Unraveling mechanism of potential toxicity of pesticides in humans using artificial intelligence

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Objectives

The already extensive use of pesticides in protection against crop loss and vector-borne diseases has further intensified in recent years. Molecular targets of pesticides are often shared between pest and non-target species, and this raises significant concerns over their potential toxic effects to non-target organisms, including humans (1). This is particularly true for the neurotoxic organochlorine, organophosphate and pyrethroid pesticides (2).

Organochlorine insecticides include DDT and its analogues; cyclodienes compounds, such as chlordane, aldrin or dieldrin; the hexachlorocyclohexanes, such as lindane; and cage-structured compounds such as chlordecone (2). Their acute toxicity is moderate (less than that of organophosphates), but chronic exposure may be associated with adverse health effects particularly in the liver and the reproductive system. Lindane and cyclodienes have moderate to high acute oral toxicity, and their primary target is the central nervous system. Dieldrin exposure has been associated with Parkinson's disease.

The goal of this study was to develop a knowledge base and algorithms that can be used to predict potential toxicities to humans due to pesticide use.

Methods

We created a computational model of biological pathways by manually annotating and processing molecular information from the literature from the public domain including PubMed articles, FDA reports, UniProt and RefSeq annotations, PubChem and IntAct information. From the public domain and proprietary company datasets, we collected data on chemicals contained in a variety of pesticides and their interactions with proteins and known toxicities within 18 different species, including humans (Figure 1).

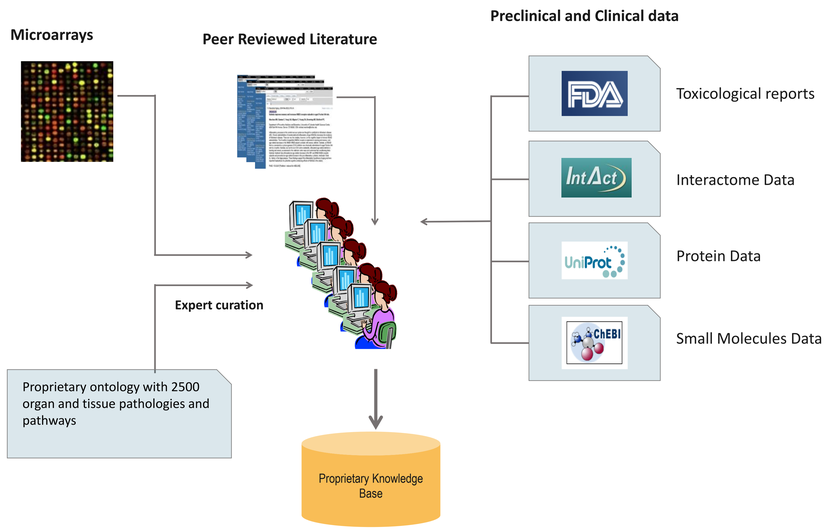

Figure 1. Manually curated database. Data was extracted from many diverse sources. Database contains complete human interactome, 2.500 organ and tissue pathologies, 500.000 synonyms/ontologies, 4 million linked articles (PubMed, FDA, clinical, patents), >10 million relationships, 50.000 biologically active chemicals.

We curated and processed the knowledge on protein function, distribution and involvement in specific pathologies. The available pathological data for each target were classified into the hierarchical structure of an ontology of cell types, tissues and organs allowing for detailed mechanistic hypothesis testing.

We generated computable networks of interacting pesticide, genes, proteins, pathways and biological effects that allowed us to predict pesticide effects on organisms.

Results

To validate our approach, we chose two well-known organochlorine compounds: lindane and dieldrin. Within our knowledge base, we identified several diseases and potential toxicities associated with their use: Non-Hodgkin lymphoma, acute renal failure, Sertoli cell toxicity, hepatotoxicity and genotoxicity for lindane; and DNA strand break, lymphoid toxicity and hepatotoxicity for dieldrin (Table 1). Our computational tool shows that lindane targets nuclear receptors involved in metabolism of lipids and toxicity (Metabolic pathways endpoint), and molecules involved in ryanodine-sensitive calcium-release channel activity, oxygen binding, steroid binding and transcription (Gene Function (GO) cluster endpoint) (Table 2). Dieldrin targets molecules that are involved in DNA dependent regulation of transcription, steroid hormone receptor activity and oxygen binding (GO cluster endpoint),

Diseases / Organ and tissue pathologies	
Lindane	**Dieldrin**
Non-Hodgkin lymphoma	Neurotoxicity syndrome
Acute renal failure	DNA strand break
Sertoli cell toxicity	Lymphoid toxicity
Hepatotoxicity	Hepatotoxicity
Genotoxicity	Kidney necrosis

