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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 to 2.5). For N-phenyl-*p*-phenylenediamine a critical effect was only identified under REACH.

Key words: Regulation, Derived no effect levels, Risk management, Cosmetics regulation, REACH

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

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 exist. 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), and the REACH chemicals legislation concerning registration, evaluation, authorization, and restriction of chemicals (REACH, EC/1907/2006, European Commission 2006).

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 2012). 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 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).

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 a 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.greensalon.dk). This list identifies groups of substances that are problematic for hairdressers work environment. The Green Salon list was cross-referenced 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 open scientific literature or published reports (both on the Internet or in print).

Finally, reported dose descriptors for each type of endpoint were extracted in order to deduce the influence of data selection on the conclusions of relevant effect and doses. No distinction was made between dose descriptors derived from studies of different classification – in other words, dose descriptors derived from key studies and those derived from supporting or weight of evidence. Furthermore, the dose-descriptors were grouped based on the type as: no effect dose-descriptors such as “no observed adverse effect levels” (NOAELs); effect dose-descriptors such as “lowest observed adverse effect levels” (LOAELs); “effect concentrations” (ECs); and lethality dose descriptors such as “lethal dose” (LD). All extracted dose descriptors were recalculated to mg per kg body weight per day, if not given in this unit, for the purpose of the present study. For most endpoints and exposure routes analyzed, more than one study was reported in the toxicological evaluations, and thus for each end-point, a range of effect levels is presented.

3. Results

The comparative analyses of the case-study substances (Tables 1 and 2) are presented in the following sections. The toxicological information in the ECHA database as well as in the SCCS opinions is organized in similar structural hierarchies; individual entries reporting on substance-specific effects are sorted based on exposure route and the type of study, and correspond to the study types included in Table 1. Figure 1 plots dose descriptors paired according to endpoint and type of effect, for which one or several dose descriptors were extracted from both the SCCS and the REACH registrant evaluations.

3.1 Resorcinol

Data related to the toxicological effects of resorcinol was identified in the ECHA database (<http://echa.europa.eu>) and in an opinion by the SCCS (1270/09, European Commission 2010b). Different types of toxicological effects after exposure to resorcinol were reported on in 95 entries in the ECHA database; 65% of the entries were associated with one or several identifiable bibliographic references. In total, 69 unique references could be identified for the review of resorcinol toxicity under REACH, of these all fulfilled the criteria of being publicly available (Table 1). The identified references were published from 1925-2007. In the opinions by the SCCS, references were listed for each entry; however, very few references were used for each set of effects. In total, 12 entries reported on toxicological effects based on 13 references, of these 5 were publicly available (Table 1). Several additional references were included in the reference list, containing 71 references in total,

Table 1: Comparison of data coverage based on identifiable cited references. Number in parentheses indicates number of studies of these that are also publicly available.

Type of study	Resorcinol			p-Phenylenediamine			p-Aminophenol			N-phenyl-p-phenylenediamine			Diethylene glycol monoethyl ether		
	Registrant	SCCS	Common	Registrant	SCCS	Common	Registrant	SCCS	Common	Registrant	SCCS	Common	Registrant	SCCS	Common
Acute toxicity	2 (2)	1 (0)	0	54 (54)	4 (3)	1	2 (2)	6 (5)	2	8 (6)	3 (3)	1	13 (13)	13 (11)	6
Irritation/ Corrosion	1 (1)	2 (0)	0	17 (17)	1 (1)	1	1 (1)	4 (3)	0	4 (2)	1 (1)	0	11 (11)	5 (2)	1
Sensitization	1 (1)	1 (0)	0	53 (53)	2 (1)	1	2 (2)	4 (4)	1	52(50)	2 (0)	0	-	-	-
Repeated dose toxicity	0 (0)	3 (2)	0	24 (24)	7 (4)	1	1 (1)	7 (5)	0	3 (3)	3 (3)	1	11 (11)	20 (15)	9
Genetic toxicity in vivo	5 (5)	1 (0)	0	10 (10)	5 (2)	0	1 (1)	9 (5)	0	4 (3)	4 (1)	1	1 (1)	2 (1)	1
Carcinogenicity	0 (0)	2 (2)	0	10 (10)	15 (13)	4	0 (0)	5 (4)	0	5 (5)	4 (3)	2	1 (1)	-	0
Reproductive toxicity	1 (1)	2 (0)	0	6 (6)	9 (5)	2	4 (4)	9 (7)	3	5 (5)	5 (3)	2	3 (3)	8 (6)	3
Specific investigations	1 (1)	-	0	46 (46)	-	0	-	21 (20)	0	1 (1)	-	0	1 (1)	2 (0)	0
Irritation/sensitization															
Human	28 (28)	-	0	108 (108)	17 (17)	3	1 (1)	2 (2)	0	1(1)	7 (7)	7 ^b	3 (3)	2 (0)	0
Other observations															
Human	4 (4)	3 (3)	0	2 (2)	3 (3)	0	2 (2)	-	0	2 (2)	-	0	-	-	-
Additional information	25 (25)	-	0	2 (2)	0	0	-	-	-	46 (45)	-	0	-	-	-
Total unique identifiable references^a	69	13	0	306	58	13	13	53	7	116	26	12	32	45	20
Total publicly available references^a	69	5	-	306	45	-	13	42	-	110	18	-	32	31	-

