West Virginia Chemical Spill: Structure-Activity Relationship Analysis

December 2014 NTP Update

Synopsis

The National Toxicology Program (NTP)[1] is studying the potential hazards from chemicals spilled into the Elk River in West Virginia using a variety of approaches. One approach uses a specific type of computer software to predict potential hazards based on the structural similarity of the spilled chemicals with other chemicals for which there is better toxicology information. This approach is broadly termed structure-activity relationship (SAR) analysis.

NTP evaluated 4-methylcyclohexanemethanol (MCHM), the main spilled chemical, in a large number of computational models for specific toxicities, such as genetic damage or effects on reproduction. The results from approximately 200 toxicity prediction models for MCHM were reviewed, and those that were considered most useful and appropriate are reported here. Four models produced potentially useful predictions. Two of the models predicted MCHM might result in effects on the development of offspring and two others suggested that MCHM might be an eye and skin irritant. Findings from SAR analysis are useful for determining the types of toxicology studies that would be most appropriate to perform; however, because they do not take into account the exposure or dose required to produce an effect, they cannot be used to directly determine the risk to humans associated with a given exposure. The SAR predictions for skin and eye irritation and developmental toxicity presented here are being evaluated in ongoing studies. Further reviews of the SAR analyses of other chemicals from the spill are also underway, and results will be reported in future updates.

Background and Limitations of SAR Analysis

SAR analysis uses chemical structure and the physical and chemical properties of a substance to predict how it may affect a particular biological activity of interest, which in this case is toxicological activity. Training sets of chemicals with known chemical structure are used to develop a computational model for a specific toxicity endpoint. The resulting model is then used to predict the activity of a test chemical based on its structural features. Confidence in the prediction depends on a number of factors, and the most important factors may be how closely a test chemical's structure matches the chemicals that were used to create the model and the extent and accuracy of the toxicology information available for those chemicals. The SAR models are, in some cases, commercial products that do not provide complete information on the data used to derive the models. Finally, a major limitation is that SAR models are used to predict potential health hazards and, in general, do not take into account the dose of the chemical or the duration of exposure needed to produce the hazard. In other words, an SAR prediction may suggest an effect is possible or likely to occur under certain conditions;

[1] NTP is a federal, interagency program whose goal is to safeguard the public by identifying substances in the environment that may affect human health. NTP is headquartered at the National Institute of Environmental Health Sciences, which is part of the National Institutes of Health. For more information about NTP and its programs, visit http://ntp.niehs.nih.gov/

however, such findings need to be confirmed experimentally to understand the dose-response relationships for the effect of interest.

SAR Analysis of MCHM

SAR analyses were performed for MCHM using six SAR software platforms: Leadscope,[2] Case Ultra,[3] Vega,[4] and Toxtree,[5] ADMETPredictor,[6] and MetaDrug[7]. Each platform uses different computational models to forecast a chemical's toxicological properties. In total, approximately 200 prediction models for a variety of toxicity endpoints varying from skin and eye irritation to rodent carcinogenicity were used. All predictions noted as positive (i.e., where the chemical is predicted to cause an effect) by the individual models were reviewed in order to judge the plausibility of the positive call. Considerations during review included the strength of a prediction as reported by the software, how well the structural features of MCHM were represented in a model's training set, and the toxicological plausibility of the chemical features driving a positive prediction (i.e., has a substructure of the test chemical been shown to be associated with the endpoint that the model is predicting). Only results deemed to be of at least moderate reliability are reported here.

For MCHM, there were 35 positive predictions from approximately 200 SAR models. Of these, 4 positive predictions were determined to be of at least moderate reliability following review. These results are described below.

Skin and Eye Irritation. MCHM was predicted to be positive in the Toxtree models for skin irritation and corrosion and eye irritation and corrosion. In experimental studies, MCHM was identified as irritating and corrosive to guinea pig skin after a single and multiple applications.[8] Crude MCHM also was identified as a skin irritant to rabbits.[9] A diluted solution (10%) of crude MCHM was not a skin irritant to guinea pigs.[10] NTP's research program includes an evaluation in mice of MCHM's potential to cause skin irritation and hypersensitivity.

Developmental Toxicity. MCHM was predicted to be positive in the Vega and Case Ultra mammalian developmental toxicity models. Developmental toxicity means any effect that interferes with normal development, both before and/or after birth. MCHM has not been evaluated for developmental toxicity in animals or studied for developmental effects in humans. NTP's research program includes an evaluation in rodents of MCHM's potential effects on the developing fetus during pregnancy.

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[2] http://www.leadscope.com/
[3] http://www.multicase.com/what-is-case-ultra
[4] http://www.vega-qsar.eu/
[5] http://apps.ideaconsult.net:8080/ToxPredict
[6] http://www.simulations-plus.com/Products.aspx?pID=13
[7] http://thomsonreuters.com/metadrug/
[8] http://www.eastman.com/Literature_Center/Misc/Pure_Distilled_MCHM-Acute_Toxicity_Battery_Containing_5_Study_Reports.pdf
[9] http://www.eastman.com/Literature_Center/Misc/Crude_MCHM-Skin_Irritation_Study.pdf
[10] http://www.eastman.com/Literature_Center/Misc/Crude_MCHM-Skin_Sensitization.pdf

Next Steps

SAR analysis, while useful, has notable limitations as outlined above. The predictions from the SAR analyses to date for the spilled chemicals have informed selection of the toxicology studies currently underway. Further SAR-based evaluation of the spilled chemicals is ongoing, and additional results will be reported in subsequent updates.