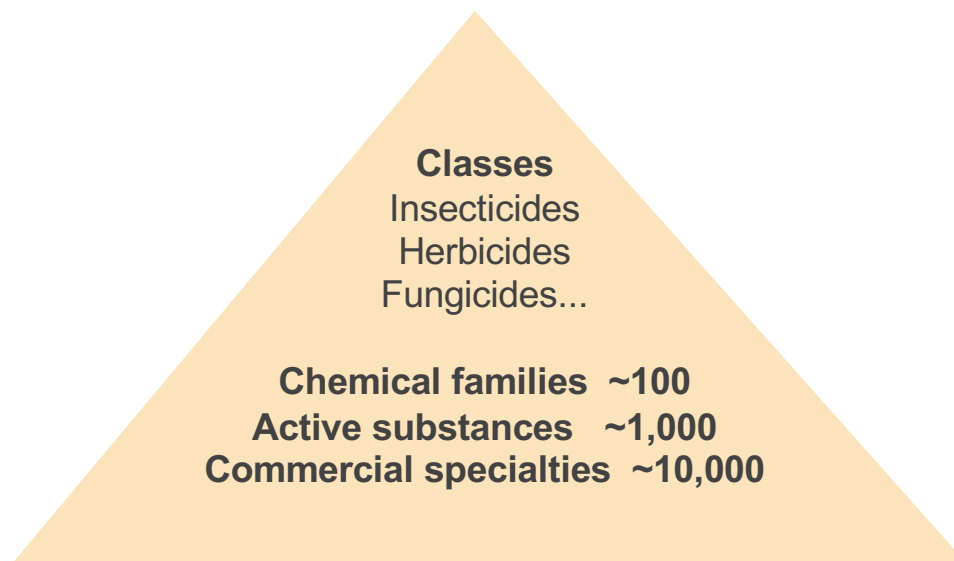
- **pathologies** potentially related to exposure to pesticides, whether occupational or not
- **glyphosate** in order to have new data available given the uncertainties on its toxicity
- **chlordecone**

What do we mean by "pesticides"?

Generic term

- Substances acting on living organisms (insects, plants, fungi) to destroy, control and repel them
- Covers "plant protection" products, biocides, products for veterinary purposes

Heterogeneity



Pesticides and health: a multidisciplinary INSERM expertise

How to study

Pesticides

X

Health



Four expertises:

- Epidemiology
- Toxicology
- Expology
- Sociology

Epidemiological approach

Pesticide exposure

Multiple and variable over time in terms of use and intensity



Health effects

Heterogeneous and can be difficult to define (types and subtypes of tumors...)

The quality and scope of the conclusions depend on:

- Study design (cohort, case-control, ecological)
- Of the population studied (adults, pregnant women, children, etc.)
- Methods for estimating exposure and health effects
- Data quality (power, bias control and confounders)

One key parameter: the level of presumption

(++) The presumption of a link is **strong**: a good quality meta-analysis that shows a statistically significant association, or several good quality studies from different teams that show statistically significant associations

(+) The presumption of a link is **average**: at least one good quality study that shows a statistically significant association

(±) The presumption of a link is **weak**: if the studies are not of sufficient quality or are inconsistent with each other or do not have sufficient statistical power to allow the conclusion that an association exists



Presumption ≠ evidence of a causal link

Mechanistic approach

Toxicological studies are essential to assess the plausibility of a link between an active substance and the occurrence of a pathology

They are based on

- **experimental** studies *in vitro and in vivo*
- **computational** analyses (in silico) -> AOP

AOP (adverse outcome pathway): a logical sequence of biological events causally linked to an adverse health effect, used in risk assessments

- *They can be initiated because associations have been found in epidemio. studies or...*
- *They may be at the initiative of epidemiological research*

Pesticides and health: a legitimate concern

Active substances targeting living organisms

- Have been developed to impact animal or plant species
- The conservation of many physio. systems across species makes it difficult to design absolutely species-specific molecules.

Widespread contamination of the environment

- 80% of contaminated groundwater

Frequent human exposure

- Professional environment
- General population: **found in more than 1/3 of food** (EAT, ANSES)
- 10% of the population consumes unregulated tap water at some point in the year (in terms of the presence of pesticides)
- 100% of the general population has levels of at least one family of detectable pesticides in the body

Historical examples

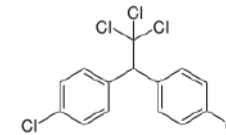
Before the beginning of the 20th century

- Nicotine, mercury, arsenic used as pesticides (since banned in the EU)

From the 1940s: beginning of the era of synthetic pesticides

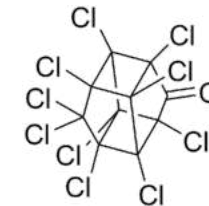
Organochlorine pesticides (1940-80)

- Many active molecules including...DDT: Effects on biodiversity highlighted in the 1960s, banned in 1970 (Sweden). Human health effects highlighted later. Global ban in 2004 (Stockholm Convention on POPs)
- Chlordecone: suspected effects on cancer risk, banned in the USA (1975), in France (1990); derogatory authorization in the West Indies in banana plantations until 1993



Organophosphate pesticides

- Action on the nervous system of target species, but also possibly in humans
- Production increased in the 1970s and then decreased in the 21st century
- Many organophosphate are banned in Europe (e.g. chlorpyrifos)



Many other families

- Neonicotinoids, pyrethroids...

