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Comparative analysis of toxicological evaluations for dermal exposure performed under two different EU regulatory frameworks

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ABSTRACT

Dermal exposure to chemicals is highly relevant in relation to the use of cosmetic products, both in consumers and in individuals exposed occupationally. Regulatory frameworks exist within the EU to limit the dermal exposure of the general population and workers to chemicals in general, as well as to limit the use of certain substances in cosmetic products. The objective of the study was to investigate and compare toxicological evaluations of dermal exposure performed under current regulatory frameworks. The publicly disseminated hazard information under the respective regulatory frameworks was compiled and compared for the five substances resorcinol, *p*-phenylenediamine, *p*-aminophenol, *N*-phenyl-*p*-phenylenediamine, and diethylene glycol monoethyl ether. A low consistency between evaluations was observed in respect to data coverage and cited dose descriptors. No systematic differences over all five substances were identified from the viewpoint of dermal hazard assessment. The critical effect and corresponding systemic effect dose descriptor was identical for two substances, differed somewhat for two other (a factor of 2–2.5). For *N*-phenyl-*p*-phenylenediamine a critical effect was only identified under REACH.

1. Introduction

Dermal exposure to hazardous substances is considered to be one of the top emerging risks to the health and safety of workers in Europe (European Agency for Safety and Health at Work 2009). Within Europe, several regulatory frameworks offering quantitative hazard assessments of relevance for dermal exposures to chemicals exists. These regulatory frameworks include the Cosmetics Directive (76/768/EEC, European Commission, 1976, replaced from July 11, 2013 by the Cosmetics Regulation EC/1223/2009, European Commission, 2009), and the REACH chemicals legislation concerning registration, evaluation, authorization, and restriction of chemicals (REACH, EC/1907/2006, European Commission, 2006a).

For cosmetics there are two levels of safety evaluation within the EU. First that of the finished product according to Article 10, Article 11 and Annex I of the Cosmetics regulation (Article 7a of the Cosmetics Directive) which is the responsibility of the producer. Second that of specific ingredients belonging to categories (e.g. UV-filters) that need approval before marketing, and hence be included in the lists of approved ingredients in Annexes IV, V and VI of the Cosmetics Regulation (previously Annexes IV, VI, VII in the Cosmetics Directive) or in case concerns for safety have been expressed. The ingredient may after evaluation be taken up in Annex III which specifies limits to concentration or applications (corresponds to Annex III of the Cosmetics Regulation). This second level safety evaluation is performed by the European Union (EU) Scientific Committee on Consumer Safety (SCCS). The SCCS performs toxicological evaluations and, if possible, identifies a critical effect and calculates a Margin of Safety (MOS) for the evaluated substance. Representing the cosmetics industry, Cosmetics Europe – The Personal Care Association (previously Colipa), submits the substance-specific safety dossiers for evaluation, while the SCCS performs the actual evaluation of the dossiers, although they consider suggestions made by the applicants as well (SCCS Notes of guidance, European Commission, 2012a). Some of the chemicals used in cosmetic products also have high-volume industrial uses and, as such, their potential health effects are regulated by REACH (EC/1907/2006). Under REACH, any producer or importer has to compile a chemical safety report, including a toxicological evaluation, for substances produced or imported in quantities above 10

Abbreviations: DNEL, derived no effect level; ECHA, European Chemicals Agency; LD, lethal dose; LOAEL, lowest observed adverse effect level; MoS, margin of safety; NOAEL, no observed adverse effect level; REACH, registration, evaluation, authorization and restriction of chemicals; SCCS, Scientific Committee on Consumer Safety.

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tons per year. One of the requirements of this report is to identify so-called Derived No-Effect Levels (DNELs) for all relevant effects and exposure routes for both workers and the general population. As a result of this requirement, the REACH regulation provides toxicological information relevant for the hazard assessment of a large number of substances. The DNELs are derived by extrapolating dose-descriptors identified from animal or epidemiological studies to the level of no concern for human health using assessment factors. A full justification should accompany the DNEL, and specify which human population group, exposure route (including dermal exposure), duration, and type of effects they are based on (ECHA, 2012a). All registered DNELs are publicly available on the webpage of the European Chemicals Agency (ECHA, http://echa.europa.eu), together with the summaries of the cited studies. The control of dossiers is quite limited, as the REACH regulation only requires ECHA to evaluate at least 5% of the submitted dossiers for each tonnage band (EC/1907/2006, Article 41(5)). In their report on the progress of the REACH implementation, the European Commission (EC) as well as ECHA highlighted the need to increase the quality of the compiled substance-specific dossiers (ECHA, 2012b; European Commission, 2013a).

