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Review Article

Human effects of lindane in a one health perspective. A review

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Abstract

Lindane or gamma-hexachlorocyclohexane is a chloro-organic insecticide marketed since 1938. The demonstration of significant toxic effects for humans, including neurological, hepatic, hematological, and carcinogenic effects, led to its ban. Since 2000, the use of lindane has declined, but attention to the possible effects on public health must remain high, given the bio persistence of the toxicant. The purpose and aim of this study were to recapitulate the effects that lindane may have on humans, based on a review of the literature. The results indicate that, despite the many years that have passed since the demonstration of the toxic effects of lindane, the high persistence and accumulation of the substance in ecosystems, make it even possible that it plays a role in the genesis of chronic degenerative diseases. The connection between human, animal, and ecosystem health which is contained according to the World Health Organization in the "One Health" model, urges us not to slow down our vigilance on these substances.

Introduction

Pesticides are chemicals, natural and industrially produced, or microorganisms, used in agriculture to control weeds and insects [1]. Among pesticides, organochlorine, pyrethroid, organophosphates, and carbamates compounds are classified as insecticides, as their most relevant role is in the control of insect pests. Organochlorine Pesticides (OCPs) represent the first important class of insecticides developed by the burgeoning chemical industry in the first half of the 20th century [2].

In recent years, growing attention has been paid to Hexachlorocyclohexane (HCH), a chlorinated cyclic saturated hydrocarbon listed as "POP" (persistent organic pollutant) by the Stockholm Convention and finally banned in 2009 [3].

The industrial synthesis of hexachlorocyclohexane through benzene photochlorination gives a mixture of isomers (α, β, γ, δ, ε) that structurally differ in the axial and equatorial orientation of the chlorine atoms with respect to the cyclohexane carbon ring. Among these isomers, only γ-HCH has specific insecticidal properties, and it is referred to as lindane [4].

The chemical was originally synthesized in 1825 but only in the late thirties the UK Imperial Chemical Industries Ltd (ICI) laboratories observed that the γ isomer was the key insecticide component. In 1949 ICI launched a seed treatment containing lindane [5]. Between 1950 and 2000, an estimated 600,000 tons of lindane were produced globally, the vast majority of which was used in agriculture [6]. A small quantity has been used as a pharmaceutical treatment for lice and scabies, formulated as a shampoo or lotion.

The widespread use of the organochlorine insecticide lindane in the world has caused serious environmental problems. In fact, in addition to being toxic to humans, pesticides also cause

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significant damage to the environment, including altering the chemical and microbiological composition of the soil, being absorbed by the plants, and because of their high water-solubility and volatility can be found in surface water and groundwater, as well as in the breathable air [7]. Since 2006, the use of lindane has been restricted in most countries, resulting in an almost total abolition of its production: currently, the only operating plant is in India for pharmaceutical purposes only [8].

There is also a problem regarding the stockpiles of the dangerous isomers produced together with lindane: to this day these waste compounds are mostly buried in uncontrolled dumps at many sites around the world [9].

An emblematic case is the Sacco Valley, in the middle of Italy, where lindane and its by-products, including β-hexachlorocyclohexane, are widely diffused and persistent. In this area, in 2005 the levels of β-hexachlorocyclohexane in cow milk were 20 times higher than the maximum allowed [10].

The consideration of the multiple damages done by many substances, such as pesticides, recalls the concept of the One Health vision proposed by WHO [11]. One Health is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems with the joint responses of government officials, researchers, and workers [12,13]. According to this principle, the prevention of risks to human health cannot be separated from the remediation and protection of the environments in which he lives or the animals on which he feeds. Man is part of a life cycle, and his health depends on that of the entire planet.

This principle has led to the enactment of laws that protect the environment and humans, this has resulted in the need to identify and punish those responsible for harming human health and the environment. Since environmental and occupational safety crimes can be committed by different people or companies, it is a high-priority issue to assess whether the harm detected in a man's health is a consequence of occupational or environmental exposure. The reconstruction of causation is a very delicate activity, requiring in-depth epidemiological and toxicological knowledge.

