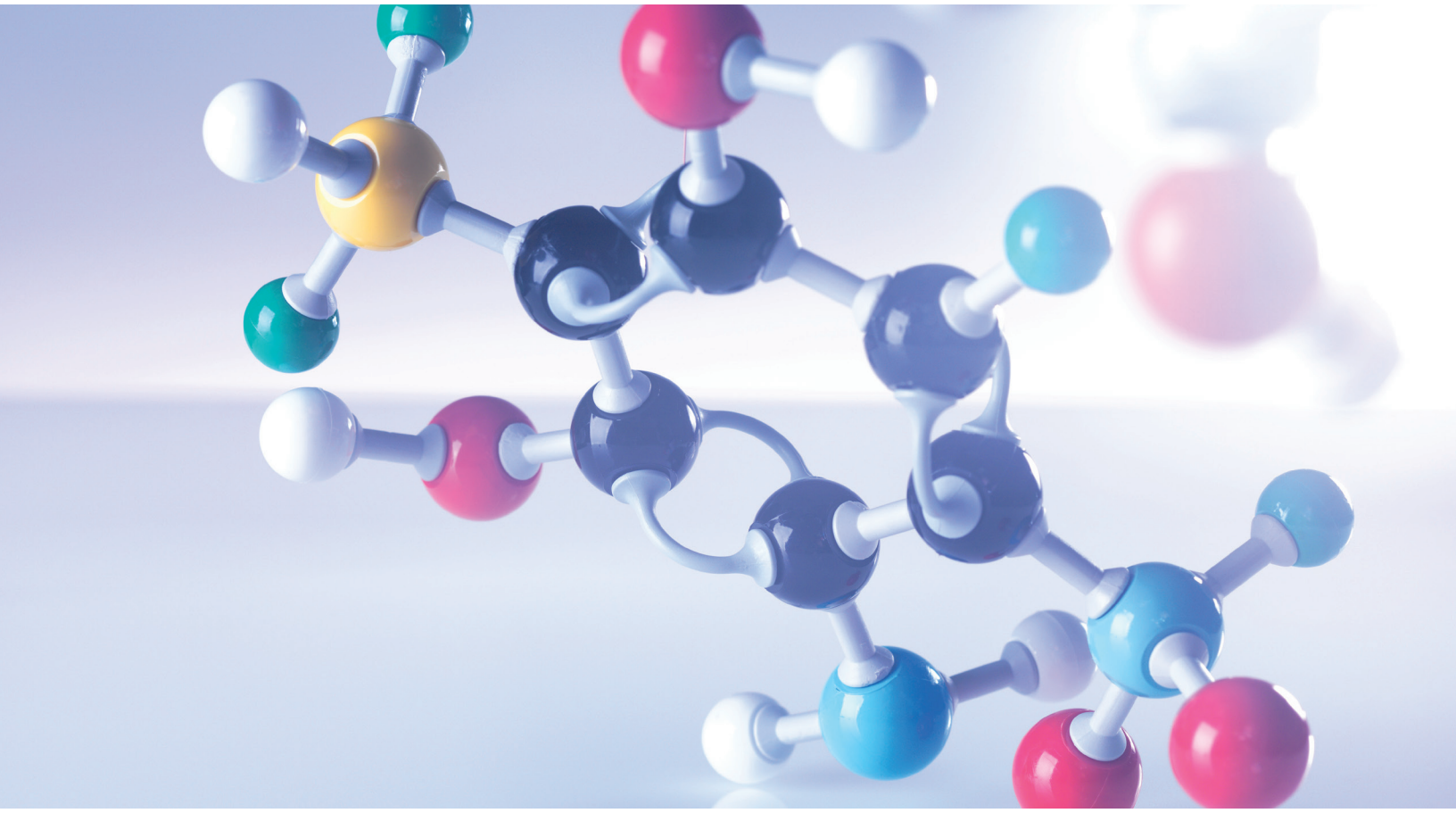
USING PREDICTIVE ANALYTICS TO ASSESS CHEMICAL SAFETY: A UL INITIATIVE

EXECUTIVE SUMMARY

The growing demand for consumer products that are safe and effective while also less harmful to the environment is driving manufacturers to identify new and alternative chemicals and chemical combinations that can support the development of innovative products that meet that demand. At the same time, the cost and time required to evaluate new chemical substances using conventional toxicological methods is increasingly incompatible with the need for rapid and continuous product innovation. Today, scientists, chemists and toxicologists require access to more advanced tools and technologies to efficiently and effectively assess new chemical substances for their potentially harmful effects.