⁻ indicates that no studies were reported under this heading: 0 means no identifiable reference.

^a Some references are cited in more than one entry as well as for some entries several references are included, in the total amount each individual reference has been counted once. In addition, as some studies may be referenced by both evaluators but under different headings, the column for common references reports the number of all common references.

^b The 7 studies reported under human sensitization in the opinion are included under the heading of sensitization by the registrant.

REACH= Legislation concerning registration, evaluation, authorization and restriction of chemicals (REACH, EC/1907/2006), based on information submitted by a registrant and made available in the database of the European Chemicals Agency (ECHA, <http://echa.europa.eu>)

SCCS=Scientific Committee on Consumer Safety opinions SCCS/1270/09, SCCS/1443/11, SCCS/1409/11, SCCS/0991/06 and SCCS/1507/13.

but not specifically referred to in the text. The references included in the opinion were published from 1975-2010. The toxicological evaluations performed by the REACH registrants and in the SCCS opinion had no references in common (Table 1). Nine studies, describing different types of effects, were classified as a Key study in the ECHA database; five of these were associated with an identifiable bibliographic reference.

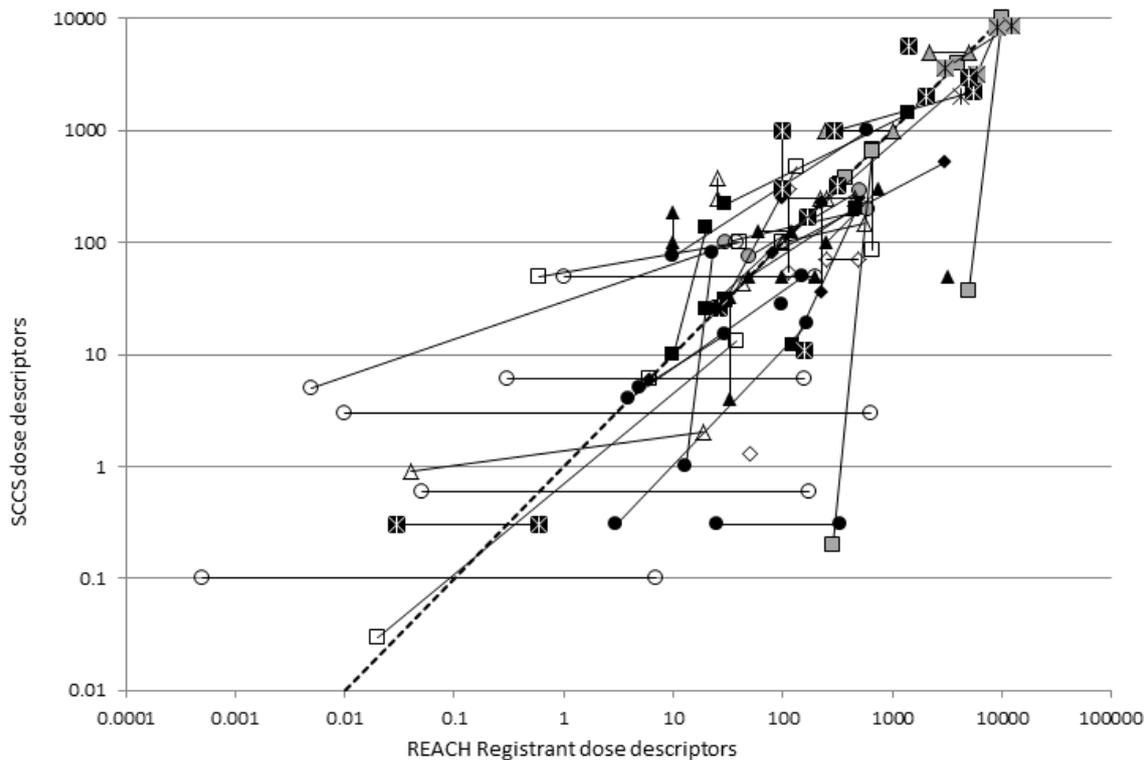


Figure 1. Dose descriptors in mg/kg bw /day as reported in the toxicological evaluations by the REACH registrants and by the SCCS and paired according to end-point and effect category. Symbols filled with black represent NOAELs, unfilled represent LOAELs and symbols filled with grey represent lethal doses. Squares: p-Aminophenol; Triangles: N-phenyl-p-phenyldiamine; Diamonds: Resorcinol; Circles p-Phenylenediamine; Star: Diethylene glycol monoethylether. Lines between symbols represent a range of dose descriptors for the same endpoint and effect category. The dotted line represents the line of unity.

According to the information available in the ECHA database, the dermal worker DNEL for systemic effects after long-term exposure was based on repeated dose toxicity. As no dermal Key study was listed, information on the most relevant effect was derived from the only oral Key study. Both the selected endpoint and the corresponding NOAEL value were identical in the registrants' Key study for oral exposure and in the oral study used for MOS calculations in the SCCS opinion, with a NOAEL of 80 mg/kg body weight (bw) for decreased body weight gain in female rats, though originating from different publications (Table 2). The teratogenicity study identified by the SCCS and used for the subsequent MOS calculation was not publicly available and to our best knowledge not included in the evaluation performed under REACH. In fact, no Key study was identified for reproductive toxicity and teratogenicity in the registrants' evaluation. The REACH key study was not identifiable by bibliographic reference and hence it was not possible to discern whether it was referenced, or even available for inclusion, in the SCCS opinion.

