Hazard Conclusion: Development, Documentation, and Confidence

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BACKGROUND

Regulatory agencies and companies are increasingly committed to characterizing and communicating chemical hazards to workers and the general public. Hazard assessment underlies several important compliance actions, including the generation of health-protective safety data sheets, the protection of confidential business information, and various government submissions (*e.g.*, chemical registrations). Hazard assessment is also key for companies' efforts to make supply chains "greener" and develop internal standards that limit potential human health and environmental risks.

This poster will cover some of the key steps needed to arrive at a scientifically supportable hazard conclusion. These steps include a reliable and robust set of toxicity information resources, a comprehensive protocol for documenting and recording toxicity information, and developing a weight-of-evidence (WoE) statement if toxicity data are conflicting. We also introduce an approach for assigning confidence ratings to assessments. Together, sound hazard assessment and an understanding of confidence in those assessments, can serve as a basis for understanding data gaps and uncertainties about chemicals in a company's portfolio. While building and maintaining a hazard assessment program requires significant toxicological, chemistry, and Information Technology (IT) resources, such programs can ensure that companies understand their vulnerabilities and can make informed decisions about chemical management.

DRAFT A WELL-RESEARCHED, DATA-DRIVEN HAZARD SUMMARY

Key Features:

- A well-researched hazard assessment is a key building block for achieving compliance and building a proactive product stewardship program.
- A hazard assessment should be sufficiently detailed to support a hazard conclusion, but will need to balance available resources. The data-driven approach to conducting hazard assessments is shown below. This approach balances the need for robust documentation with resource and time constraints.
- ALL hazard summaries should have a clear weight-of-evidence statement **(Figure 1)**.
- To improve consistency among complex evaluations and among staff, it is useful to develop a classification criteria protocol. This can be a living document that evolves as new evaluation scenarios develop.
- If chemical-specific data are not available, an attempt should be made to identify an appropriate chemical surrogate (*i.e.*, "read-across").
- All references should be recorded.

Data-Driven Hazard Assessment Summary Approach

- For compounds with one study or consistent data indicating no hazard, provide overall summary with limited supporting details.
- For compounds with inconsistent data, provide overall summary with details on available studies.
- For compounds with one study or consistent data indicating a hazard, provide overall summary with details on available studies.

Figure 1 Data-Driven Hazard Assessment Summary Example (Consistent Data Indicating an Adverse Effect)

Reproductive Toxicity (Including Developmental Toxicity)

Weight-of-Evidence (WoE) Statement Should Always Note:

- If only one or several studies were used.
- If the data are based on the compound of interest (CoI) or a surrogate (and name of surrogate[s] if applicable).
- If the studies were conducted according to established guidelines.
- Specific justification why a conclusion was reached if data are inconsistent.
- Conclusions reached by other authoritative agencies.

Weight of Evidence: Based on the results of a reproductive/developmental screening study and of developmental toxicity studies in rats, Chemical X is considered to pose a clear developmental hazard. Post-implantation loss was the critical adverse effect. In the key guideline study the fetal LOAEL was 10 mg/kg-day and no NOAEL was identified.

The classification is further supported by Globally Harmonized System (GHS) classifications as a Category 1 Reproductive Toxicant in Australia, European Union (EU), Japan, New Zealand, and Taiwan.

An Animal Toxicity Study Summary Should Always Specify:

- Study type, especially if guideline study.
- Species (with strain if available).
- Study duration.
- All doses and exposure routes.
- The no observable adverse effect level (NOAEL) and the lowest observable adverse effect level (LOAEL).

In a reproductive/developmental toxicity study (OECD 421), Wistar rats (n = 10/sex/dose) were administered 10, 50, and 200 mg/kg-day of the Chemical X (CAS No. XX-XX-X) *via* oral gavage for up to 53 days in dams. Clinical signs were observed in dams at 200 mg/kg-day. Body weight gain was less for both males and females at 200 mg/kg-day. At 200 mg/kg-day, post-implantation loss was 100%. At 50 mg/kg-day, there was an increase in the number of stillborn births. There were also elevated abnormalities in pups at 10 and 50 mg/kg-day. Since effects on the pups occurred at doses lower than where maternal toxicity occurred, these effects were considered adverse (ECHA, 2021). The parental LOAEL and NOAEL were 200 mg/kg-day and 50 mg/kg-day, respectively. The fetal LOAEL was 10 mg/kg-day; no NOAEL was identified.

