

1 **Linking existing *in vitro* dermal absorption data to physicochemical properties: contribution to the**  
2 **design of a weight-of-evidence approach for the safety evaluation of cosmetic ingredients with low**  
3 **dermal bioavailability**

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17 **Abbreviations**

18 A, (daily amount of product exposed to per kg body weight); CDK, (Chemistry Development Kit); DA,  
19 (dermal absorption); DE, (Directorate-General); KNIME, (Konstanz Information Miner); log P,  
20 (logarithm of the octanol:water partition coefficient); MOE, (Molecular Operating Environment);  
21 MoS, (margin of safety); MP, (melting point); MW, (molecular weight); NO(A)EL, (no observable  
22 (adverse) effect level); SCCS, (Scientific Committee on Consumer Safety); SED, (systemic exposure  
23 dose); SMILES, (simplified molecular-input line-entry specification); TPSA, (topological polar surface  
24 area); TTC, (threshold of toxicological concern); WHO, (World Health Organisation)

25

26 **Keywords**

27 *In silico* prediction, dermal absorption, modelling, bioavailability, risk assessment, cosmetic  
28 ingredient, physicochemical properties, safety evaluation

29 **Abstract**

30 To characterize the risk of cosmetic ingredients when threshold toxicity is assumed, often the  
31 “margin of safety” (MoS) is calculated. This uncertainty factor is based on the systemic no observable  
32 (adverse) effect level (NO(A)EL) which can be derived from *in vivo* repeated dose toxicity studies. As  
33 *in vivo* studies for the purpose of the cosmetic legislation are no longer allowed in Europe and a  
34 validated *in vitro* alternative is not yet available, it is no longer possible to derive a NO(A)EL value for  
35 a new cosmetic ingredient. Alternatively, cosmetic ingredients with a low dermal bioavailability  
36 might not need repeated dose data, as internal exposure will be minimal and systemic toxicity might  
37 not be an issue. This study shows the possibility of identifying compounds suspected to have a low  
38 dermal bioavailability based on their physicochemical properties (molecular weight, melting point,  
39 topological polar surface area and log P) and their *in vitro* dermal absorption data. Although  
40 performed on a limited number of compounds, the study suggests a strategic opportunity to support  
41 the safety assessor’s reasoning to omit a MoS calculation and to focus more on local toxicity and  
42 mutagenicity/genotoxicity for ingredients for which limited systemic exposure is to be expected.

43

## 44 Introduction

45 According to the European Cosmetic Regulation (EC 1223/2009), every cosmetic product on the  
46 market has to be safe for human health. This safety is based on the safety of its composing  
47 ingredients, their chemical structure, toxicological profile and exposure pattern. To characterize the  
48 risk of a cosmetic ingredient when threshold toxicity is assumed, the calculation of a so-called  
49 “margin of safety” (MoS) is applied. This uncertainty factor is used to extrapolate from test animals  
50 to humans and takes into account the systemic no observable (adverse) effect level (NO(A)EL) and  
51 the systemic exposure dose (SED). The former is derived either from *in vivo* oral repeated dose  
52 toxicity studies or reproductive toxicity data. The SED is estimated by taking into account the  
53 concentration (C) of the ingredient in the product, the daily amount of product exposed to per kg  
54 body weight (A, derived from consumer studies) and the dermal absorption (DA) [  $MoS = \frac{NOAEL_{sys}}{SED}$  ;  
55  $SED (mg/kg\ bw/day) = A(mg/kg\ bw/day) \times C(\%)/100 \times DA(\%)/100$ ]. As proposed by the World Health  
56 Organisation (WHO) an ingredient with a MoS  $\geq 100$  is considered to be safe (SCCS/1564/15).