A comparison of the dose descriptors, defined as no-effect, effect, or lethality dose descriptors, was also performed between the toxicological evaluations under REACH and the Cosmetics Directive (Figure 1). Some overlap in the effect levels reported for the included studies was observed. In cases where effect levels were included for an effect and dose descriptor type, the effect levels were generally lower in the SCCS opinion. Acute toxicity and genetic toxicity in vivo was only reported after oral exposure in the SCCS opinion, while several exposure routes were included in the ECHA database. The REACH registrants' evaluation of resorcinol under REACH also contained human data to a larger extent. The effect level in studies categorized as Key studies in the ECHA database was lower than the corresponding levels reported in the SCCS opinion for genetic toxicity, and higher for skin sensitization.

3.2. p-Phenylenediamine

Data related to the toxicological effects of PPD was identified in the ECHA database (<http://echa.europa.eu>) and in an opinion by the SCCS (1443/11, European Commission 2012b). Different types of toxicological effects after exposure to PPD were reported on in 422 entries in the ECHA database; 86% of the entries were associated with one or several identifiable bibliographic references (Table 1). In total, 306 unique references were used for the review of PPD toxicity under REACH. The identified references were published from 1896-2007 and all also fulfilled the criteria of being publicly available (Table 1). In the opinion by the SCCS, 60 entries reported on toxicological effects derived from 58 references, of these 45 were publicly available. In total, 197 references published between 1956 and 2006 were included. The registrants' evaluation under REACH and the evaluation in the SCCS opinion had 13 references in common (Table 1). Eight studies, describing different types of effects, were classified as a Key study in the ECHA database; no Key study was however associated with an identifiable bibliographic reference.

According to the information available in the ECHA database, the dermal worker DNEL for systemic effects after long-term exposure was based on repeated dose toxicity. As no dermal Key study was available under the heading of repeated dose toxicity, information on the most relevant effect was derived from the only oral Key study. The study categorized as a Key study for oral exposure on the ECHA database was most likely the same as the oral study used for MOS calculations in the SCCS opinion. A bibliographic reference was not included in the ECHA database, but the studies were identical with regard to the experimental details described in respective evaluation. The NOAEL value identified by the registrants under REACH and by the SCCS did differ however; the registrants established a NOEL of 4 mg/kg bw based on slight organ weight changes, and a NOAEL of 16 mg/kg bw (highest dose tested); meanwhile, the SCCS established a NOAEL of 8 mg/kg bw based on myodegenerative effects (Table 2).