Working with researchers at the Bloomberg School of Public Health at the Johns Hopkins University, UL has developed an innovative, cheminformatics software-based tool to predict chemical hazards that can be used wherever chemical hazard data is needed. The first module in the UL cheminformatics suite, REACH*Across*, utilizes an advanced, predictive algorithm, as well as machine learning, to assess the endpoint behavior of any chemical of interest. By analyzing millions of chemical combinations, REACH*Across* can predict potentially-harmful health and environmental outcomes associated with chemical substances, including skin sensitization, acute oral- and dermal-toxicity, eye-and dermal-irritation, mutagenicity and acute- and chronic-aquatic toxicity. Additional modules in the cheminformatics suite are expected to follow in the near future to take full advantage of the increasing availability and use of big data in predictive toxicology.

This UL white paper will discuss the importance of developing more efficient methods of chemical toxicological assessment, and how UL's REACH*Across* software can assist product developers in verifying the safety of alternative chemicals and chemical formulations. The paper begins with an overview of the process of assessing the health and safety of chemicals used in products, as well as anticipated regulatory changes that are increasing the demand for more efficient and cost-effective methods of toxicological evaluation. The white paper then provides a summary of the concepts behind UL's REACH*Across* software platform, and details its potential benefits.



CHEMICALS IN THE MODERN WORLD

Chemicals are an essential aspect of the world as we know it. Virtually all forms of matter found throughout the universe, including solids, liquids and gases, are comprised of various, naturally-occurring combinations of the approximately 100 chemical elements that have been identified by scientists over the centuries. Even the human body (a complex organism to be sure!) represents the unique combination of some 60 different chemical elements, with just six chemicals comprising 99 percent of our total body mass.

In modern times, researchers have masterfully leveraged the remarkable potential of chemicals by experimenting with specialized combinations of individual chemicals to create new chemical compounds and substances. This experimentation has resulted in the creation of more than 100 million unique chemical substances,[1] and have led to important innovations in science, technology, industry and medicine, along with dramatic improvements in the quality of life on our planet.

Today, the global chemical industry continues to invest heavily on chemical research and development activities as part of the effort to bring new and even more advanced chemical compounds and substances to market. According to one estimate, the U.S. chemical industry alone spends nearly $100 billion (USD) annually on research and development activities.[2] While economic pressures have resulted in some narrowing of research activities in recent years, chemical companies are still making significant investments in key areas, such as in the development of specialty chemicals and advanced material compositions, to take advantage of current and emerging market opportunities.[3]

THE U.S. CHEMICAL INDUSTRY ALONE SPENDS

$1 BILLION

USD ANNUALLY ON RESEARCH AND DEVELOPMENT

ADDRESSING CONCERNS ABOUT CHEMICAL SAFETY

At the same time, the ubiquitous presence of chemicals and chemical compounds in everyday life has raised growing concerns about their safety. The use of chemicals in products and in production processes in the workplace can potentially expose people to physical risks, as well as both short- and long-term health hazards.

EVEN EXPOSURE TO SEEMINGLY MINUTE AMOUNTS OF SOME CHEMICALS CAN HAVE A TOXIC EFFECT, ESPECIALLY ON VULNERABLE POPULATIONS, SUCH AS INFANTS, CHILDREN, PREGNANT WOMEN AND THE ELDERLY.

Further, the potential toxicity of certain chemicals can also result in environmental impacts. For example, chemicals are extensively used in the agricultural industry, such as in fertilizers and insecticides in crops and as additives in animal feeds and liquids. The use or misuse of such chemicals can lead to soil and groundwater contamination, potentially compromising the health and sustainability of natural and aquatic environments.