57 However, with the introduction of the animal testing and marketing bans in the European cosmetic  
58 legislation and due to the absence of validated *in vitro* replacement methods for repeated dose or  
59 reproductive toxicity studies, it is no longer possible to derive a NO(A)EL to calculate the MoS for  
60 newly developed cosmetic ingredients. The consequences of this legal implementation start to  
61 become visible as no new UV-filters, preservatives or other cosmetic active ingredients have  
62 emerged in the last 2 years. So far only substances for which *in vivo* repeated dose studies were  
63 carried out before March 2013 have been evaluated by the SCCS. But for some particular ingredients  
64 the safety assessment might not be jeopardised. Indeed, ingredients with a negligible dermal  
65 bioavailability do not necessarily need repeated dose data, as internal exposure would be minimal  
66 and systemic toxicity might not be a potential issue. Adding the assumption that the main route of  
67 exposure to a cosmetic product is dermal and the dermal bioavailability will be in most cases even  
68 lower than the oral bioavailability, it might be justifiable to base the safety assessment of such

69 compounds on local toxicity and mutagenicity/genotoxicity test results, this on the assumption that  
70 no bioaccumulation is expected. In this context it is important to define when an ingredient is  
71 considered to have a low bioavailability.

72 Bioavailability, defined as the fraction of the dose administered (orally, dermally or via another  
73 route) that reaches the systemic circulation unchanged, is a composite parameter dependent on  
74 both absorption from the site of administration and metabolism of the compound. Within the area of  
75 drug discovery much research has been carried out on predicting bioavailability, particularly with  
76 respect to oral administration. As absorption is a key component, simple rules have been established  
77 that can be used to indicate the likelihood of absorption from the gastro-intestinal tract; the most  
78 well-known of these being the Lipinski rules (Lipinski et al., 2001). Briefly, the Lipinski “rule of fives”  
79 states that a logarithm of the octanol:water partition coefficient ( $\log P$ )  $>5$ ; molecular weight (MW)  $>$   
80 500; number of hydrogen bond acceptors  $>10$ ; and number of hydrogen bond donors  $> 5$  are  
81 features associated with poor oral absorption. Veber et al (2002) showed that compounds with high  
82 topological polar surface area (TPSA) and a high number of rotatable bonds are also associated with  
83 poor oral absorption. Furthermore a relationship has been shown between oral absorption and  
84 melting point (MP): chemicals with a higher MP are less likely to be absorbed (Chu et al. 2009). The  
85 “General Solubility Equation” relates melting point to solubility and partition coefficient. The  
86 advantage of using MP is that it is more easily determined than oral absorption. Additionally, Newby  
87 et al. (2015) have recently published decision trees to characterise the roles of certain  
88 physicochemical properties on the prediction of oral absorption. Whilst these rules are broad, and  
89 many exceptions are known, they demonstrate the principle that these simple physicochemical  
90 descriptors may be useful in classifying compounds as to high or low (oral) absorption.

91 Similarly, models have been developed to predict the extent of dermal penetration based on simple  
92 physicochemical properties; the most notable example being the work of Potts and Guy (1992) who  
93 demonstrated a correlation between  $\log P$  and MW with skin permeability. Refinements to the Potts

94 and Guy model have since been published and the inherent difficulty modelling skin permeability  
95 data has been acknowledged (Steinmetz et al 2015). One problem is that measurements of dermal  
96 uptake are associated with high experimental variability, due to differences in assay conditions (e.g.  
97 differences in test protocols, skin type, use of solvents/vehicles, etc) making the development of  
98 robust, reliable quantitative models challenging. Another complication in modelling absorption is  
99 bias within the datasets. As skin is an effective barrier, dermal absorption data tend to be highly  
100 skewed towards low dermal absorption. The converse is observed for oral absorption data, as most is  
101 derived from drug development where high oral absorption is desirable, consequently most  
102 publically available data are for high oral absorption compounds. Despite these challenges, it would  
103 clearly be beneficial if rules based on simple physicochemical descriptors could be used to identify,  
104 accurately, compounds with low dermal absorption and thus low dermal bioavailability.