The comparison of reported dose descriptors in the two toxicological evaluations of PPD showed that a larger number of effect types and exposure routes were included in the ECHA dossier. In cases where dose descriptors were included for a specific endpoint and effect group type in both evaluations, the NOAELs were generally lower in the data reported in the ECHA database, while the LOAEL values covered a wider range than reported in the SCCS opinion (Figure 1). Acute toxicity was only reported after oral exposure in the SCCS opinion, while several exposure routes were included in the ECHA database. The REACH registrants' evaluation of PPD also contained human data to a larger extent.

The dossier on PPD toxicity submitted to the ECHA also contained two studies on repeated dose toxicity in rats and guinea pigs that reported an aberrant and unjustified dose descriptor: a TDLo-value of 105-28000 mg/kg bw, which could not be verified in the listed references. Further scrutiny of this specific dose descriptor was performed due to its high numerical value. The first study, reporting on 30 weeks exposure in rats and guinea pigs, was published in Russian in 1958, and could not be retrieved or verified. The second study, reporting on 80 weeks dietary exposure in rats, was not

Table 2: Description of the most relevant effects in the substance-specific data submitted under REACH (key study) or under the Cosmetics directive (critical study)

	Dermal DNEL ^a	Experimental details				
		Type of study	Route	Species	NO(A)EL	Description
Resorcinol						
Key study ^b SR 2006	LT: 40 mg/kg bw	Repeated dose toxicity	Oral	Rat	80 mg/kg bw	Physical effects, decreased body weight gain
Critical study ^c Foulon 2005 (SR)	-	Sub- chronic toxicity	Oral	Rat	80 mg/kg bw	Decrease in body weight gain (maternal effects in teratogenicity study)
p-Phenylenediamine						
Key study SR 1995	LT: 0.32 mg/kg bw	Repeated dose toxicity	Oral	Rat	4 mg/kg bw 16 mg/kg bw	Slight organ weight changes, no pathological findings
SR 2003	ST: 0.06 µg/cm ²	Sensitization	Dermal	Mouse	0.06%	LLNA EC ₃ value
Critical study ToxLab 1995 (SR)	-	Sub-chronic toxicity	Oral	Rat	8 mg/kg bw	Myodegenerative effects
p-Aminophenol						
Key study SR 1995	LT: 1 mg/kg bw	Repeated dose toxicity	Oral	Rat	10 mg/kg bw	Nephrotoxicity, decreased body weight gain (slight effect at 10mg/kg in females)
Critical study CIT 1994 (SR)	-	Sub-chronic toxicity	Oral	Rat	10 mg/kg bw	Nephrotoxicity (decreased body weight gain at 10 mg/kg bw)
N-phenyl-p-phenylenediamine						
Key study Singh 1986	LT: 4 mg/kg bw	Repeated dose toxicity	Oral	Rat	100 mg/kg bw	Haematotoxicity and hepatotoxicity Reliable with restrictions
	ST: 8 mg/kg bw	Not specified.	-	-	-	Sensitization is also mentioned as a local effect after both short and long term exposure, but no DNEL is specified for these entries.
Critical study	-	-	-	-	-	No proper NO(A)EL could be established
Diethylene glycol monoethyl ether						
Key study SR 1995	LT: 50 mg/kg bw	Repeated dose toxicity	Dermal	Rabbit	100 mg/kg bw (local effects)	Reversible irritation (erythema/ oedema) The systemic NOAEL was 1000 mg/kg bw ^d
Critical study Gattefosse 2007 (SR)		Sub/chronic toxicity	Oral	Dog	400 mg/kg bw	Nephrotoxicity