For these reasons, regulatory authorities in key jurisdictions around the world have implemented mechanisms to monitor and control the use of potentially-harmful chemical substances. In the U.S., the Environmental Protection Agency (EPA) has established reporting, record-keeping and testing requirements for chemical substance under the Toxic Substances Control Act (TSCA) of 1976. The EPA also maintains a list of all chemical substances manufactured or processed in the U.S. under its TSCA Chemical Substance Inventory, which currently includes about 85,000 different chemicals. U.S. consumer concerns about chemicals were a major driver for amending TSCA with the June 2016 passage of the Frank R. Lautenberg Chemical Safety for the 21st Century Act (LCSA).

For companies intending to bring new chemicals to market, the EPA regulation of greatest significance require advanced notification of intent to manufacture "new chemical substances." As recently amended by the U.S. Congress, the LCSA provisions dealing with notice of new chemical production requires the EPA to make "affirmative determinations" about all new chemical notices it receives, using a risk-based approach as part of its determination process that accounts for both potential chemical hazards and potential exposure risk.[4]

In addition, the EPA has broad authority to require the testing of certain chemical substances and mixtures "where risks of exposure of concern are found." This testing is used to develop data about potential health or environmental effects when there is insufficient data for the EPA to reasonably assess those effects.

REACH REGISTRATION REQUIREMENTS IN THE EU

In the European Union (EU), the Regulation concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH)[5] represents perhaps the most comprehensive effort ever to regulate the production and use of chemical substances. The Regulation, which came into force in June 2007, requires any company that either manufactures or imports chemical substances into the EU to register those products with the European Chemicals Agency (ECHA). The ECHA was expressly established by the REACH Regulation to address all technical and administrative aspects related to the implementation and management of the Regulation's requirements.

Compliance deadlines with the provisions of the REACH Regulation have been gradually phased in since the Regulation came into force. Large producers and importers producing or importing 1,000 or more metric tons per year have been required to register chemical products since the end of 2010, while those producing or importing between 100 and 1,000 tons per year have been required to register their products since June 2013. The last group to be subject to the Regulation, those who produce or import between 1 and 100 tons per year, must complete the registration of their products by no later than May 31, 2018.

Under the REACH Regulation, the registration of a new chemical or a chemical substance that has not been previously registered requires the submission of a registration dossier to the ECHA. In most cases, the dossier must include the results of comprehensive safety assessment of the chemical under specific exposure scenarios. The intent of the chemical safety assessment is to demonstrate that any potential risks associated with inherent hazards or exposure associated with a specific chemical substance under the identified exposure scenarios have been adequately controlled.

It is important to note that the REACH Regulation attempts to minimize the use of animal testing to assess the toxicity of new or previously-unregistered chemicals. Any planned animal testing must be approved by ECHA before it is conducted. Further, permission to conduct animal testing is generally given only in cases where a chemical substance to be submitted for registration has not been previously tested, and only when an alternative, non-animal testing method is not available.

UL'S REACH*ACROSS* SOFTWARE

The search for more efficient methods of assessing the toxicity of new chemicals and chemical substances is being facilitated by a development of advanced, software-based analytical tools that can quickly assess the endpoint behavior of any chemical of interest. An integral component of UL's chemiformatics suite of integrated software applications, the REACH*Across* software tool, assesses a chemical's structure and its physical and chemical properties to predict chemical toxicity. As such, it provides an efficient and cost-effective mechanism for assessing the potential toxicity of a chemical substance at any stage in the product development process.

Developed through a partnership between Thomas Hartung of the Bloomberg School of Public Health at Johns Hopkins University, his colleague Thomas Luechtefeld and UL's team of scientists and toxicologists, UL's REACH*Across* software uses a complex machine learning algorithm to compare the structure of the chemical under evaluation with other chemicals with identified toxicity profiles. The software first identifies the structure and substructure of the chemical being evaluated. It then searches the entire REACH*Across* database to find chemicals with the same classification (for example, skin sensitizer), as well as other reference chemicals to produce a map showing their comparative chemical structures, and assist in the identification of toxic probabilities based on the comparative set.