105 In order to investigate this possibility, a retrospective analysis of available safety evaluation data of  
106 cosmetic ingredients could provide valuable information. Although the safety of cosmetic products  
107 and their ingredients in Europe has to be assured by the companies' responsible person, for  
108 ingredients with some concern for human health *i.e.* colorants, preservatives, UV-filters and hair dyes  
109 (*i.e.* Annex substances), industry has to submit a full toxicological dossier to Directorate-General (DG)  
110 Sante when a mandate has been issued by DG Grow (Directorate-General for Internal Market,  
111 Industry, Entrepreneurship and SMEs of the EU). Risk assessment is then carried out according to the  
112 SCCS' Notes of Guidance (SCCS/1564/15). The resulting risk assessments, known as "opinions", are  
113 publically available via:

114 [http://ec.europa.eu/health/scientific\\_committees/consumer\\_safety/index\\_en.htm](http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm). These contain  
115 summaries of the studies on the different toxicological endpoints as well as the physicochemical  
116 characteristics and DA of the ingredient under investigation. Data collated from these opinions can  
117 provide a high quality dataset for analysis. To formulate rules to identify low bioavailability  
118 compounds we undertook an empirical analysis of the cosmetic ingredients, assessed between 2000  
119 and 2014 by the SCCS and its predecessors, to investigate the link between DA measured *in vitro* and

120 their physicochemical properties. In this study we propose a pragmatic approach that might aid in  
121 assessing whether a new cosmetic ingredient is likely to have a low dermal bioavailability.

## 122 **Method**

123 When preparing the data of all compounds from the SCCS opinions for modelling, the following  
124 criteria were used:

125 (i) DA measurements obtained using rat skin were excluded because of the relatively high uptake  
126 when compared to human or porcine skin.

127 (ii) if more than one DA measurement per compound were available an arithmetic mean was  
128 calculated.

129 (iii) descriptors were obtained for the parent form of the compounds.

130 A simplified molecular-input line-entry specification (SMILES) string for each compound was entered  
131 into the Molecular Operating Environment (MOE) software (version 2011.10) and processed to  
132 derive the neutralised form for the organic component. Topological polar surface area (TPSA) and  
133 molecular weight (MW) were calculated using a Chemistry Development Kit (CDK) node (molecular  
134 properties) available via the Konstanz Information Miner (KNIME) platform (KNIME version 2.10). The  
135 octanol:water partition coefficient (log P) was calculated using KowWin® (v1.68 available within EPI  
136 Suite 4.1, US EPA). Melting points (MPs) were extracted from the SCCS reports where possible. As the  
137 MPs of salts differ significantly from the MP of the parent compound, data was only included if  
138 available for the parent and not a salt form. This led to the creation of the data set (n = 70) used for  
139 further analysis.

140 For this data set a series of rules was defined in order to classify compounds as having a high or low  
141 DA. For this purpose a preliminary investigation was done using a Decision Tree Builder (KNIME  
142 version 2.10), employing log P, MW, TPSA and MP to determine which descriptors performed better  
143 in classifying compounds as high or low DA (data not shown here). Although the results from the  
144 decision tree alone were not conclusive, they provided guidance on the key descriptors, and

145 appropriate cut-off values that could be used to distinguish between high and low DA compounds.  
146 Based on these preliminary investigations, compounds were initially split into classes of low DA  
147 (<1.3%) or high DA ( $\geq$ 1.3%). The value of 1.3% was empirically derived to enable clear distinction  
148 between the classes. Because of the skew in % DA values (*i.e.* the majority of compounds have a low  
149 DA) the  $\log_{10}$  of the DA values was used for ease of visualisation. Compounds showing greater DA  
150 have greater potential to induce systemic toxicity and therefore chemical features associated with  
151 higher percentage of DA are referred to here as physicochemical “alerts”. The performance of the  
152 rules for the data set was investigated by calculating the sensitivity (correct classification of  
153 compounds with high DA) and specificity (correct classification of compounds with low DA). Rigid and  
154 flexible implementation of the derived rules was applied to optimise sensitivity and specificity of the  
155 results.

