Scientists devise more accurate system for predicting risks of new chemical products

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The approach used by regulators to initially screen new chemical products for toxic effects is wrong almost half the time, according to scientists at the University of North Carolina at Chapel Hill. They have proposed an improvement that could increase accuracy to as much as 85 percent, saving millions of dollars and years of development time for new drugs and other products while improving safety.

Regulatory agencies, such as the U.S. Food and Drug Administration and the Environmental Protection Agency, that are charged with evaluating new drugs and other chemical products rely on an initial screening of a product's molecular structure. Any groups of atoms that are believed to be linked to chemical toxicity trigger a structural alert. A product that generates a structural alert is sent back for more testing.

Researchers led by Alex Tropsha, K. H. Lee Distinguished Professor at the UNC Eshelman School of Pharmacy, determined that structural alerts are accurate in predicting toxicity only about 50 to 60 percent of the time. They developed a computational approach that uses statistical analysis to determine how trustworthy an alert is. Their improvement augments the simple-but-often-wrong thumbs up or thumbs down currently provided.

"A lot of chemicals are incorrectly identified as potentially toxic even though in the end they are not toxic and that could have been predicted," Tropsha said. "Companies are forced to run a lot of unnecessary and costly experiments, and because companies run these checks themselves before submitting their products to regulators, there are products that never see the light of day because they are flagged as toxic when they are not."

However, some make it to market after the alerts have been later deemed nontoxic. For example, Lipitor, the best-selling drug of all time that treats cholesterol, has five elements in its molecular structure that are flagged as structural alerts, but is not toxic.

By layering a technique called quantitative structure-activity relationship, or QSAR, modeling over the existing alerts system, the UNC-Chapel Hill researchers are able to account for the structure of the entire chemical molecule and assign a numerical value to the chance that an alert is accurate. Their innovative strategy is published in the journal *Green Chemistry*.

"Structural alerts are a convenient system, but there are few consequences for being wrong even though the stakes are potentially very high," Tropsha said. "If the alert is right, then it's 'we told you so.' If it's wrong, 'well, it was just a warning anyway.' But unfounded alerts unnecessarily add years and millions of dollars to the cost of bringing a new drug or product to market without improving safety. That is unacceptable, we think."

Tropsha's group plans to make their system freely available to regulators and scientists as web-based computer software.

"We want to alarm regulators that structural alerts over-predict toxicity while missing truly toxic substances, and offer them much more accurate tools to support regulatory decisions," Tropsha said.

More information: Vinicius M. Alves et al. Alarms about structural alerts, *Green Chem.* (2016). DOI: 10.1039/C6GC01492E

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