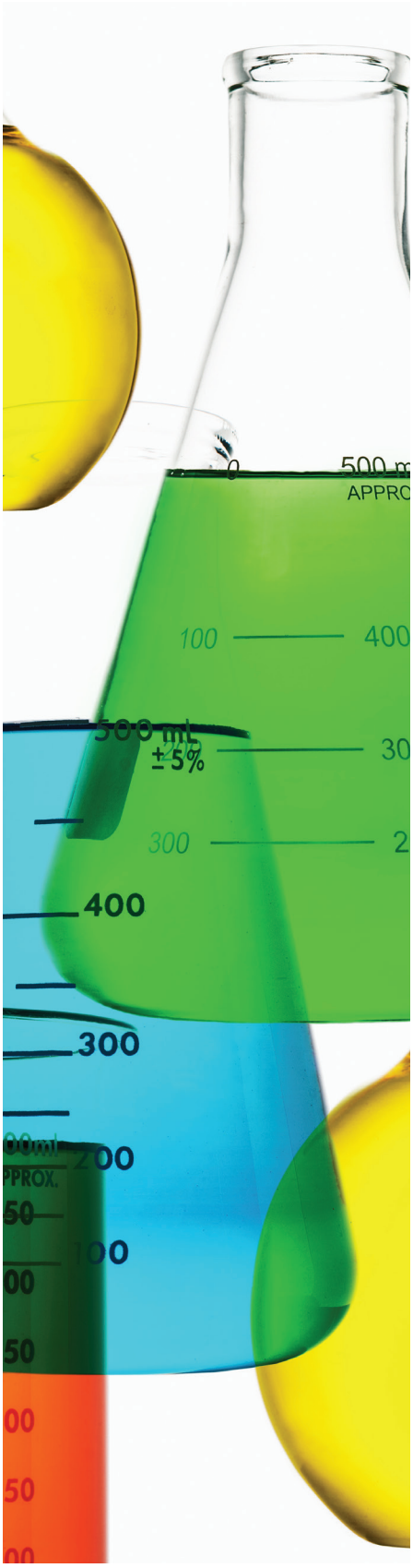
REACH*ACROSS* SOFTWARE INCLUDES **MORE THAN**

20,000

DIFFERENT CHEMICALS AND CHEMICAL SUBSTANCES

The database on which the REACH*Across* software is built includes more than 20,000 different chemicals and chemical substances classified under the United Nation's Global Harmonization System (GHS), most of which are also listed under the EU's REACH registration system maintained by the ECHA. This scope of available coverage provides access to over 300,000 endpoints and more than 70 million different chemical structures. The database will soon expand to include nearly 72,000 additional chemicals from PubChem, a chemical database maintained by the U.S. National Institutes of Health (NIH) under its National Center for Biotechnology Information. The addition of these chemicals will provide access to data sources with GHS classifications for an additional 65 distinct endpoint types.

UL has performed an internal validation of the REACH*Across* software for nine endpoints, following the principles for quantitative structure activity relationships (QSAR) model variations developed by the Organization for Economic Cooperation and Development (OECD).[6] For each of the endpoints evaluated, the balanced accuracy (average of sensitivity and specificity) was over 70 percent, with a domain of applicability covering more than 75 percent of ECHA-registered compounds. These results affirm the accuracy and versatility of the REACH*Across* software as a cheminformatics hazard prediction tool.



THE BENEFITS OF REACH*ACROSS*

UL's REACH*Across* software was originally designed to address the specific needs of chemical companies seeking to identify the United Nation's GHS hazard classifications for toxicological endpoints as required under the EU's REACH Regulation. As such, it can be an effective tool in facilitating the registration of new chemicals in the EU. However, the GHS hazard classifications can be used wherever chemical classification information is required or needed. This includes registration requirements of other chemical regulatory authorities, required content for material safety data sheets (MSDS), and other chemical transportation and product labeling requirements.

