

Evaluation of Skin Sensitization Classification Rules to Reflect Human Potency

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To support development of Organisation for Economic Co-operation and Development (OECD) Guideline 497 on Defined Approaches for Skin Sensitisation, we curated a human reference data set of 2277 human predictive patch tests (HPPT) for 1366 unique substances. The current United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS) criteria were used to review evidence for each test response and assign subcategorization to the represented chemicals. The human evidence for classification of sensitizers into GHS subcategories 1A (strong, with at least one sensitized subject at an induction dose per skin area [DSA] of 500 $\mu\text{g}/\text{cm}^2$ or less) or 1B (other than strong, with at least one sensitized subject at induction DSA greater than 500 $\mu\text{g}/\text{cm}^2$) does not sufficiently reflect potency, as the DSA only considers the dose used and not the fraction of sensitized test subjects.

The use of an extrapolated DSA that incorporates the number of sensitized individuals, such as the DSA at which hypothetically one individual is sensitized (DSA1+) or the DSA at which hypothetically 5% of individuals are sensitized (DSA05) was evaluated. The uncertainty in the potency classifications was accounted for by incorporating an uncertainty zone of +/- 25% around the 500 $\mu\text{g}/\text{cm}^2$ cutoff value.

All dose metrics, DSA, DSA1+, and DSA05, provided 605 test results as supporting classification for sensitizers and 1650 tests as not being supportive (nonsensitizers). The DSA1+ metric subcategorized 208 test results as GHS 1A, while the DSA and DSA05 classified 59 and 182 test results as supportive of GHS 1A, respectively. The DSA1+ metric was used to classify substances for human skin sensitization hazard and potency as reference data for development of OECD Guideline 497. For substances with multiple tests, reproducibility for the DSA1+ was 97–98% for binary classification and 77–83% for classification into GHS subcategories. Of the 200 reference chemicals for the OECD project, 91 substances had binary GHS classifications for both HPPT and local lymph node assay (LLNA) data, and 87 substances had GHS potency classifications. HPPT and LLNA classifications were concordant for 95% (86/91) of the substances using binary classifications and for 86% (75/87) of the substances using potency classifications. A modified GHS approach to classify and subcategorize sensitizers with HPPT data has addressed issues of potency and uncertainty while providing good reproducibility and concordance with animal reference data. The results obtained here have been brought to the attention of the UN GHS sub-Committee for consideration in the further development of the GHS section on skin sensitization.

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