^aDermal DNELs derived either for Long term exposure systemic effects (LT) or Short term exposure local effects (ST) in workers ^bThe most relevant studies for derivation of dermal DNELs for workers as identified by a registrant in the information submitted as part of a dossier for registration of the individual substance under REACH and made available in the database of the European Chemicals Agency (ECHA, <http://echa.europa.eu>) ^cThe most relevant study identified in information submitted by an applicant and evaluated by the Scientific Committee on Consumer Safety (SCCS) in a substance specific opinion (SCCS/1270/09, SCCS/1443/11, SCCS/1409/11, SCCS/0991/06 or SCCS/1507/13/). Abbreviations: SR- Study report; considered unavailable DNEL= Derived no effect level; EC= Effect concentration; LLNA= Local lymph node assay; MoS= Margin of safety; NO(A)EL= No observed (adverse) effect level; SCCS=Scientific Committee on Consumer Safety

correctly referred to. The authors of the article identified by publication year, journal, volume number, and pages as specified by the registrants, did not correspond to the author as specified by the registrants in the same reference. The retrieved article (Imaida et al. 1983) concerned the correct substance; however, the dose in this study was given as a concentration in diet and not calculated in the form of a total dose per kg body weight. If this was the intended reference, the dose-descriptor transformation was not justified in the presented study summary. The same article (Imaida et al. 1983) was also included and correctly referred to by the registrants for other types of effects.

3.3. p-Aminophenol

Data related to the toxicological effects of PAP was identified in the ECHA database (<http://echa.europa.eu>) and in an opinion by the SCCS (1409/11, European Commission 2011b). Different types of toxicological effects after exposure to PAP were reported on in 40 entries in the ECHA database. One or several identifiable bibliographic references were given for 50% of the entries, corresponding to a total of 13 references (Table 1). The identified references were published from 1977-2008, and all were publicly available. The registrants' evaluation also referred to an earlier version of the SCCS opinion on PAP (SCCP/0867/05, European Commission 2005) as supporting evidence for exposure-related sensitization in humans. In the SCCS opinion toxicological effects of PAP were described in 55 entries based on information from 53 references, of which 42 were also publicly available (Table 1). In total 106 references published from 1948-2011 were included in the opinion, one cited reference was published in 2011, and hence considered unavailable at the time of dossier submission under REACH. The registrants' evaluation under REACH and the evaluation in the SCCS opinion had 7 references in common (Table 1). Ten studies, describing different types of effects, were classified as Key study in the ECHA database; 6 of these were associated with an identifiable bibliographic reference, and only 4 were included among the 7 references in common for both evaluations.

According to the information available in the ECHA database, the dermal worker DNEL for systemic effects after long-term exposure was based on repeated dose toxicity. As no dermal Key study was available under the heading of repeated dose toxicity, information on the most relevant effect was derived from the only oral Key study. The study categorized as a Key study for oral exposure in the ECHA database and the oral study used for MOS calculations in the SCCS opinion was most likely the same. A bibliographic reference was not included in the ECHA database, but the studies were identical with regard to experimental details. A NOAEL value of 10mg/kg bw for nephrotoxicity was selected by both the registrants and the SCCS (Table 2).

Similar effect levels were observed in a comparison between references submitted to the ECHA and references evaluated by the SCCS. When differences were observed, lower levels were found in the SCCS opinion in 4 out of 6 cases (Figure 1). The SCCS opinion contained information that was lacking in the ECHA database on repeated dose toxicity, carcinogenicity, and reproductive toxicity after dermal exposure. For human sensitization, the only reference included in the ECHA database was the SCCS opinion, and no effect levels were specified. A very low dose was reported for acute lethality after inhalation in one of the studies included in the SCCS opinion.

3.4. N-phenyl-p-phenylenediamine

Data related to the toxicological effects of N-P-PPD was identified in the ECHA database (<http://echa.europa.eu>) and in an opinion by the SCCS (SCCP/0991/06, European Commission 2006). Different types of toxicological effects after exposure to N-P-PPD were reported on in 103 entries in the ECHA database. For 83% of the entries, the information was associated with an identifiable bibliographic reference. In total, 116 unique references were used for the review of N-P-PPD toxicity under REACH (Table 1). The identified references were published from 1941-2009, and 110 were publicly available. Four references are considered unavailable to SCCS due to time constraints (three

references published in 2006, and one in 2009). The REACH registrants also repeatedly referred to the SCCS opinion on N-P-PPD (SCCP/0991/06) as supporting evidence for genetic toxicity in vivo and carcinogenicity, and as non-significant evidence for skin sensitization and additional toxicological information. In the opinion by the SCCS, toxicological effects of N-P-PPD were described in 31 entries corresponding to 26 references, of which 18 were publicly available (Table 1). Several additional references as well as references considered by the SCCS but not individually referred to in the text were included in the reference list of the opinion, containing 51 references in total. The references were published from 1957-2005.