We conceived his study looking at the One Health holistic vision, i.e. a healthcare model based on the integration of different disciplines, based on the recognition that human health, animal health, and ecosystem health are inextricably linked. This strategy is officially recognized by the Italian Ministry of Health, the European Commission, and all international organizations as a relevant strategy in all sectors that benefit from collaboration between different disciplines [13]. One Health is an ideal approach to achieving global health because it addresses the needs of the most vulnerable populations based on the intimate relationship between their health, the health of their animals, and the environment in which they live, considering the broad spectrum of determinants that emerge from this relationship.

In this paper, we intend to briefly review the main damage that lindane can cause to human health, to trace the most correct line of investigation and respect the scientific evidence.

Methods

We followed the scoping review method [14]. Scoping reviews are an excellent tool through which to determine the relevance of a given topic in the literature and provide a clear indication of the number of studies available, as well as an overview of their objective, to identify and map the available evidence. They also allow you to identify the type of evidence available, clarify key concepts and definitions present in the literature, examine how research is conducted, and identify and analyze gaps in knowledge.

According to the steps suggested by the Joanna Briggs Institute [15] we went through the following phases: protocol, questions, and objective; eligibility criteria; selection of relevant sources of evidence (screening); extracting and charting the results; conclusions and implications.

The protocol predefined the objectives and methods and detailed the research plan. As we explained in the introduction, our main goal was to know the effects that lindane can have on humans. The secondary objective of the research was to investigate the ways in which human beings can meet the toxicant; therefore, we considered both occupational and environmental exposure.

We took care to define the review questions in a way consistent with the title. To obtain the fastest search speed, we have chosen to investigate only one database (PubMed / Medline). The research was conducted without date limits, to ensure that most relevant studies have been identified. According to the "One Health" concept, we collected both ecological and medical papers; however, given the interest in the effects on human health, we have given priority to the latter. To find relevant articles and studies on similar topics, we used the keywords "pesticide, organochlorines, lindane, pollution, environmental, occupational exposure, occupational disease" variously combined.

Eligibility criteria included all clinical studies, case reports, and population analyses, published in English, on any date. Literature reviews, commentaries, and editorials were excluded; however, they were consulted to verify the existence of any articles of interest to be included in the review. Unpublished literature (grey literature) was also introduced in the search strategy, subject to a careful check of the authority of the source. Titles and abstracts were independently screened by 2 researchers (G.A. and M.M.), with the assistance, in doubtful cases, of a third authoritative researcher (P.M.S.). The studies deemed relevant were read and two authors independently extracted the salient data: author's name, country of origin, and population examined. Recommendations for future research based on gaps identified were thus identified. Implications for practice were also identified.

Results

Absorption and distribution

In humans, as in animals, lindane is absorbed by inhalation [16], but also percutaneously as shown by both in vitro and

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in vivo studies [17,18]. After absorption, it is distributed to various organs, particularly the foregut showed in some experiments the highest content of accumulated lindane [19]. Adverse effects of lindane may include intestinal damage from oxidative stress [20].

An autopsy analysis performed in a suicide case with a solution containing 20% lindane showed an accumulation of the substance in various tissues including the brain, subcutaneous fat, muscle, liver, and kidney [21].

Absorption of the pesticide is also possible in the prenatal period. Prenatal exposure to low doses of lindane produced increased mRNA expression of Cytochrome P450 (CYP) and associated transcription factors in the frontal cortex, cerebellum, and corpus striatum [22].

The metabolism of lindane in humans is predominantly hepatic [23]. The half-life of lindane in the body is around 160 h. Owing to this long half-life, repeated exposures in contaminated environments can lead to the accumulation of lindane in tissues [21].

The distribution is not homogeneous across parenchyma, but there is a selective tropism for the nervous system. Lindane is heterogeneously distributed in the brain, with higher concentrations in white matter than in gray matter, due to its lipophilicity [24]. There are currently no studies that allow us to specify an internal dose of lindane, to be correlated to the effects on humans.

Neurological

Lindane is a neurotoxin that interferes with Gamma-Amino-Butyric-Acid (GABA) neurotransmitter function by interacting with the GABAA receptor-chloride channel complex at the picrotoxin binding site [25]. Lindane induces in mammals a hyperexcitability syndrome that can progress until the production of tonic-clonic convulsions, peripheral paresthesia and neuropathy, muscular weakness, and impaired coordination. [26].

