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Decision trees for evaluating skin and respiratory sensitizing potential of chemicals in accordance with European regulations

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ABSTRACT

Guidance for determining the sensitizing potential of chemicals is available in EC Regulation No. 1272/2008 Classification, Labeling, and Packaging of Substances; REACH guidance from the European Chemicals Agency; and the United Nations Globally Harmonized System (GHS). We created decision trees for evaluating potential skin and respiratory sensitizers. Our approach (1) brings all the regulatory information into one brief document, providing a step-by-step method to evaluate evidence that individual chemicals or mixtures have sensitizing potential; (2) provides an efficient, uniform approach that promotes consistency when evaluations are done by different reviewers; (3) provides a standard way to convey the rationale and information used to classify chemicals. We applied this approach to more than 50 chemicals distributed among 11 evaluators with varying expertise. Evaluators found the decision trees easy to use and recipients (product stewards) of the analyses found that the resulting documentation was consistent across users and met their regulatory needs. Our approach allows for transparency, process management (e.g., documentation, change management, version control), as well as consistency in chemical hazard assessment for REACH, EC Regulation No. 1272/2008 Classification, Labeling, and Packaging of Substances and the GHS.

1. Introduction

Currently, the US Environmental Protection Agency (EPA) estimates that there are more than 84,000 chemicals in commerce and roughly 1000 new chemicals are added each year (US EPA, 2010). In order to meet the growing need for rapid hazard assessment of chemicals, toxicologists are continually developing new methods for evaluating chemicals, and regulatory entities have developed guidance documents for interpreting results of these tests and developing protective measures. End users of this information are often faced with voluminous information that must be distilled into practical approaches in order to assess effectively and communicate potential risks. Providing clarity and transparency regarding the methods used and rationale for arriving at decisions related to risk is often challenging.

Various chemicals have been implicated in a wide variety of hypersensitivity (allergic) reactions. The most commonly encountered are allergic contact dermatitis and respiratory allergic reactions, including asthma, rhinitis/conjunctivitis, and alveolitis (Selgrade and Meade, 2007). In the case of contact dermatitis the sensitizing chemical is a low molecular weight chemical (hapten). Haptens are too small to induce a specific immune response, but are reactive (often electrophilic) and can covalently bind to larger molecules, usually a protein, to form conjugates of sufficient size to induce a hapten-specific immune response (Selgrade and Meade, 2007). Respiratory allergies can occur as the result of exposure to certain haptens or to larger molecules, e.g., enzymes. In all cases hypersensitivity occurs as a 2-step process: sensitization (during which the immune system is primed) and elicitation (during which allergic responses occur). The dose responses for sensitization and elicitation are different, but not entirely independent (Friedmann et al., 1983; Scott et al., 2002), and in practice it is sometimes difficult to determine the point in time at which sensitization ends and elicitation begins.

Abbreviations: CLP, European Council requirements for Classification, Labeling and Packaging of substances and mixtures; EC, the concentration of chemical required to induce a 3-fold stimulation index in the local lymph node assay; ECHA, European Chemicals Agency; EPA, US Environmental Protection Agency; GHS, United Nations Globally Harmonized System; HRIPT, human repeat insult patch test; ICCVAM, Inter-Agency Coordinating Committee on the Validation of Alternative Test Methods; LLNA, local lymph node assay; MEST, mouse ear swelling test; REACH, Registration, Evaluation, Authorisation, and Restriction of Chemicals.

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Allergic disease causes a large economic burden on industry and society (Pawankar et al., 2011). Due to globalization, manufacturers and importers need to comply with regulations worldwide. Recently, REACH (Registration, Evaluation, Authorisation, and Restriction of Chemicals) (2006) regulations have been adopted by the European Union. The first step in meeting information requirements (referred to in Article 10 of the REACH regulation) is to gather all available relevant information from the literature and other sources to determine whether information requirements have been met or data gaps exist. Assuming a chemical does not meet the criteria for corrosivity, is not a strong acid or base, and is not self-flammable at room temperature, the regulation requires assessment of skin sensitizing potential (Annex VII: 8.3). All available information must be evaluated. A determination is then made as to whether existing data is sufficient to classify a chemical as a skin sensitizer or non-sensitizer, or whether sufficient data gaps indicate a need for further testing. Because there are no accepted test methods for assessing respiratory sensitizers, REACH does not contain specific information requirements for respiratory sensitization (ECHA, 2008). However, there is a need to evaluate existing information for purposes of harmonized classification and labeling (REACH Article 115). Respiratory sensitizers are also mentioned in Annexes I and XI. Finally, there is a limited amount of guidance available for assessing the sensitizing potential of mixtures. Guidance for evaluating the sensitizing potential of chemicals is available in the European Council requirements for Classification, Labeling and Packaging of substances and mixtures (CLP, 2008), REACH guidance from the European Chemicals Agency (ECHA, 2008), and the United Nations Globally Harmonized System (GHS, 2009).