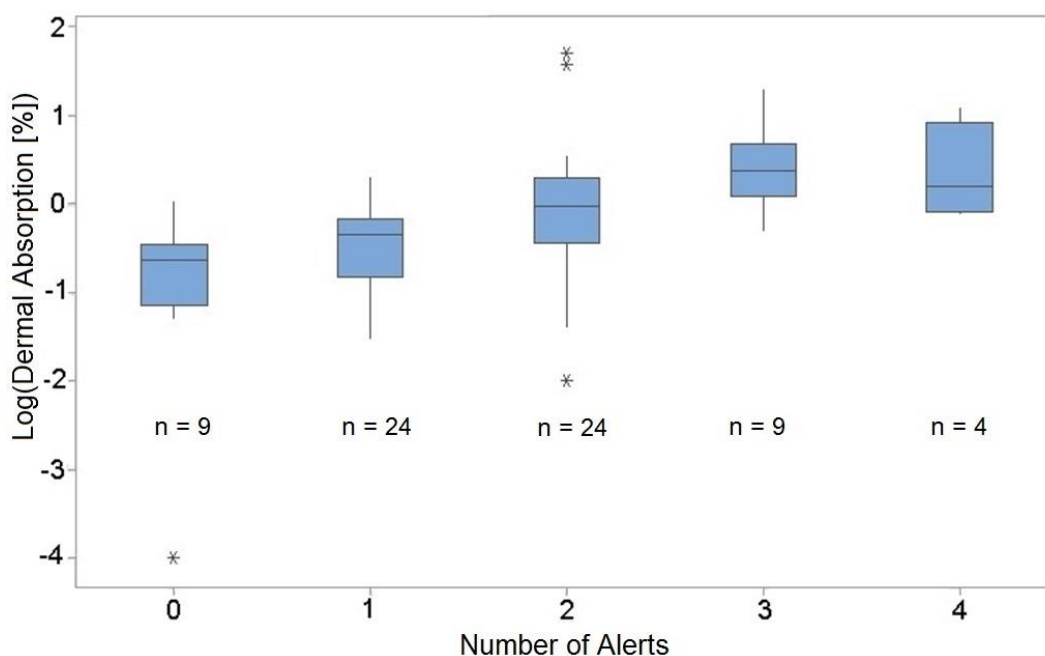
156

157

158 **Results**

159 The following physicochemical alerts, derived from preliminary investigation, were applied: (i) MW <  
160 180 Da, (ii) log P  $\geq$  0.3, (iii) MP < 100°C, (iv)TPSA < 40 Å<sup>2</sup>.

161 Compounds with MW < 180 Da and/or log P  $\geq$  0.3 and/or MP < 100°C and/or TPSA <40 Å<sup>2</sup> are more  
162 likely to be dermally absorbed. TPSA correlates with hydrogen bonding ability and preliminary  
163 investigations indicated that TPSA performed better than counts of hydrogen bond donors/acceptors  
164 in modelling the data here. The results are illustrated in figure 1, which shows that, in general, as the  
165 number of alerts increases the DA increases.



166

167 **Figure 1:** Boxplot of log<sub>10</sub> % DA versus number of alerts for the data set (n=70). The alerts applied here are: MW  
168 <180 Da, log P  $\geq$  0.3, MP <100°C and TPSA < 40 Å<sup>2</sup> (MW= molecular weight, log P = octanol:water partition  
169 coefficient, MP = melting point, TPSA = topological polar surface area, \* = outlier), horizontal bars indicate the  
170 median.

171

172 These rules can be interpreted as follows:

173 If any of the following criteria applies: (i) MW < 180 Da, (ii) log P  $\geq$  0.3, (iii) MP < 100°C and/or (iv)  
174 TPSA < 40 Å<sup>2</sup>, then the compound is predicted as highly absorbed. If none of the criteria applies, the  
175 compound is predicted as poorly absorbed. Table 1 summarises the results of applying this rule set to  
176 the data set (n=70).



177 **Table 1:** Performance of the rule set on the data set (n=70). The number of compounds in each category is  
178 given, with the percentage of the total data set between brackets.

n = 70	Predicted High Absorption	Predicted Low Absorption	Total
High Absorption ( $\geq 1.3\%$ )	23 (32.9%)	0 (0%)	23 (32.9%)
Low Absorption ( $< 1.3\%$ )	38 (54.3%)	9 (12.9%)	47 (67.1%)
Total	61 (87.1%)	9 (12.9%)	70 (100%)

179

180 The rule set shows a high sensitivity of 100% for the data set (*i.e.* for all 23 compounds in the high DA  
181 class all 23 were correctly predicted as being highly absorbed). The specificity of the rules is low as 38  
182 out of 47 low DA compounds were incorrectly classified as highly absorbed rendering a specificity of  
183 19.1%.