The registrants' evaluation under REACH and the evaluation in the SCCS opinion had 13 references in common (Table 1). Twelve studies, describing different types of effects, were classified as a Key study in the ECHA database; 8 of these were associated with an identifiable bibliographic reference, though only one was also cited in the SCCS opinion.

According to the information available in the ECHA database, the dermal worker DNEL for systemic effects after long-term exposure was based on repeated dose toxicity. The only study categorized as a Key study for repeated dose toxicity was an oral study considered reliable with restrictions (Table 2). A NOAEL value of 100 mg/kg bw for haematotoxicity and hepatotoxicity was identified in this study (Table 2). The study was most likely also cited in the SCCS opinion on N-P-PPD, as identified by experimental details, since an identifiable bibliographic reference was not included in the ECHA database. The SCCS did, however exclude the study in their evaluation based on qualitative considerations, stating that the study was a journal publication and not a study report; it was not performed according to guidelines or GLP, and it did not include females. In fact, the SCCS concluded that no proper NOAEL could be established for effects observed after exposure to N-P-PPD based on the shortcomings of the experimental data provided.

The comparison of reported dose descriptors revealed that for a majority of the effect types included, the levels did not overlap. When the same type of effect levels were included in both evaluations, lower levels were generally observed in the studies submitted to the ECHA as part of the registration under REACH (Figure 1). The registrants' evaluation lacked information on repeated dose and reproductive toxicity after dermal exposure present in the SCCS opinion, while the opinion lacked information on eye irritation/ corrosion and human sensitization. The effect levels in studies categorized as key studies in the ECHA database were lower than the effect levels included in the SCCS opinion for the corresponding effects for acute lethality and repeated dose toxicity after oral exposure.

3.5. Diethylene glycol monoethyl ether

Data related to the toxicological effects of DEGEE was identified in the ECHA database (<http://echa.europa.eu>) and in an opinion by the SCCS (1507/13, European Commission 2013). Different types of toxicological effects after exposure to DEGEE were reported on in 89 entries in the ECHA database; 61% of the entries were associated with an identifiable bibliographic reference. In total, 32 unique references were used for the review of DEGEE toxicity under REACH (Table 1). The identified references were published in 1931-2005, and were all publicly available. In the opinion by the SCCS 58 entries reported on toxicological effects derived from 45 references, of which 31 were publicly available (Table 1). A total of 60 references published in 1939-2007 were included in the opinion. The registrants' evaluation under REACH and the evaluation in the SCCS opinion had 20 references in common (Table 1). Twelve studies, describing different types of effects, were classified as a Key study in the ECHA database; only one of these was however associated with an identifiable bibliographic reference.

According to the information available in the ECHA database, the dermal worker DNEL for systemic effects after long-term exposure was based on repeated dose toxicity. One dermal study was

categorized as a Key study for repeated dose toxicity, considered reliable with restrictions (Table 2). In addition an oral study was listed as a Key study under repeated dose toxicity. Both these studies concluded a NOAEL of 1000 mg/kg bw per day for systemic toxicity. The dermal study also identified local NOAELs of 100 mg/kg bw for reversible effects, and 300 mg/kg bw for local histopathology. Most likely both these studies were also cited in the SCCS opinion, as identified by experimental details since an identifiable bibliographic reference was not included in the ECHA database. In addition, the oral Key study seems to be identical to the critical study in the SCCS opinion. However, the study authors identified a NOAEL of 1000 mg/kg bw and day, as used by the REACH registrants, while the SCCS considers the results to show nephrotoxicity at 1000 mg/kg bw per day. The SCCS thus considers the NOAEL for nephrotoxicity to be 400 mg/kg bw.

A comparison of the effect levels, defined as no-effect, effect or lethality dose descriptors, was also performed between the toxicological evaluations. In cases where effect levels were included for a specific effect and dose descriptor type in both evaluations, similar effect levels were largely observed. When differences were observed, lower levels were found in the review under REACH in 4 out of 7 cases (Figure 1). A report of irritation/ corrosion to the eye after exposure to DEGEE was only included in the SCCS opinion. The dose descriptors in studies categorized as key studies in the ECHA database on DEGEE were lower than the corresponding dose descriptors reported in the SCCS opinion for repeated dermal dose toxicity and reproductive toxicity after oral exposure.