The mechanism of action is complex and depends on doses. Primary adverse neurological effects are directed at the inhibition of GABA (A) and glycine receptors, although GABA-independent effects have also been reported [27].

The neurotoxic effects of lindane have resulted in cases of human toxicity. A very high level of urine metabolites (4.95 mg BHC/100 mL) was found in a woman who had washed two calves with a solution of BHC. She developed severe seizures but survived [28].

The spread of lindane pollution in the environment and the long persistence of the toxicant, has raised fears of neurotoxic effects in the population, mainly because unregulated disposal of HCH muck has created various dumpsites all over the world, leading to serious environmental concerns [29]. There is sparse evidence, in people who lived near agricultural crops, for an association between exposure to specific pesticides including lindane, and the risk of Parkinson's disease [30]. Another study suggests that Lindane can be a contributor to the development of Parkinson's disease, especially if combined with the usage of Dieldrin, another widely used insecticide, since both were found if substantia nigra of postmortem Parkinson disease brains; The underlying mechanism may be the synergistically induced production of reactive oxygen species (ROS) in microglia, causing oxidative damage to dopamine neurons [31].

Cancerogenic

Lindane acts at the cellular level like a prototypical chemical disruptor. It typically disrupts key pathways and mechanisms associated with cell death, thus increasing the risk of cancer [32]. The mutagenic ability of lindane is also demonstrated by epidemiologic studies [33]. There is strong evidence that lindane causes immunosuppressive effects in humans [34].

In addition, lindane has shown genotoxic effects. A significant increase in the incidence of micronuclei in bone marrow cells was induced by lindane in an animal experiment [35].

Both genotoxic and nongenotoxic mechanisms would be behind the increase in cases of non-Hodgkin's lymphoma that has been demonstrated in case-control [36].

Lindane is classified as carcinogenic to humans (group 1) by the International Agency for Research on Cancer [37] and is classified as a possible human carcinogen by the U.S. Environmental Protection Agency (B2/C) [38].

Hematological

Lindane has been shown to have dangerous effects on hematological cell lines. A case-control study of agricultural workers who handled Hexachlorocyclohexane (HCH) for 2-5 years found changes in hemoglobin as an early effect of HCH exposure [39]. An in vitro study showed that some insecticides including lindane inhibit the development of granulocyte and macrophage progenitors (CFU-GM), in particular, several phenomena have been observed: cell destruction, blockage of mitosis, and decreased or delayed mitosis [40].

A study done on a South American population sample shows an altered blood count, especially for eosinophilia, low hemoglobin, and low erythrocyte count, suggesting that organochlorine pesticides may exert adverse effects on hematopoietic tissue and liver in populations chronically exposed to high levels of these compounds [41].

A higher level of organochlorine pesticides has been observed in patients with leukemia in comparison to the healthy controls, giving rise to the hypothesis that lindane or other pesticides could be linked to leukemia [42].

Hepatic

Lindane is moderately hepatotoxic. Lindane disrupts the autophagic pathway and inhibits spontaneous apoptosis, leading to necrosis in primary cultured rat hepatocytes [43]. Oxidative stress caused by lindane intoxication produces a derangement of some antioxidant mechanisms of the liver

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cells, resulting in an elevated risk of morphological tissue lesions [44]. Experimental studies in rats showed that lindane sensitizes the liver to the damaging effects of iron overload, further increasing the oxidative stress state of the tissue, all of which may contribute to the alteration of Kupffer cell respiratory activity and the development of an inflammatory response [45]. Moreover, OCPs might enhance hepatic secretion of cholesterol into bile which promotes gallstone disease as well as lipogenesis [46].

Elevated levels of bilirubin, Gamma-Glutamyl Transferase (GGT), Glutamic-Oxalacetic Transaminase (GOT), and Glutamic-Pyruvic Transaminase (GPT) were observed in a Brazilian population heavily exposed to organochlorine pesticides [41].

