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Toxic or harmless? Computer-aided estimation of the toxicity of substances based on structural features

Computer-aided estimation of the toxicity of substances based on structural features

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Introduction

"Toxic or harmless?" Interlabor is repeatedly confronted with this question by customers. It often arises after unexpected substances have been found and identified during analyses, e.g. within the framework of Extractables & Leachables studies according to ISO 10993[1], during clarifications according to the ICH M7 Guideline[2], the USP <1031>[3] or during the control of raw materials.

The question is simple, but the answer complex!

The polymath Paracelsus (1493 - 1541), born near Einsiedeln in the canton of Schwyz and working as a doctor, was the first to recognize and formulate a connection between the quantity and effect of substances on the basis of his observations:

"All things are poison, and nothing is without poison. The dosage alone makes it so a thing is not a poison."[4]

With this revolutionary statement, Paracelsus laid the foundation for today's interdisciplinary field of modern toxicology. Advances in medicine, pharmacy, pharmacology, chemistry and biochemistry as well as many painful experiences with poisoning, the effects of which only become apparent months or years after exposure, have helped us to assess the "toxicity" of compounds and evaluate the risk of damage to health in the case of exposure. Based on this knowledge, we are finally able to take measures to prevent poisoning.

While Paracelsus was only confronted with naturally occurring "poisons", even well into the later 19th century only a few substances were produced synthetically and were thus not in contact with larger population groups. The situation changed with the rapid increase in chemistry knowledge and the possibilities of producing substances with specific properties synthetically on a large scale making them available not only for large population groups but also using them for products made of novel materials (e.g. plastics). However, it is not only the production but also the improper disposal that can lead to the chronic exposure of humans, animals and the environment with pathogenic effects (e.g. dioxins).

Today, the field of toxicology classifies "toxicity" with respect to very different aspects as described below:

Duration of exposure

- Acute: Single exposure; effect lasts up to 14 days after exposure
- Subacute / Subchronic: Repeated exposure; exposure lasts for a short period of time compared to the average lifetime
- Chronic: Exposure lasts over a longer period of time compared to the specific lifetime (months to several years)

Substance uptake

- Oral: by swallowing, e.g. with food
- Inhalation: by breathing
- Parenterally: bypassing the digestive tract, e.g. by injection
- Transdermal: through the skin

Effect / damage

- Genotoxicity: Damage to genetic material (DNA)
- Mutagenicity: Permanent change of genetic material and thus potentially cancer-causing effect and/or heritable damage
- Clastogenicity: Damage to the chromosomes; mutagenic or potentially carcinogenic
- Carcinogenicity: Property of a substance to cause cancer
- Reproductive toxicity: Affects the fertility
- Teratogenicity: Irreversible harm to the unborn child; leads to malformations of the child

Affected functional system

- Immunotoxicity: damage to the immune system
- Haemotoxicity: damage to blood cells
- Myelotoxicity: damage to the bone marrow and thus the blood cell formation

Affected organ

- Cytotoxicity: cell- or organ-specific damage
  - Nephrotoxicity: damage to the kidney
  - Hepatotoxicity: damage to the liver
  - Neurotoxicity: damage to the nervous system and/or the brain

Number of chemical compounds with which humans and the environment are confronted

Between 1880 and 1937, the number of described organic compounds increased from 15'000 to about 450'000. In 2004, around 5 million chemical compounds were known in total, of which 100,000 were in use. Every year about 500 to 1'000 new compounds are added to the market. Not only the number of compounds but also the production of chemicals itself has significantly increased. Between 1930 and 2004, the production increased from 1 million tons up to 400 million tons. While the main quantity was deduced from only 1000 compounds, another 10'000 compounds were produced with quantities greater than 10 tons. [5]

In 2021, the Chemical Abstracts Service (CAS) database contains more than 188 million organic and inorganic compounds [6]. The quantities currently produced worldwide and the substances placed on the market have increased exponentially again since 2004.

Although the legal requirements for placing new substances on the market are constantly increasing, for many substances there is little or no experimental data available, i.e. data obtained by means of animal experiments or cell cultures. This is aggregavated by the fact that data determined for one species cannot necessarily be transferred to another species, e.g. to humans (keyword: "thalidomide affair").

