Understanding WoE Under New OSHA Guidance: Endpoint-by-Endpoint Considerations for Rigorous GHS-Based Hazard Evaluations

Jiaru Zhang, M.P.H.
Daniella M. Pizzurro, Ph.D.
Ari S. Lewis, M.S.

INTRODUCTION

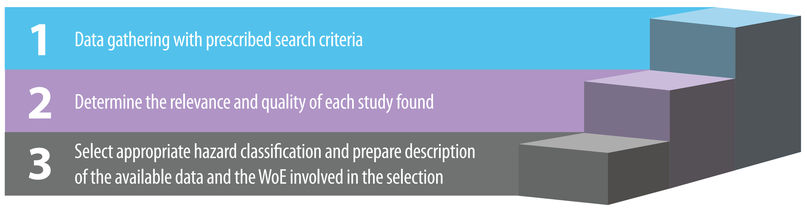
The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) is a hazard identification and communication framework being implemented around the world. Despite GHS's widespread adoption, there are many gray areas in its interpretation that could lead to conflicting hazard conclusions. Recognizing these gray areas, in early 2016, the Occupational Safety and Health Administration (OSHA) released two guidance documents to improve the quality and consistency of hazard classification, focusing on weight of evidence (WoE). This poster highlights applications of WoE evaluations to key GHS gray areas.

OSHA WoE Guidance Highlights

- OSHA expects classifiers to perform WoE evaluations. Stopping after identifying one positive study is not due diligence. All the information available (*e.g.*, *in vitro*, humans and animals, and positive/negative studies) should be considered.
- A hazard classification can be made based on one good-quality positive study. To determine whether a study is of good quality, a classifier has to take into account its validity, scientific strength, protocol, and all other available data on the chemical.
- OSHA expects classifiers to err on the side of conservatism (*i.e.*, more hazardous classifications) when there are uncertainties.
- If a classifier performed an independent hazard evaluation and arrived at a different conclusion about a chemical than the International Agency for Research on Cancer (IARC) or the National Toxicology Program (NTP), a written rationale and supporting data must be provided in the event of a compliance inspection.
- OSHA's recent Hazard Classification Guidance noted that "[a] lack of qualified workers [*e.g.,* toxicologists] does not exempt a manufacturer or importer from compliance" (OSHA, 2016). In addition, it lists eight pages of available sources to assist with hazard classification.

How to Conduct WoE Analyses?

Determining the WoE for a substance means considering all the available information that may be relevant for assessing its toxicity, including *in vitro* tests, data from animal studies, and human studies. Both positive and negative study results for the substance are assembled, and the quality and consistency of the data are evaluated to make a judgment on its hazard classification.



WoE Approach Applied to GHS Gray Areas: Mammalian

Carcinogenicity

Gray Area	WoE Approach
Questionable human relevance	Hazard classification should not be based on malignant tumors found only in animal forestomachs, which humans do not have, or mediated through PPAR-α for liver cancer or α 2u-globulin proteins, which humans have much less of compared to rodents.
Conflicting evidence in animal studies	A WoE analysis should take the following into consideration: 1) Studies conducted in accordance with established test guidelines (*e.g.*, OECD or US EPA) should carry more weight. 2) Treatment durations in studies need to be sufficiently long for tumors to develop (standard is two years for animal studies). 3) The route of exposure should parallel human exposure scenarios (*e.g.*, oral, inhalation, or dermal). Intravenous, intraperitoneal, or intramuscular exposures are unlikely for humans and may result in unrealistically high internal dose, among other issues. If available, IARC and NTP conclusions can be relied on for classification purposes.

Reproductive and Developmental Toxicity

Gray Area	WoE Approach
Maternal toxicity	Generally, the presence of maternal toxicity should not be used to negate findings of fetal effects. A substance should be classified as hazardous if it causes significant toxic effects in offspring (*e.g.*, irreversible effects such as structural malformations, embryo or fetal lethality). Developmental effects, which occur even in the presence of maternal toxicity, are considered to be evidence of developmental toxicity, unless it can be demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity. *In practice, studies rarely investigate whether the effects found are secondary or non-specific to maternal toxicity.*
Limit dose	There is no limit dose for reproductive or developmental studies in humans or animals. However, if the dosage is too high, the effects observed may be non-specific and secondary to maternal toxicity.

Single Target Organ Toxicity (STOT) Repeated Exposure

Gray Area	WoE Approach
Role of human data	Although threshold values are available in the 2016 OSHA WoE guidance for animal studies, no similar values (*e.g.*, dose cut-offs) are available for human studies. Human evidence usually trumps evidence from animal studies, unless the quality of the human evidence is a concern. Human studies for this endpoint are usually neglected in REACH Dossiers. If present, they are generally under the Special Investigation section.
Duration	Threshold values for Categories 1 and 2 are based on 90-day animal studies. If the available data are 28-day studies, then adjustments must be made. For example, the upper threshold value following oral exposure for Category 1 is ≤10 mg/kg-bw for a 90-day study and ≤30 mg/kg-bw for a 28-day study.
Adverse *vs.* adaptive effects	For STOT endpoints, a substance is only classified as toxic based on adverse effects. Transient or adaptive effects that do not trigger hazard classification include small changes in body weight gain, food consumption, water intake, clinical biochemistry, or organ weights with no evidence of organ dysfunction.

Skin/Eye Corrosion or Irritation

Gray Area	WoE Approach
Outdated scoring systems	GHS and OSHA scoring systems are out of a maximum of 4 for skin irritation and 8 for eye irritation. Many of the older scoring systems have different scales, such as a maximum score of 110 for eye irritation. When interpreting older studies, careful attention should be paid to the scoring scale.

Acute Toxicity

Gray Area	WoE Approach
Greater than data	Toxicity classification is not necessary if mortality was not observed or if the Lethal Dose (LD)/ Lethal Concentration (LC_{50}) cannot be calculated for a substance. For example, if the oral LD_{50} of a substance is >2,000 mg/kg-bw in the rat, the substance should not be classified as Category 4 or 5.
Species differences	Oral and inhalation toxicity: Rat studies are preferred. Dermal toxicity: Rabbit studies are preferred.

WoE Approach Applied to GHS Gray Areas: Aquatic

Acute and Chronic Toxicity

Gray Area	WoE Approach
LL_{50} *vs.* LC_{50}	For insoluble chemicals, toxicity data reported as loading level (LL_{50}) are preferred and are more accurate compared to the LC_{50}.
Solubility	A chemical's LC/Effective Concentration (EC_{50}) should be above its solubility in water. Some studies employ a different solvent or vigorous shaking to dissolve chemicals beyond their usual water solubility limit. Such studies should be interpreted with caution.

Biodegradability and Bioaccumulation

Gray Area	WoE Approach
Inorganic substances	Biodegradability and bioaccumulation studies were designed for organic chemicals. These endpoints are not applicable to inorganic substances.
Log K_{ow} >8	Although a log K_{ow} value ≥4 can be used as basis for the potential for bioaccumulation, its reliability for classification drops off above 8. With a log K_{ow} value ≥8, the chemical is unlikely to leave the initial partition in order to bioaccumulate. This is particularly true for surfactants because they have a tendency to accumulate at phase interfaces or form emulsions.

CONCLUSION

Applying a WoE approach to GHS gray areas can help accurately determine the hazards and risks of chemicals, which can then be conveyed to both workers and the public. Documenting and consistently executing said approach are vital for a company to meet its chemical compliance obligations.

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