The use of REACH*Across* can also significantly reduce the investment needed to conduct toxicology assessments of chemical substances under development. Conventional methods of toxicological assessment methods are generally time-consuming and expensive to execute, and multiple rounds of testing may be required to verify or correct anomalous results. REACH*Across* can generate toxicological assessment results in minutes, versus weeks or months for conventional assessment approaches, allowing product development teams to quickly and accurately assess proposed chemical structures early in the development cycle.

Further, using REACH*Across*, researchers can simultaneously evaluate multiple chemical structures to identify options that are the least potentially toxic. The approach mimics the concept of rapid prototyping commonly applied throughout the technology industry in which development teams are able to quickly evaluate various combinations of features to arrive at an optimal solution. The use of REACH*Across* offers many of the same advantages to new product development in chemical companies, ultimately leading to the more rapid development of safer chemical substances.

Finally, an important benefit of REACH*Across* is the ability to develop safer chemicals using processes that reduce overall exposure to potentially harmful substances. By minimizing or eliminating the dependence on animal testing, REACH*Across* offers chemical manufacturers an effective and ethical alternative for evaluating the potential toxicity of new chemical substances. Such an approach is also consistent with the growing demand for products and production processes that embrace larger health and environmental sustainability principles.

WHAT'S AHEAD FOR REACH*ACROSS*

In the future, UL will increase the usefulness and effectiveness of its cheminformatics database by adding additional toxicity testing data from public and private sources. Further refinements in the REACH*Across* software are also underway to increase the accuracy of its toxicological assessments. Specifically, the REACH*Across* development team is evaluating ways to enhance the methods for comparing chemical similarities through its assessment of the three-dimensional structure of chemicals, as well as the assessment of the physical properties of chemical molecules. Improvements in the software's prediction modeling will also consider additional biological information on chemicals, such as toxicity and efficacy data from in-vitro and biochemical assays.

The REACH*Across* team is already working on adding additional toxicity endpoint predictions, as well as modifying the flexibility of the software for use in Green Chemistry applications for chemical research and development programs. Since many chemical substances already on the market have never been fully evaluated for their safety, the Green Chemistry module will enable chemical manufacturers to proactively predict the toxicity of chemicals before they are in use, and select alternatives early in the development process.

Additional uses for UL's cheminformatics suite software and REACH*Across* predictions include assisting companies in complying with hazard communication, such as filling in the gaps in safety data sheets, product labels, hazard information for transportation and industrial hygiene for workers or laboratory safety.

Finally, efforts are under way to help ensure the accessibility of UL REACH*Across* and other software applications under the UL cheminformatics suite. Examples include the introduction of an application programming interface (API) and, potentially, a stand-alone REACH*Across* application that would allow companies to run REACH*Across* software behind their own security firewalls.

ACCESS TO OVER
300,000
ENDPOINTS

AND MORE THAN
70 MILLION
DIFFERENT CHEMICAL STRUCTURES

AND COUNTING...

SUMMARY + CONCLUSION

Today, regulatory mandates and widespread public concern make it imperative for chemical manufacturers to thoroughly assess new chemical substances to determine their potential toxicity prior to placing them on the market. Until recently, meeting this requirement has meant lengthy and expensive toxicological testing, often requiring the use of animal subjects, to produce the necessary documentary evidence regarding chemical safety. However, conventional approaches to chemical safety testing increasingly places severe limitations on manufacturers who are seeking to introduce to the market new and innovative chemical substances that are also demonstrably safer than predecessor substances.

Developed in partnership with world-renowned scientists and researchers, UL's REACH*Across* software provides chemical manufacturers with an efficient, cost-effective and ethical approach to evaluating the potential toxicity of chemical substances. Toxicological assessments conducted using REACH*Across* can be used to support of chemical safety assessments required in the EU and by other regulatory authorities for the registration or approval of new chemical substances. And REACH*Across* can also serve as an important analytical tool during the product development process, enabling researchers to rapidly assess multiple chemical structure options in their effort to develop new chemicals that are both safe and effective.

For further information about UL's REACH*Across* software, or UL's other Green Chemistry initiatives, contact **PAM.WALKER@UL.COM**.

END NOTES

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