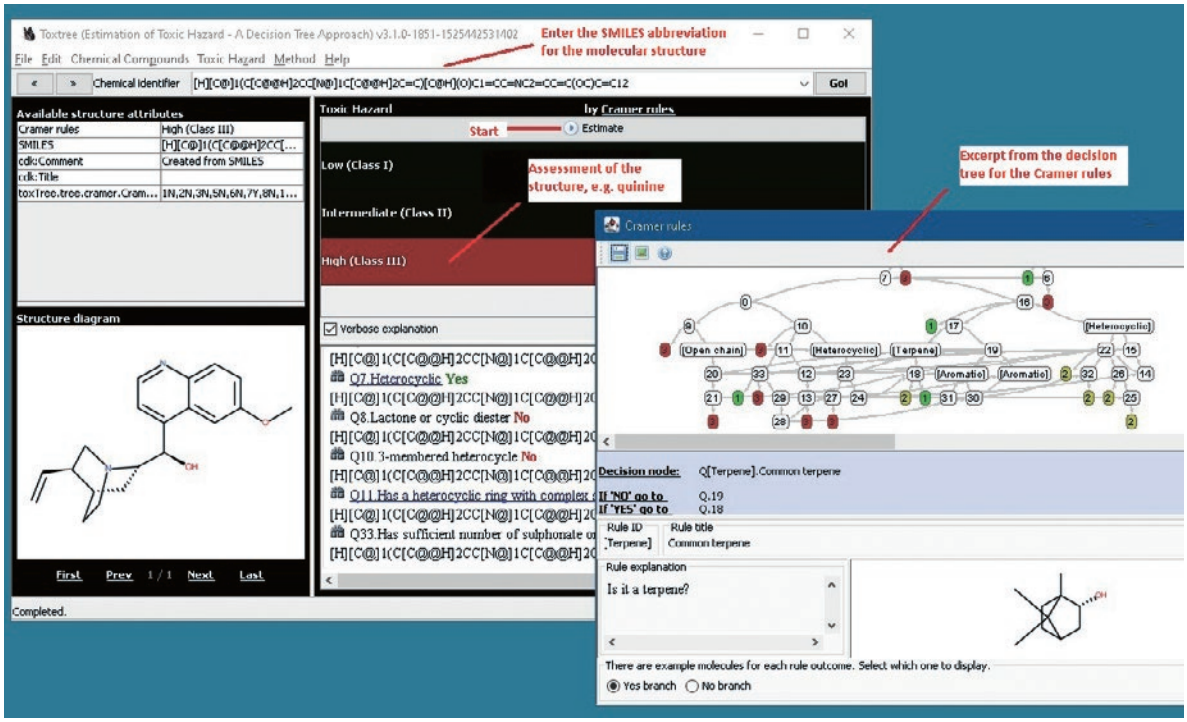

Fig. 1: Screenshot of the software Toxtree with the exemplary structure of quinine; Background: Main window; foreground: section of a decision tree

The first scientific publications from the late 1970s addressed the question of whether structural features of known chemical compounds correlate with their specific type of toxicity and thus, conversely, whether the toxicological effects of undescribed compounds can be predicted on the basis of their structural features. [7]

Advances in computer science and programming now make it possible to carry out such investigations using algorithms.

One of the best-known software programs is Toxtree (Estimation of Toxic Hazard - A Decision Tree Approach). [8]

The software Toxtree is not a substitute for experimental data or the assessment by an experienced toxicologist, but it can be helpful for an initial rough estimation if no information can be found in the relevant databases or elsewhere.

Toxtree is suitable for the following clarifications of substances that have to be assessed within the framework of ISO 10993 [1], ICH M7 [2] or USP <1031>:

- General systemic toxicity based on the Cramer rules, incl. their extensions
- Mutagenicity (prediction of the result of the Ames test)
- Carcinogenicity (genotoxic and non-genotoxic) and mutagenicity according to the rules of Benigni and Bossa
- Identification of structural alerts for the in-vivo micronucleus assay
- Identification of critical degradation products in cytochrome P450 metabolism
- Structural alerts for the binding of molecules to proteins and DNA

Conclusion

The multitude of toxicological aspects that need to be taken into account when assessing a substance and the complexity of the potentially harmful interactions of a substance with an organism cannot be completely simulated by any program. Thus, even today the “toxicity” of a substance cannot be predicted with absolute certainty. However, computer-assisted programs allow important indications of potentially harmful structures at an early stage.

Key data

Interlabor offers its customers to perform assessments of known or unknown substances using the software Toxtree as well as a database research. The need for such assessments may arise for example in the case of secondary by-products of syntheses, degradation products formed during stability studies or within the framework of analyses for medical devices (ISO 10993 [1], USP <1031> [3] or ICH M7 [2]).

If the chemical structure of a compound is not known, Interlabor will gladly help you to analyze and identify the structure. Various techniques are available, for example preparative liquid chromatography, high-resolution mass spectrometry or NMR. The identified structure can afterwards be checked using the program Toxtree. Interlabor also collaborates with qualified toxicologists if further clarifications are required.

Contact our customer service and tell us about your request!

References

[1] *ISO 10993: Biologische Beurteilung von Medizinprodukten*

[2] *ICH M7(R1): Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk*

[3] *USP <1031>: The biocompatibility of materials used in drug containers, medical devices and implants*

[4] *https://de.wikipedia.org/wiki/Paracelsus; retrieved on 08.09.2021*

[5] *MAGAZIN DES UFZ-UMWELTFORSCHUNGSZENTRUMS LEIPZIG-HALLE IN DER HELMHOLTZ-GEMEINSCHAFT; Ausgabe 11, November 2004 https://www.ufz.de/export/data/2/84198_ufz_magazin_umweltchemie.pdf*

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[7] *Cramer G. M., R. A. Ford, R. L. Hall, Estimation of Toxic Hazard - A Decision Tree Approach, J. Cosmet. Toxicol., Vol.16, pp. 255-276, Pergamon Press, 1978*

[8] *Toxtree (Estimation of Toxic Hazard - A Decision Tree Approach) http://www.ideaconsult.net/ http://toxtree.sourceforge.net/*

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