Environmental pollution

Although the use of these pesticides was banned about two decades ago, they still represent a problem for human health because of their stability: the soil is a matrix that can largely retain these contaminants [47].

The environmental impacts of persistent organic pollutants (POPs) are an increasingly prominent topic in the scientific community. POPs are stable chemicals that accumulate in living beings and can act as endocrine disruptors or carcinogens during prolonged exposure. As a result, it is imperative that POPs in the ecosystem are degraded efficiently and safely to avoid long-lasting environmental damage [48]. Although many countries have banned the production and use of lindane, there are still a large number of sites and soils that are severely polluted by various isomers of HCH, including lindane, due to the large-scale production and storage of lindane over the past 70 years and mainly due to its persistence, which gives it the name along with the other pesticides of Persistent organic pollutant (POP) [49,50].

Lindane, in fact, can be released by contaminated materials, including glass, polypropylene carpet, latex-painted drywall, ceramic tiles, vinyl floor tiles, and gypsum ceiling tiles, for many years after the first use [51].

Various studies demonstrated the presence of this pesticide in the environment. In rainwater, lindane appears to be among the most frequently found pesticides. Data reported in 28 studies conducted in Europe indicate that 90% - 100% of samples taken in some countries contained this pesticide in concentrations between 0.02 and 0.833 µg/l [52]. In surface waters, lindane concentrations ranging from 0.01-0.1 µg/l have been measured, with peaks of 12 µg/l in wastewater/contaminated rivers. In deep water, lindane was found at levels of ng/l (3-163). Studies have shown the toxic effects of lindane on a fish (Etroplus maculatus) and suggest that the application of this pesticide close to rivers is a dangerous threat to aquatic life [53]. The concentration of lindane in drinking water, however, is generally less than 0.001 µg/l [54].

Human exposure to lindane occurs mainly through the diet. In industrial countries, it has been estimated that more than 90 percent of lindane absorbed by humans comes from food [54].

In contrast, this is not true for populations exposed to pollution, since assessments of long-term effects can be more reliably made if large segments of citizens who have long consumed lindane-derived compounds indirectly are analyzed. This was the case, e.g., in Italy for food following contamination of soil, fodder, or milk derivatives in contaminated areas of the Sacco Valley (central Italy) due to the burial of lindane-containing waste bins. Spillage of the compound resulted in widespread pollution of groundwater, nearby crops, and dairy products produced by cattle fed in the area, which for years have been consumed by people in the Sacco Valley area [55-57].

Occupational and today's use

Studies on occupational exposure are rather scarce since the product has been banned in more developed countries, while research is lacking in those where it is still in use. The data that emerges, and which deserves confirmation, is that non-Hodgkin lymphoma is common among farmers, where pesticides have been widely used and could be the culprit [36].

Other research has looked at the relationship between pesticides and metabolism. A recent meta-regression demonstrates that hexachlorocyclohexane exposure increases the risk of developing Metabolic Syndrome (MetS), and this is true also for other pesticides. The risk ratio is increasing with time, reflecting a probable increase in the use of pesticides worldwide [58,59].

Conclusion

The ban on lindane has had beneficial effects on wastewater quality, unintentional exposures, and clinical practice. However, occupational exposure may still be possible in developed countries for those who have contact with highly contaminated environments, such as industrial or agricultural waste repositories, as well as for workers living in countries where lindane and other toxic pesticides were not banned.

A lot of evidence exists on the role of pesticide exposure in the onset of human diseases such as cancers, neurological diseases, infertility, birth defects, and respiratory diseases. However, a great difficulty is inherent in the attempt to evaluate, from a medico-legal point of view, the occupational or environmental origin of a pathology potentially associated with lindane.

Given the many damages to human health and the strong exposure until the early 2000s in some areas, it is important for some categories of workers, such as farmers, to consider this risk when evaluating the periodic examination by the occupational physician. Particularly peripheral blood tests and liver function exams can be good predictors of exposure.

Author contributions

Conceptualization: GA, MM, NM, PMS and AM; methodology: NM; data curation: MP, LC and MT; writing-original draft preparation: GA and MM; writing—review and editing: NM; supervision: NM and PMS.

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