In a non-guideline study, female Sprague-Dawley rats were exposed to Chemical X *via* oral gavage at concentrations of 0, 20, 40, or 80 mg/kg-day during gestation days 6-19. The mean maternal adjusted body weight of the high-dose group was reduced in comparison to controls. There was a marked increase in the number of early resorptions and a corresponding increase in the number of post-implantation losses in the high-dose group. An increase in the number of fetuses and litters with unossified sternebrae was noted in the mid- and high-dose group compared to controls. Based on these findings, a developmental NOAEL of 20 mg/kg-day and LOAEL of 40 mg/kg-day were identified based on unossified sternebrae in the absence of overt material toxicity (US EPA, 2007).

Record References

- If data are from a source or website that undergoes periodic updates, save a PDF of the study.

References:

European Chemicals Agency (ECHA). 2021. "REACH dossier for Chemical X (CAS No. XXX-XX-X)." Accessed on April 06, 2021 at https://echa.europa.eu/cs/registration-dossier/-/registered-dossier/X.

United States Environmental Protection Agency (US EPA). 2007. "Screening Level Evaluation of High Production Volume Chemicals: Chemical X.

ASSIGN CONFIDENCE IN HAZARD RESULTS

- Hazard conclusions may be made based on data of variable quality. Some companies find it useful to evaluate the confidence in their assessment **(Table 1)**.
- Confidence evaluations are a function of data availability, data consistency, and data quality.

Table 1 Rating System for Assessing Confidence in Hazard Conclusions Example

Very High	• Consistent results from multiple high-quality studies with the compound itself or salt with a different cation.
High	• Consistent results from high- or mixed-quality studies with the compound itself or salt with a different cation. • There may be conflicting results from older/poor-quality studies. • Single result from one high-quality study. No conflicting data.
Medium	• Based on surrogate data (suitable) or lower-quality studies. • Inconsistent results across multiple studies, but with a clear weight-of-evidence. • May be missing some types of studies for an endpoint (*e.g.*, only *in vitro* genotox data available; only repro, no developmental data).
Low	• Based on surrogate data (suitable with reservations) and/or low-quality studies. • May be missing key types of studies for an endpoint.
Very Low	• Based on quantitative structure-activity relationship (QSAR)/structure-activity relationship (SAR) results only.

CONDUCT A VULNERABILITY ASSESSMENT USING HAZARD CONCLUSION AND CONFIDENCE RATING

- A vulnerability analysis is a way to identify compounds that have the highest potential to pose a human health (or environmental) risk, are of emerging concern, and/or may garner more regulatory scrutiny **(Table 2)**. A vulnerability analysis can guide a company's or industry's active role in managing or innovating products that maximize public health, societal, and environmental sustainability goals.
- At a high level, a vulnerability assessment will assign colors or scores to individual chemicals based on a set of user-defined hazard, risk, and regulatory criteria.
- The criteria can then be viewed for individual chemicals, across groups of chemicals, or across all chemicals. The tool is useful for giving a high-level snapshot of the current vulnerability, but can also be used to prioritize further research and inform ingredient replacement/process changes.

Table 2 Individual Chemical Vulnerability Assessment Example

CAS Number	Skin Corrosion	Skin Sensitization	Mutagenicity	Reproductive Toxicity	Carcinogenicity
Chemical A					
Chemical B					
Chemical C					
Chemical D					
Chemical E					
Chemical F					
Chemical G					

More Vulnerable/Less Sustainable

No Hazard, Very High Confidence	No Hazard, High or Medium Confidence	No Hazard, Low or Very Low Confidence	Hazard, Low or Very Low Confidence	Hazard, Medium Confidence	Hazard, High or Very High Confidence	No Data/Insufficient Information