What are the main highlights of the 2021 INSERM expertise ?

Pesticides – pathologies : strong presumption

	Pathology	Exhibition
Effects on the health of the child	Impaired motor, cognitive and sensory skills	Exposure during pregnancy to organophosphate (indiscriminate)
	Behavioral disorders, especially internalized (anxiety)	Exposure during pregnancy to pyrethroids (without distinction)
	Tumours of the central nervous system (childhood)	Exposure to pesticides (indiscriminate) during the prenatal period
	Acute myeloid leukemias (AML, childhood)	Domestic exposure to pesticides (without distinction)
Effects on adult health	Cognitive impairment in adults	Exposure to organophosphate pesticides
	Parkinson's disease	Occupational exposure to pesticides (without distinction)
	Prostate cancer	Exposure to Chlordecone
	Non-Hodgkin lymphoma	Organophosphate pesticides (++) ; of which diazinon (++)
	Multiple myeloma	Occupational exposure to pesticides (without distinction)
	COPD, chronic bronchitis	Indiscriminate exposure to pesticides

Pesticides – pathologies : average presumption

	Pathology	Exposure
Effects on child health	Impaired motor, cognitive and sensory skills	Residential exposure during pregnancy (domestic use, proximity to agricultural activities)
	Behaviour suggestive of autism spectrum disorders	Exposure during pregnancy to organophosphate (indiscriminate)
Effects on adult health	Alzheimer's disease	Indiscriminate exposure to pesticides
	Breast cancer	Exposure to DDT in childhood
	Non-Hodgkin lymphoma	Organophosphate pesticides; chlordane (+), glyphosate (+)
	Multiple myeloma	Permethrin (+)
	Leukaemia	Deltamethrin, terbufos, DDT
	Kidney and bladder cancer	Occupational exposure to pesticides without distinction
	Soft tissue and viscera tumours	Indiscriminate exposure to pesticides
	Thyroid pathologies	Indiscriminate exposure to pesticides

DDT and breast cancer

Early exposure to DDT likely increases the risk of breast cancer



Follow-up of the
→
"G0" cohort
(1960-1998)

No association
between DDT in
adulthood and breast
cancer incidence

(Cohn, *EHP*, 2007)

Determination of DDT (c. 1960)

↓
Childbirth



Follow-up of the
→
"G1" cohort
(1960-2010)

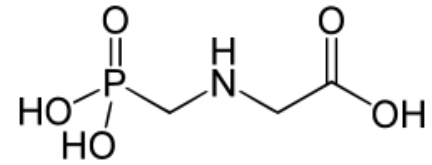
Combination of
DDT (perinatal
level) and breast
cancer

(Cohn, *JCEM*, 2015)

Follow-up of the
→
"G2" cohort
(2010-2013)

Link between DDT
(grandmother) and
age at menarche?

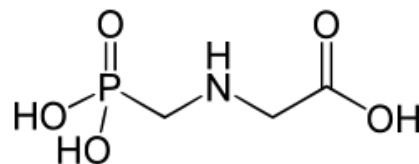
(Cirillo, *C Epid Biom
Prev*, 2021)



Scientific and societal debates dating back at least to

- **IARC's** classification of glyphosate as a "probable carcinogen" (category 2A) in 2017
- This classification was not in line with the assessment of the EU scientific authorities (**EFSA**)
- EU classification of glyphosate as a proven or suspected carcinogen could lead to its ban

Glyphosate



- A non-selective herbicide used in a wide number of formulations since its introduction on the market in 1974
- Use prohibited in France in public spaces in 2017 and for individuals in 2019
- Its mode of action is based on the inhibition of an enzyme, not present in humans or animals, necessary for the synthesis of aromatic amino acids in plants, certain fungi, certain bacteria
- Classified as a "probable" carcinogen by IARC but not considered a carcinogen by most national and international health agencies. The discrepancy can be explained by the different approaches and criteria of interpretation, including the distinction between danger and risk

The collective expertise aimed to analyze

- the expology data (use, contamination of environments and the population)
- the epidemiological data published since 2013 and
- the mechanisms of toxic action of glyphosate and its formulations on the basis of recent literature