Table 1. A sample of diseases/pathologies associated with the use of lindane and dieldrin

Targeted pathways	
Lindane	**Dieldrin**
Metabolism of lipids and toxicity	DNA dependent regulation of transcription
Ryanodine-sensitive calcium-release channel activity	Steroid hormone receptor activity
Oxygen binding, steroid binding and transcription	Oxygen binding

Table 2. A sample of metabolic pathways/GO clusters targeted by the lindane and dieldrin

Diseases / Organ pathologies		
Organ system	**Lindane**	**Dieldrin**
Nervous system	Epilepsy, migraine, nerve toxicities	Brain ischemia, brain inflammation, dyskinesia
Reproductive system	Prostate toxicities	
GI system	Intestine toxicities and hepatocyte toxicity	

Table 3. Analysis of lindane and dieldrin with their respective target molecules identified potential diseases/pathologies

The analysis of chemicals together with their target molecules identified pathologies on cellular, organ and organ system level related to nervous system (brain ischemia, brain inflammation and dyskinesia for dieldrin; and epilepsy, migraine and nerve toxicities for lindane), reproductive system (prostate toxicities) and GI system (intestine toxicities and hepatocyte toxicity) (Table 3). Indeed, literature search showed that organochlorine chronic exposure is associated with adverse effects, particularly in liver and reproductive system.

Vast amount of processed data in our system presents the potential for generation of valuable mechanistic hypothesis. We generated the hypothesis of mechanism of action that is supported by current knowledge. Each of the specific toxicities comes with the detailed list of proteins associated with that condition. Our system also provides easy access to literature evidences supporting the hypothesis. As an illustration, we chose hepatotoxicity. We could identify groups of different molecules that are related to hepatotoxicity, thus providing a mechanistic view of the effect (Figure 2).

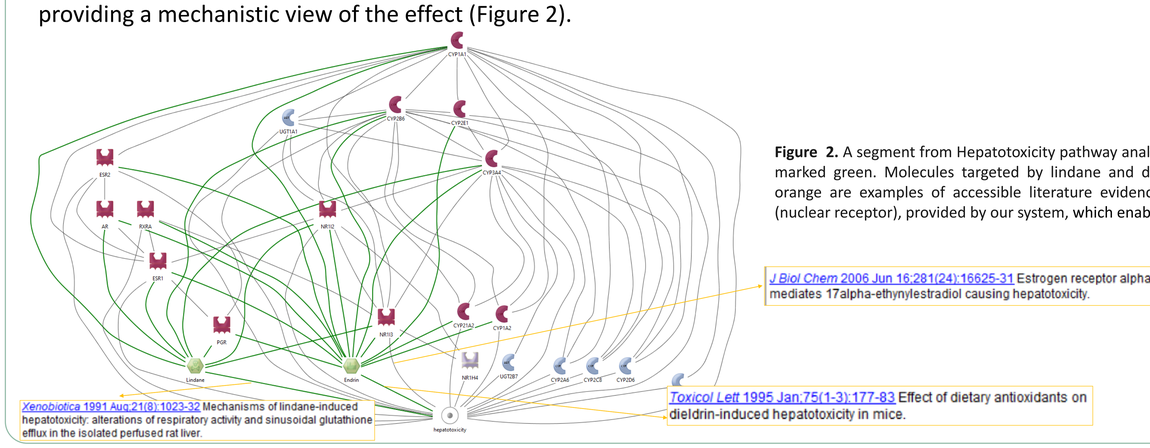

Figure 2. A segment from Hepatotoxicity pathway analysis. Lindane and dieldrin (endrin) are marked green. Molecules targeted by lindane and dieldrine are labeled violet. Boxed in orange are examples of accessible literature evidences for lindane, dieldrine and NR1I3 (nuclear receptor), provided by our system, which enable confirming hypothesis.

Conclusion

We have developed manually curated database of genes, proteins and chemicals, their interactions, and involvement in specific pathologies. The developed system allowed us to identify groups of molecules, proteins and chemicals, interacting between each other, which are related to potential toxicities caused by pesticides use, thus providing a mechanistic view of the effect, supported by current knowledge. Bioinformatics analysis provided the underlying mechanism of how exposure to pesticides can induce hepatotoxicity. In this example, we show how our tool can contribute to a quick chemical toxicological assessment.

References

1. Richardson JR *et al*, 2019, Acta Neuropathol. 2019 Sep;138(3):343-362

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