Although differing in scope and aim, substance-specific hazard assessments are required under both REACH and the Cosmetics Directive. Under both frameworks, industry is responsible for compiling the primary data for the toxicological evaluation. However, in the case of evaluations under the Cosmetics Directive, an independent expert group performs the evaluation of data and draws the conclusion; while under REACH, industry is responsible for all steps from data selection to determining which exposure level is deemed safe for humans. As both frameworks are aimed at ensuring human safety, though concerning different kinds of products, the respective evaluations performed under the regulatory frameworks may serve as a source of toxicological information on substance-specific hazards relevant for a quantitative risk assessment of dermal exposure to chemicals.

The purpose of the present study was to investigate and compare the consistency of toxicological evaluations of relevance for dermal exposure to industrial chemicals as performed by REACH registrants and to cosmetics as performed by the SCCS.

2. Materials and methods

The present study originates from at study concerning the regulations of hairdressers' exposure to chemicals. Hence identification of case-study substances was initially based on the Danish initiative Green Salon's list of prohibited substances (www.groensalon.dk). This list identifies groups of substances that are problematic for hairdressers work environment. The Green Salon list was cross-references with the registry of cosmetic ingredients (CosIng, http://ec.europa.eu/consumers/cosmetics/cosing), yielding 128 individual substances. CAS numbers and EC numbers were used for substance identification. Four of these 128 substances were both evaluated by the SCCS and have a dermal DNEL registered under REACH: resorcinol (CAS 108-46-3), *p*-phenylenediamine (PPD; CAS 106-50-3), *p*-aminophenol (PAP; CAS 123-30-8) and *N*-phenyl-*p*-phenylenediamine (*N*-P-PPD; CAS 101-54-2). All of these are active hair-dye ingredients and might represent a specific subcase of cosmetic ingredients that also have a high volume use. Hence, a fifth substance was added for the purpose of the present study: diethylene glycol monoethyl ether (DEGEE; CAS 111-90-0). This substance is used as a solvent in a variety of cosmetic products, and was recently evaluated by the SCCS.

From each of the ten substance-specific evaluations identified the bibliographic references citing in vivo or epidemiological data were extracted together with any cited dose descriptor. Subsequently, the data coverage and identified effects were analyzed for these ten evaluations. The compiled information was compared between the evaluations performed for each substance under the respective regulatory framework. The study has, with one exception for an aberrant dose descriptor for PPD, been based on information as made available by the ECHA through the dissemination portal (found at www.echa.eu and henceforth referred to as the ECHA database), and the SCCS in the published opinions.

The toxicological endpoint considered pivotal in respective evaluation was identified. The effect considered the most relevant toxicological effect by the SCCS is clearly stated in the published substance-specific opinions, defined as the effect for which the NOAEL used for the MOS calculation was extracted. In the case of N-P-PPD, the SCCS could not establish a proper NOAEL, and therefore, no effect was considered as the most relevant. For evaluations under REACH, the most sensitive endpoint, e.g. "repeated dose toxicity" or "carcinogenicity", used for DNEL derivation is generally listed in connection to each registered DNEL in the ECHA database. Sometimes, but most often not, this information also includes detailed information about the dose descriptors used for DNEL derivation. Since this was not the case for our five substances, studies with the purpose flag "key study" under the category of the most sensitive endpoint were identified. If most sensitive endpoint was not specified, we assumed it was repeated dose toxicity. Also, dose descriptors from dermal key studies were given priority over oral key studies (only relevant for DEGEE).

For the five selected substances the data coverage was analyzed by comparing all bibliographic references in the two different evaluations for each substance. The common references, in other words those referred to by both evaluations, were identified as far as possible. In the case of the registrants' evaluation under REACH, not all references were given in full and non-identifiable data sources and duplicates were excluded from the data coverage analysis. As an example, the ECHA database for Resorcinol contained eight individual entries under the heading of repeated dose toxicity; however, all were unidentifiable and are hence not included in the analysis of bibliographic references. Sometimes a study was reported repeatedly under different headings, in the data coverage analysis each study was counted once for each different heading specified in Table 1. Also, the details offered on bibliographic references in the ECHA database have changed during the course of the work of the present study. The first data collection was performed in December 2012. When the ECHA database was accessed on February 12, 2013, all reference identifications, – author, title, and journal identifiers – had been removed from the evaluation of PPD, although it seems the same studies are still included. The references were displayed as a reference type such as "Publication" or "Study report" together with the year of publication. The number of cited studies had not changed, nor had the range of effect levels. All bibliographic information for PPD presented herein is thus based on the data extraction performed during December 2012. The data presented for the other substances was collected in June 2013, and checked for updates following the update on September 12th 2013. As new information was included for N-P-PPD, a new data compilation was performed for this substance. The availability of references was also taken into consideration, as only publications from 2009 or earlier were considered to be available for REACH registrants in order to meet the first REACH registration deadline of November 30, 2010 for evaluation under REACH. In the case of opinions, references were considered available if published the year before the publication of the opinion. In addition, as both frameworks rely on company submitted data, which include non-published as well as confidential reports, consideration has also been given to whether the references are publicly available. By publicly available we refer to studies found in the