4. Discussion

Despite the fact that dermal exposure to hazardous substances is considered a top emerging risk, quantitative assessment of dermal exposures as well as specific regulations offering guidance on such exposures are scarce. REACH is the only regulatory framework on the EU-level where the assessment of dermal exposure is specified (through the derivation of dermal DNELs). Cosmetics are not per se covered by this regulation, though some cosmetic ingredients also have high volume industrial uses. By definition, dermal exposure should be an important focus of the Cosmetics Directive, since cosmetics are primarily intended to be applied to the external parts of the human body (Cosmetics Directive, article 1), resulting in a major dermal contact with such products. The Cosmetics Directive is focused on consumers, and cases of occupational exposure to cosmetics – such as hairdresser exposure to hair dye ingredients – a monumental difference in exposure frequency is apparent. Four of the five substances included in the present analysis are known as strong to moderate sensitizers. For one of these, PPD, a short-term dermal DNEL for sensitization has been derived. In the conclusions of the SCCS opinions for each of these four substances, the SCCS states that no risks to the health of consumers were observed if the established restrictions were followed, apart from the sensitizing potential. This statement indicates that the SCCS is aware of the problem with sensitization and that sensitization should be a prioritized area for the committee. However, studies reporting lower effect levels for sensitization were included for PPD and N-P-PPD in the information found in the ECHA database than in the opinion by the SCCS. No human data on sensitization was included in the SCCS opinions on resorcinol, PPD, or N-P-PPD, while an abundance of such data was found in the REACH registrants' evaluations. Under the cosmetics regulation entering into force on July 11, 2013, reports of serious undesirable effects related to the use of cosmetic products should be collected by cosmetic companies (Cosmetics Regulation, Article 23). The cosmetic industry, represented by Cosmetics Europe - The Personal Care Association (previously Colipa), has also published guidelines on the management of undesirable event reports in relation to cosmetic use (Colipa 2005). Allergenic and irritant effects are an area of focus of the guidelines, indicating that human data related to such effects are compiled by the cosmetics industry and would be available for evaluation to a larger extent than currently is the case.

Expert judgment is an important, if not crucial, part of risk assessment. Ideally the evaluation process should be systematic and consistent, cover all relevant data, and transparently justify all selections and constraints applied. A standardized and transparent approach would greatly increase the

understanding of evaluation-specific conclusions and, at least in theory, result in an increased consistency between evaluations performed by different assessors. Differences in conclusions drawn in evaluations performed under different regulatory frameworks can be justified based on differing focuses of the regulatory frameworks, such as the importance of dermal exposure for chemicals used in cosmetics, or the importance of oral exposure for food additives. In the presented case of a comparative analysis focusing on dermal exposure under REACH and the Cosmetics Directive, a high level of consistency would be anticipated. The comparison, however, revealed differences in the overall data included in the evaluations.

The same types of toxicological effect categories are included under the REACH regulation and under the Cosmetics Directive, and yet the total number of cited bibliographically-identified references, as well as the actual references, differed substantially between the corresponding assessments. Despite the inclusion of a large number of references in some cases, the number of common references referred to by both evaluations was low. The respective reference lists contain references to reports of compiled data and studies performed directly by the cosmetic or industrial companies, or their contractors. It is beneficial that the resourceful industry performs toxicological testing, deriving new toxicological information; however, from a transparency point of view, it is problematic that data is not made publicly available. Some evaluations also contained references of questionable scientific significance such as an annual plan of the National Toxicology Program for the fiscal years 1985-1987, included as a reference for the evaluation of N-P-PPD under REACH, or a doctoral thesis from 1901 included as a reference for the evaluation of PPD under REACH. The inclusion of some very old publications of questionable relevance could perhaps be defended if the intention was to give a full coverage of the area; however, the evaluations under REACH failed to include (or to give proper bibliographic reference to) relevant and publicly available studies deemed to be of importance in the corresponding evaluation by the SCCS. For example, most of the publicly available studies cited in the SCCS opinions were not, as far as it was possible to identify by bibliographic reference, included by the REACH registrants.

