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Use of read-across and computer-based predictive analysis for the safety assessment of PEG cocamines

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ABSTRACT

In the European Union animal testing has been eliminated for cosmetic ingredients while the US Cosmetic Ingredient Review Expert Panel may request data from animal studies. The use of read-across and predictive toxicology provides a path for filling data gaps without additional animal testing. The PEG cocamines are tertiary amines with an alkyl group derived from coconut fatty acids and two PEG chains of varying length. Toxicology data gaps for the PEG cocamines can be addressed by read-across based on structure–activity relationship using the framework described by Wu et al. (2010) for identifying suitable structural analogs. Data for structural analogs supports the conclusion that the PEG cocamines are non-genotoxic and not expected to exhibit systemic or developmental/reproductive toxicity with use in cosmetics. Due to lack of reliable dermal sensitization data for suitable analogs, this endpoint was addressed using predictive software (TIMES SS) as a first step (Laboratory of Mathematical Chemistry). The prediction for PEG cocamines was the same as that for PEGs, which have been concluded to not present a significant concern for dermal sensitization. This evaluation for PEG cocamines demonstrates the utility of read-across and predictive toxicology tools to assess the safety of cosmetic ingredients.

1. Introduction

The use of structure–activity relationships (SARs) for read-across to fill data gaps has become an important alternative approach in many toxicological assessment initiatives including the category approach for High Production Volume (HPV) Chemicals and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) monograph reviews. In addition, the Research Institute for Fragrance Materials (RIFM) has taken an approach of grouping structurally similar fragrance ingredients in recent safety reviews (Belsito et al., 2010a,b). A read-across approach is particularly important for cosmetic ingredients because in the European Union animal testing was eliminated. In contrast, in the United States if the Cosmetic Ingredient Review (CIR) Expert Panel concludes that data are insufficient to support the safety of a cosmetic ingredient, the Expert Panel will identify additional data needs which may involve testing in animals. There is global interest in eliminating the use of animals for assessing the safety of cosmetic ingredients unless there are no other means to adequately establish safety. One path forward for filling data gaps without additional animal testing is the use of read-across and predictive toxicology tools.

The polyethylene glycol (PEG) cocamines are surfactants that function as emulsifying and solubilizing agents. A series of PEG cocamines of varying PEG chain lengths are listed in the International Cosmetic Ingredient Dictionary and Handbook (Nikitakis and Breslawec, 2014), although their current use in cosmetic products in the United States is limited. In their final report on the safety assessment of PEG cocamines, the CIR Expert Panel concluded that the limited data on these ingredients were not sufficient to support the safety of PEG cocamines for use in cosmetic formulations (Andersen, 1999).

Abbreviations: CIR, Cosmetic Ingredient Review; GD, gestation day; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; NOEL, no observed effect level; PEG, polyethylene glycol; SAR, structure–activity relationship; SOI, structure of interest; TIMES SS, Tissue metabolism simulator platform for predicting skin sensitization; UDS, Unscheduled DNA Synthesis.

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Recently Wu et al. (2010) published a framework for evaluating the suitability of analogs for use in SAR assessments, and a series of blinded case studies designed to test the framework has produced encouraging results (Blackburn et al., 2011). This framework is consistent with the Organization for Economic Cooperation and Development (OECD) guidance (OECD, 2014). In this paper, a SAR assessment is described for the PEG cocamines by read-across from data (genotoxicity, repeat dose toxicity, and developmental/reproductive toxicity) for analogs identified by the use of this framework. For dermal sensitization, reliable data for suitable analogs were not found. Therefore, this endpoint was addressed using the Tissue metabolism simulator platform for predicting skin sensitization (TIMES SS) as a first step. For cosmetics, local effects of an ingredient (skin and eye irritancy) are significantly influenced by formulation matrix and therefore these endpoints cannot be adequately assessed based on data on individual constituents of the formulation and/or their analogs. Procedures for making inferences about the potential irritancy of a formulation based on precedent formulation data are outside of the scope of this assessment.

2. Methods

The approach for categorizing analogs has been described previously (Wu et al., 2010); it involves identifying potential analogs based upon their degree of structural, reactivity, metabolic and physicochemical similarity to the chemical with missing toxicological data (i.e., the structure of interest or SOI). The decision tree of Wu et al. (2010) for categorizing the suitability of analogs is shown in Fig. 1. Analogs are categorized as (1) suitable (2) suitable with interpretation (3) suitable with preconditions, or (4) not suitable. Suitable analogs have the same functional groups and core structure, as well as similar potential for bio/chemical reactivity, metabolic pathways and physicochemical properties as the SOI. Analogs categorized as suitable with interpretation have the most salient features relevant for bio/chemical reactivity and toxicological activity in common with the structure of interest, but have other characteristics that differ, i.e., primarily physicochemical properties. Nevertheless, these differences do not significantly affect bio/chemical reactivity and/or metabolism in a way that would be expected to result in different toxicological profiles. Analogs categorized as suitable with precondition would be considered suitable (or suitable with interpretation as just described) assuming a particular condition is met. The pre-condition typically involves a hydrolytic or enzymatic process to yield the structure of interest itself, a suitable analog of the SOI or a metabolite of the SOI.