Glyphosate contamination

- Low volatile (its occasional presence in the air is related to the drift of spray droplets)
- On treated surfaces, it can persist as well as its degradation product (AMPA) depending on the physico-chemical nature of the soils
- Soil leaching can lead to contamination of surface water.
 - In France, glyphosate or AMPA were quantified in 22% (2007) to 9% (2017) of the measurement points
 - Only one point, in 2014, showed an exceedance of the environmental quality standard
- For drinking water, the rate of non-compliance (0.1 µg/l) ranged from 0.05% (2007) to 0.26% (2017), without any point reaching the health thresholds
- In an analysis of pesticide residues in European food (2017), glyphosate was quantified in only 2.5% of 8,672 samples analysed and 0.2% exceeded the MRL

Glyphosate : toxicokinetics & biomonitoring

- Poorly metabolized (<1%)
- Rapidly eliminated by urine (half-life in the blood of 5 to 10 h) in humans
- Determination of glyphosate in urine requires validated chemical methodologies such as gas chromatography
- The impregnation of populations is mostly low
 - urinary concentrations of the order of $\mu\text{g} / \text{l}$
 - exposures 100 to 1000 times lower than the acceptable daily intake currently in force
- Water quality standards cannot be compared with urinary concentrations or health reference values such as the ADI

Glyphosate: new epidemiological data (2013 – 2021)

- **NHL: presumption of weak link (\pm) in 2013**; the results of new meta-analyses reinforce the level of presumption of a link between occupational exposure and an increase in the risk of NHL (from 30-40%): **presumption of medium link (+) in 2021**
- The results of a meta-analysis of 3 case-control studies and two AHS cohort analyses lead to the weak presumption (\pm) of a link to multiple myeloma.
- A link with a low level of presumption (\pm) is identified for leukemias; it is based solely on the results of the AHS cohort that will need to be confirmed
- Links are identified for respiratory disorders (wheezing, asthma) or thyroid disorders (hypothyroidism). These results are mainly based on the AHS cohort and presumption levels are considered low (\pm)

What about the biological plausibility of the observed associations?

Glyphosate: mechanisms (cancer)

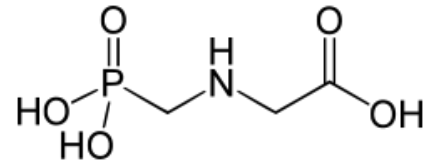
- Although sometimes contradictory, mutagenicity tests in bacteria or eukaryotic cells are rather negative, while **genotoxicity tests are rather positive**.
- These results are consistent with the induction of **oxidative stress** demonstrated in different species and cellular systems and potentially involved in genetic instability.
- Experimental carcinogenesis studies in rats or mice show excess cases and suggest a tumor-promoting effect, but they are not convergent
- In exposed animals, there are different tumours, usually limited to a single sex, which occur only at very high doses or only on certain strains. The level of evidence in rodents, although not zero, remains limited

Other mechanisms of toxicity are mentioned in the recent scientific literature

Glyphosate: mechanisms (other)

- **Mitotoxicity:** in vitro and in vivo models show the induction of oxidative stress that can lead to apoptosis or neurotoxicity
- **Suggested pro-estrogenic activity** via activation of the ER α receptor by non-genomic mechanisms and **anti-aromatase activity:** stimulation of cell proliferation?
- **Endocrine disrupting effects** on developmental or reproductive functions in rodents of both sexes (disruption of steroidogenesis, epigenetic modifications, intergenerational effects)
- **Dysbiosis of the gut microbiota in humans and animals**

These mechanisms deserve to be confirmed, deepened and further taken into account in regulatory evaluation procedures.



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This collective expertise from Inserm concludes that:

- There is a presumption of a medium link regarding the risk of NHL, and lower for other cancers
- Animal experimentation is rather in favor of a genotoxic effect of glyphosate
- There could be other mechanisms of action of glyphosate on the body (endocrine disruption, effect on the intestinal microbiota...)

Conclusion: Pesticides and health

- Significant societal concern justified by the widespread exposure to pesticides, the health effects of many pesticides and the existence of alternatives to produce with a minimum intake of pesticides
- The rise of molecular epidemiology (based on exposure biomarkers) now allows it to provide more results specific to certain pesticides, in addition to toxicological work.
- Many of the conclusions of the Inserm collective expertise on the same subject of 2013 have been reinforced (and not weakened)
- Beyond cancers and neurodegenerative diseases (already identified in 2013), the expertise identifies other possible systemic effects of certain pesticides (multiple myeloma and permethrin, respiratory health, thyroid disorders ...)
- The European regulatory framework is protective for health, but this protection can only be achieved by strongly supporting research, given the number of substances to be considered and the diversity of possible effects and mechanisms of action.

Thanks to all experts and ...

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