

Database analysis more reliable than animal testing for toxic chemicals

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Advanced algorithms working from large chemical databases can predict a new chemical's toxicity better than standard animal tests, suggests a study led by scientists at Johns Hopkins Bloomberg School of Public Health.

The researchers, in the study that appears in the journal *Toxicological Sciences* on July 11, mined a large database of known chemicals they developed to map the relationships between [chemical structures](#) and toxic properties. They then showed that one can use the map to automatically predict the toxic properties of any chemical compound—more accurately than a single animal test would do.

The most advanced toxicity-prediction tool the team developed was on average about 87 percent accurate in reproducing consensus animal-test-based results—across nine common tests, which account for 57 percent of the world's animal toxicology testing. By contrast, the repetition of the same animal tests in the database were only about 81 percent accurate—in other words, any given test had only an 81 percent chance, on average, of obtaining the same result for toxicity when repeated.

"These results are a real eye-opener—they suggest that we can replace many animal tests with computer-based prediction and get more reliable results," says principal investigator Thomas Hartung, MD, Ph.D., the Doerenkamp-Zbinden Chair and professor in the Department of Environmental Health and Engineering at the Bloomberg School.

The computer-based approach could also be applied to many more chemicals than animal testing, which could lead to wider safety assessments. Due to costs and ethical challenges only a small fraction of the roughly 100,000 chemicals in consumer products have been comprehensively tested.

Animals such as mice, rabbits, guinea pigs and dogs annually undergo millions of chemical toxicity tests in labs around the world. Although this animal testing is usually required by law to protect consumers, it is opposed on moral grounds by large segments of the public, and is also unpopular with product manufacturers because of the high costs and uncertainties about testing results.

"A new pesticide, for example, might require 30 separate animal tests, costing the sponsoring company about 20 million dollars," says Hartung, who also directs the Center for Alternatives to Animal Testing, which is based in the Bloomberg School's Department of Environmental Health and Engineering.

The most common alternative to animal testing is a process called read-across, in which researchers predict a new compound's toxicity based on the known properties of few chemicals that have a similar structure. Read-across is much less expensive than [animal testing](#), yet requires expert evaluation and somewhat subjective analysis for every compound of interest.

As a first step towards optimizing and automating the read-across process, Hartung and colleagues two years ago assembled the world's largest machine-readable toxicological database. It contains information on the structures and properties of 10,000 chemical compounds, based in part on 800,000 separate toxicology tests.

"There is enormous redundancy in this database—we found that often

the same chemical has been tested dozens of times in the same way, such as putting it into rabbits' eyes to check if it's irritating," says Hartung. This waste of [animals](#), however, gave the researchers information they needed to develop a benchmark for a better approach.

For their study, the team enlarged the database and used machine-learning algorithms, with computing muscle provided by Amazon's cloud server system, to read the data and generate a "map" of known chemical structures and their associated toxic properties. They developed related software to determine precisely where any compound of interest belongs on the map, and whether—based on the properties of compounds "nearby"—it is likely to have toxic effects such as skin irritation or DNA damage.

"Our automated approach clearly outperformed the animal test, in a very solid assessment using data on thousands of different chemicals and tests," Hartung says. "So it's big news for toxicology." Underwriter's Laboratories (UL), a company that specializes in developing public safety standards and testing against them, co-sponsored this work and is making the read-across software tool commercially available.

The U.S. Food and Drug Administration and the Environmental Protection Agency have begun formal evaluations of the new method, to test if read-across can substitute for a significant proportion of the animal tests currently used to evaluate the safety of chemicals in foods, drugs and other consumer products. The researchers also are starting to use it to help some large corporations, including major technology companies, to determine if they have potentially toxic chemicals in their products.

"One day perhaps, chemists will use such tools to predict toxicity even before synthesizing a [chemical](#) so that they can focus on making only non-toxic compounds," Hartung says.

"Machine learning of toxicological big data enables read-across structure activity relationships (RASAR) outperforming animal [test](#) reproducibility" was written by Tom Luechtefeld, Dan Marsh, Craig Rowlands, and Thomas Hartung.

Provided by Johns Hopkins University Bloomberg School of Public Health

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