The evaluation of analogs for the PEG cocamines involved the use of Derek for Windows™ (version 12.0.0) (Lhasa Limited) and TIMES (version 2.26.4) (Laboratory of Mathematical Chemistry) for identification of structural alerts as part of the process for assessing analog suitability. Derek for Windows™ alerts extend across multiple endpoints, while the TIMES models focus on skin sensitization (TIMES SS) and a series of mutagenicity/genotoxicity (chromosome aberrations) modules. The point of distinction of the TIMES models is that they explicitly show metabolites as a separate step through a metabolic simulator whereas Derek for Windows™ implicitly takes metabolites into account within the construction of alert patterns. Metabolism evaluation was undertaken as described by Wu et al. (2010). Briefly, an evaluation of the potential for the metabolism of the analog and the SOI to diverge was accomplished using combinations of metabolism databases (e.g., Discovery Gate® or Metabolism®), scientific literature searches, substructure searches, software prediction tools (e.g., METEOR®), *in vitro* test results, and expert judgment of a medicinal chemist.

2.1. PEG cocamines chemical group

Polyethylene glycol (PEG) cocamine (CAS No. 61791-14-8, generic) is the common name used in the International Cosmetic Ingredient Dictionary for a series of tertiary amines that conform to the formula shown in Fig. 2 where *R* represents the alkyl groups derived from the fatty acids of coconut oil and the other two functional groups are polyethoxyl chains where $x + y$ has an average value equal to the number in the common name. According to this description, the smallest member of the group (PEG-2 cocamine) actually does not contain PEG functional groups, since x and y must both be equal to 1 and the resulting structure includes two hydroxyethyl groups rather than polyethoxyl groups. The distribution of chain lengths and degree of unsaturation of the fatty acids in coconut oil are shown in Table 1. Each PEG cocamine named by PEG chain length is therefore a mixture of compounds with the major fatty acid-derived chain lengths of C12 and C14 and with an average PEG chain length of $x + y$. The PEG cocamines listed in the International Cosmetic Ingredient Dictionary include the following: PEG-2 cocamine, PEG-3 cocamine, PEG-4 cocamine, PEG-5 cocamine, PEG-8 cocamine, PEG-10 cocamine, PEG-12 cocamine, PEG-15 cocamine, and PEG-20 cocamine.

2.2. PEG cocamines analog identification

To cover the range of PEG cocamines, four of the PEG cocamines in the series with differing polyethylene glycol (PEG) chain lengths (with $x + y$ ranging from 2 to 15) were selected as SOIs, and structural analogs were identified. The decision to select four different SOIs differing in PEG chain length was made in order to consider the potential impact of PEG chain length on bio/chemical reactivity, metabolism, and physicochemical properties. Due to the mixture of alkyl chain lengths and degree of unsaturation of the alkyl group derived from coconut oil, each of these four representative PEG cocamines is actually not a single molecular entity. The impact of the alkyl amine chain length and degree of unsaturation was considered when evaluating the suitability of the analogs identified for each of these four PEG cocamines. The four PEG cocamines selected as SOIs were PEG-2 cocamine (Analog Group 1), PEG-4 cocamine (Analog Group 2), PEG-10 cocamine (Analog Group 3), and PEG-15 cocamine (Analog Group 4). The analogs identified for each of these four SOIs are shown in Tables 2–5. Both a chemical name and a common name are provided for each analog. The common names will be used in the text of this paper. Note that, where appropriate, when one of the four PEG cocamines selected as an SOI was considered to be an analog for another of the PEG cocamines, it was also included among the group of identified analogs, even if toxicological data for that PEG cocamine were not available for read-across.

Analogs with toxicological data were identified by searching an in-house database developed by the Procter & Gamble Company with more than 800,000 chemicals linked to toxicological data and by searching SciFinder and ToxNet by CAS number and relevant chemical name. In addition Scopus was used to search for articles citing relevant references or sharing similar key words. Google searches by CAS number and CAS number and chemical name were also conducted. Original sources were the preferred source when available. Where an unpublished study was available for review, these have been included in the reference list. Secondary sources (HPV and EPA documents) were sometimes the only available source for unpublished studies. The HPV source provided a review of study quality by Klimisch score and the US EPA review documents provided expert review by US EPA scientists; these sources were therefore considered acceptable in the absence of accessibility of original reports. Chemical identities and CAS numbers