184 The results show that for the compounds studied here, when the rules predict a compound as having  
185 a low DA then the compound is likely to be poorly absorbed (no false negatives were identified using  
186 these rules). However, when the rules predict a compound as having a high absorption, then the  
187 compound may in fact have either a high or a low DA.

188

### 189 **Flexible analysis of the data set**

190 The same rule set was again applied to the same data set, however in this case additional flexibility  
191 was introduced. When a compound triggered none or only 1 of the alerts then it would still be  
192 predicted as low DA. Only compounds triggering two or more alerts would be assigned to the high  
193 absorption class. Table 2 shows the results for the data using the rule set with this more flexible  
194 interpretation.

195

196

197

198 **Table 2:** Performance of the rule set on the data set (n=70) with flexible interpretation (*i.e.* compounds must  
199 trigger two alerts to be placed in the high absorption class). The number of compounds in each category is  
200 given, with the percentage of the total data set between brackets.

n = 70	Predicted High Absorption	Predicted Low Absorption	total
High Absorption ( $\geq 1.3\%$ )	19 (27.1%)	4 (5.7%)	23 (32.9%)
Low Absorption ( $< 1.3\%$ )	18 (25.7%)	29 (41.4%)	47 (67.1%)
total	37 (52.9%)	33 (47.1%)	70 (100%)

201  
202 Table 2 shows that application of the rule set with flexible interpretation (*i.e.* two or more alerts  
203 need to be triggered to classify the compound as high DA) leads to an increased specificity (61.7%),  
204 but to a decreased sensitivity of 82.6% (*i.e.* 4 high DA compounds are now predicted as low DA). The  
205 increase in specificity may be out-weighed by the loss of sensitivity, as greater “cost” is associated  
206 with a false negative (*i.e.* predicting a high absorption compound as low DA).

207  
208 However, it was noted that the 4 compounds that had been incorrectly classified into the low DA  
209 class all had a DA of  $< 2\%$ . For this reason the analysis of the data set was repeated but in this case  
210 new boundaries were set for the two classes *i.e.* compounds for which DA was  $\geq 2\%$  were classified  
211 as high DA compounds, whereas those with DA  $< 2\%$  were taken as low DA compounds.

### 212 213 **Results with new boundary criteria**

214 The same rule set was applied to the data set, but with the cut-off value between high and low DA  
215 being set at 2%. Tables 3 and 4 show the results of applying the new cut-off value. In table 3 a  
216 compound is considered to belong to the class of high DA compounds if one or more alerts are  
217 triggered. In Table 4 the rule set is applied more flexibly and a compound is considered to belong to  
218 the high DA class only if two or more alerts are triggered.

219

220 **Table 3:** Performance of the rule set on the data set (n=70); triggering one or more alerts indicates a high DA  
221 compound. The number of compounds in each category is given, with the percentage of the total data set  
222 between brackets.

n=70	Predicted High Absorption	Predicted Low Absorption	Total
High Absorption ( $\geq 2\%$ )	13 (18.6%)	0 (0%)	13 (18.6%)
Low Absorption ( $< 2\%$ )	48 (68.6%)	9 (12.9%)	57 (81.4%)
Total	61 (87.1%)	9 (12.9%)	70 (100%)

223  
224 **Table 4:** Performance of the more flexible rule set on the data set (n=70); triggering two or more alerts  
225 indicates a high DA compound. The number of compounds in each category is given, with the percentage of the  
226 total data set between brackets.

n=70	Predicted High Absorption	Predicted Low Absorption	Total
High Absorption ( $\geq 2\%$ )	13 (18.6%)	0 (0%)	13 (18.6%)
Low Absorption ( $< 2\%$ )	24 (34.3%)	33 (47.1%)	57 (81.4%)
Total	37 (52.9%)	33 (47.1%)	70 (100%)

227  
228 The results given in tables 3 and 4 show that, when a cut-off value for DA of 2% is used, the  
229 sensitivity of the prediction is 100% in both cases. Indeed, compounds of high DA are always  
230 classified as highly absorbed; there are no false negatives. Allowing for a more flexible interpretation  
231 of the rule set, *i.e.* that 2 or more alerts need to be triggered in order for the compound to be  
232 predicted as having a high DA, increases the specificity – fewer true low DA compounds are predicted  
233 as having a high DA.