Both differences and similarities were observed in the selection of the most relevant effect in the substance-specific evaluations. The same study was classified as the most relevant in both evaluations for PAP, identifying the same most relevant effect and corresponding NOAEL value. In the case of resorcinol, different studies were used for the evaluation, but the same conclusion was reached regarding the most relevant effect and corresponding NOAEL. For PPD and N-P-PPD, the same studies were used, though different conclusions were reached, based on either differing assessments of study quality (N-P-PPD), or of the adversity and relevance of observed effects (PPD). For DEGEE different studies and different effects were identified.

The transparency of the assessment process was found to be especially low in the case of evaluation towards DNEL derivation under REACH. The toxicological evaluations submitted under REACH, available in the ECHA database, often lack identifiable bibliographic references. This is also the case for the studies categorized as a key study and for the five substances included in the current analysis; 33-100% of the key studies lacked an identifiable bibliographic reference. Hence, thorough third party assessment of the toxicological evaluations, including a review of the quoted data and the robustness of the subsequent conclusions on safe exposures, are practically impossible based on the publicly available information. In several cases, the information on specific details in the individual entries available in the ECHA database was also insufficient to allow a more thorough investigation. In the PPD case, an especially low transparency in the evaluation process was observed. Very old references of questionable relevance were included, and during a follow-up visit to the ECHA database, all specific reference identifiers besides type of reference and publication/ release year had been removed. The evaluation of PPD under REACH also included a dose descriptor that could not be verified: a TDLo value of 28000 mg/kg bw. It is by far the highest dose reported in the material compiled by the registrant; the original reference, as identified by the displayed information in

December 2012, did not confirm this dose descriptor. It should be noted that the investigation was solely prompted by this dose descriptor's surprisingly high value, and investigations of the accuracy of dose descriptors has not been performed for any of the other studies referred to by the registrants.

In their opinions, the SCCS specifically states which study NOAEL they have used for the MOS calculations, while for the derivation of DNELs, presented in the ECHA database, it is very hard to know which studies the values are derived from, although a recent addition specifies information on the most sensitive endpoint used for derivation of each registered DNEL. In the SCCS opinions, the included studies are often discussed in some detail, justifying the selection of critical effect for MOS calculations. There are a few indications that the evaluations under REACH are performed in a less systematic way than the evaluations performed under the SCCS. This was noted especially for PPD, for which the registrants included some very old references reporting data derived when e.g. methods for assessing exposure were less refined or incorrectly citing dose descriptors. Variations in the approach to data selection and evaluation are expected, as for industrial chemicals registrants (most often) differ for each substance, while for cosmetic ingredients the same expert group (although with some variations in membership) performs all evaluations. Hence, it would also be plausible to assume a more pronounced conflict of interest for registrants under REACH than under the Cosmetics Directive. However, the differences observed in the present study were not systematically related to the regulatory frameworks. In some cases, lower effect levels were observed in the evaluation under REACH, and sometimes in the evaluation under the Cosmetics Directive. Although no systematic bias was observed, the results still indicate that data selection does affect the range of effect doses. As an illustration, the SCCS recorded an effect at half the dose shown by the data registered under REACH in a repeated dose study after oral exposure to resorcinol (Figure 1). Conversely, for PPD, an effect after acute oral exposure is noted in data reviewed by the registrants at a dose 50 times lower than in the corresponding data reviewed by the SCCS (Figure 1).

Conclusion

In conclusion, the consistency between the examined evaluations performed under REACH and under the Cosmetics Directive was low, although no systematic differences were identified. Four of the substances are known sensitizers, and sensitisation was included quantitatively for PPD by the REACH registrants' by deriving a dermal short-term DNEL based on sensitization. For two substances the critical effect and corresponding NOAELs for systemic long-term effects were identical. For another two the critical effects differed, but the systemic NOAELs were within a factor of 2.5. The most pronounced difference in this respect was that the SCCS considered data insufficient for determining a critical effect for N-P-PPD. In comparison, an analysis of all dose descriptors for the same endpoint reported in the substance-specific evaluations revealed a significantly larger variation than was observed for the critical effects. In several cases, the studies included by the REACH registrant could not be identified by a bibliographic reference. We also observed that some of the studies included by the registrants were of questionable relevance for toxicological risk assessment.

Conflict of Interest Statement

The work was funded by the Swedish Council for Working Life and Social Research (FAS). The authors declare that there are no conflicts of interest.

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