In order to meet these regulatory requirements, we created decision trees for evaluating potential skin and respiratory sensitizers and chemical mixtures with the following goals: (1) summarize all of the relevant regulatory information into one brief document that provides a transparent, step-by-step method to evaluate the evidence that individual chemicals or mixtures have sensitizing potential; (2) provide an efficient, uniform approach that promotes consistency when evaluations are done by different reviewers with differing degrees of expertise; and (3) provide a standard way to convey the rationale and information used to classify chemicals in a clear and transparent fashion. The decision trees are a flexible framework that can incorporate new assays or analyses as they are developed (and accepted) in support of a weight of evidence approach to classification. We also provide details on how to evaluate the quality of human and animal skin sensitizing data, as well as the types of notations that should be made to document information used to classify a chemical. We used these decision trees to assess 50 chemicals for sensitizing potential. Chemicals ranged from well know sensitizers (such as chromium) with more than adequate data to support a decision to chemicals for which modest information was available that were judged to either have or not have sensitizing potential, to chemicals for which the data base was too meager to make a determination. Examples (from among the 50 chemicals assessed) demonstrate how the guidance provided was used to document classification of skin and respiratory sensitizers in a standard format.

2. Methods

In order to evaluate more than 50 chemicals for sensitizing potential, we provided written guidance (decision trees) outlining the process used to classify and label the test substances to 11 evaluators with varying expertise. (This written guidance was improved based on our experience applying it and was subsequently captured in the figure formats depicted here.) As part of this written guidance, evaluators were tasked with reviewing a dataset on a particular test substance. The literature search strategy used to obtain the data sets provided to evaluators included review of hazard assessments conducted and peer-reviewed as well as data sets from sources agreed upon in an international forum (OECD, SIDS), review of supplier MSDS, and then full exhaustive search of the published original manuscripts as needed. At this stage a read-across strategy or full QSAR analysis was not included. Details of the literature search are provided in Table 1. In most cases datasets for each chemical were reviewed and sensitization potential determined by one of eight junior (primary) evaluators (B.S. or B.A. degrees and 1–3 years of experience in toxicology/risk assessment), who each reviewed and classified 4–5 different chemicals. These evaluations were then reviewed by one of three senior reviewers (M.S. or Ph.D. and 10 or more years of experience in toxicology), who worked with several different primary evaluators (and were

Table 1
Literature search strategy used to obtain data sets.

Source[a]	URL
EU Annex 1 (or VI) Classification	http://esis.jrc.ec.europa.eu/index.php?PGM=cla
ECHA REACH Chemicals	Classification of REACH Chemicals http://apps.echa.europa.eu/registered/registered-sub.aspx#search
AEL	AEL Database (Confluence)
EU RAR/SIAR	http://ecb.jrc.ec.europa.eu/esis/ http://www.echemportal.org/echemportal/page.action?pageID=9
OECD SIDS	http://www.inchem.org/pages/sids.html http://www.echemportal.org/echemportal/page.action?pageID=9
New Zealand	http://www.epa.govt.nz/search-databases/Pages/HSNO-CCID.aspx
HPV / HPVIS	http://www.epa.gov/hpvis/index.html http://cfpub.epa.gov/hpv-s/ HPV Chemical Hazard Characterizations: http://iaspub.epa.gov/oppthpv/hpv_hc_characterization.get_report_by_cas?doctype=2
IUCLID	http://esis.jrc.ec.europa.eu/index.php?PGM=dat
FDA GRAS	ChemID: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CHEM HSDB: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB
e-ChemPortal Primary sources. Print doc not found in above links	http://www.echemportal.org/echemportal/page.action?pageID=9 ESIS GHS-J OECD HPV SIDS UNEP
e-ChemPortal Secondary sources. Mark if data are available. Print if no data from primary sources	http://www.echemportal.org/echemportal/page.action?pageID=9 Includes data base: ACToR, CESAR, CHRIP, EnviChem, ESIS, GHS-J, HPVIS, HSDB, HSNO CCID, INCHEM, JECDB, NICNAS PEC, OECD HPV, SIDS UNEP, UK CCRMP Outputs, US EPA IRIS
Haskell Lit Search	s:/search/lsarchive
MSDS (DuPont)	http://cdcrs77.lvs.dupont.com/msds/msdsen.htm
EPA Reregestration documents	http://www.epa.gov/pesticides/reregistration/
Before searching sources listed below, review results. Only search for end points not covered in above searches	
TLV	Printed copy in Library or s:/info_sci/Kathy/TLV/CS-TLV (2005 and earlier)
HSDB	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB
Toxline/PubMed	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE
MSDS (Vendor)	http://cdcrs77.lvs.dupont.com/msds/msdsen.htm OR http://www.google.com
IARC	http://monographs.iarc.fr/index.php
ATSDR	http://www.atsdr.cdc.gov/toxprofiles/index.asp
ECOTOX	http://www.atsdr.cdc.gov/toxprofiles/index.asp

[a] The top three in the list are always required. Searches are conducted in order listed until information is found.