234  
235 In summary, using the rule set with a cut-off value of 2% will lead to high DA compounds always  
236 being predicted as high (for this data set). However compounds with true low DA may be predicted  
237 as either high or low. More of the true low DA compounds are correctly classified when the more  
238 flexible rules are applied (specificity has increased from 15.8% to 57.9%).

239  
240

241 **Discussion**

242 For the vast majority of cosmetic products the dermal route is the main route of human exposure.  
243 Therefore DA is a crucial factor in assessing the systemic toxicity of cosmetic ingredients. Another  
244 determining factor is the NO(A)EL. This value is in most cases derived from long-term *in vivo*  
245 repeated dose toxicity studies. Both factors are incorporated in the calculation of the MoS, an  
246 uncertainty factor to extrapolate from animals to humans (SCCS/1564/15). However, if evidence  
247 suggests that the compound under investigation has a low dermal bioavailability and thus systemic  
248 exposure is minimal, one might consider omitting the assessment of systemic toxicity. In the light of  
249 the animal testing and marketing bans of the European Cosmetic Regulation this would imply that  
250 data derived from an *in vivo* repeated dose toxicity study, for which no *in vitro* alternative yet exists,  
251 might not be needed for compounds with a negligible dermal bioavailability. In this context, it is  
252 important to define when a compound is considered to have a negligible dermal bioavailability. As  
253 described in the introduction, it is generally acknowledged that certain physicochemical properties  
254 such as MW, MP, TPSA and log P of a chemical may play an important role in oral and/or dermal  
255 uptake (Potts and Guy 1992, Pugh et al. 2000, Lipinski et al. 2001, Magnusson et al. 2004).  
256 By linking the DA values from the publically available SCCS opinions to the physicochemical  
257 properties MW, MP, TPSA and log P, we have shown that rules can be extracted to identify  
258 compounds suspected to have a low DA and which may be associated with a low dermal  
259 bioavailability.

260 According to this study the rule set showed a sensitivity of 100% and a specificity of 20%. After  
261 setting new boundary criteria and applying more flexible rules the performance of the rule set was  
262 optimised. The sensitivity of the predictions remained 100%, implying that compounds with a high  
263 DA are always predicted as such and the specificity was increased to 58%, without compromising the  
264 sensitivity. It is indeed preferable not to identify compounds with a high DA as having a low DA. So in  
265 case a compound triggers none or only one of the following alerts:  $MW < 180 \text{ Da}$ ,  $\log P \geq 0.3$ ,  $MP <$   
266  $100^\circ\text{C}$  or  $TPSA < 40 \text{ \AA}^2$ , it is likely to have a low DA and thus a low dermal bioavailability. The

267 presented rule set offered the best consensus between specificity and sensitivity. Adding more  
268 criteria to classify a compound as high dermal absorption, did not lead to a better prediction.

269 It should be noted that this study comprises a limited set of compounds. Furthermore, several  
270 difficulties were encountered in modelling these DA data. The data have been collated from the  
271 results of different assays using inconsistent methodologies in terms of species, exposure times,  
272 concentrations, matrices, detection methods etc. Also, it must be noted that the data set analysed  
273 here is skewed very much towards low DA values and that the same rules may not apply when  
274 investigating compounds from different chemical domains. Also, the possibility of bioaccumulation is  
275 not taken into account in this study. Nonetheless, this pragmatic approach shows that when  
276 physicochemical evidence suggests that a cosmetic ingredient has a low DA and thus low dermal  
277 bioavailability, it might be worthwhile to further investigate this by performing more extensive *in*  
278 *vitro* DA studies to get more reliable mean values and to confirm the very low DA (*i.e.* testing  
279 different concentrations, using relevant excipients, increased sample size...). Although the data are  
280 skewed towards low DA, in many cases the DA value used in the SCCS safety dossiers is still over-  
281 estimated and more extensive *in vitro* DA studies might enforce the reliability of the obtained results.  
282 Especially when taking into account that two standard deviations are added to the mean DA value  
283 when the variability between the different measurements is high or when the DA studies have not  
284 been carried out under ideal test conditions.

285

286 To add further to the weight of evidence, existing computational tools could be used to predict oral  
287 bioavailability (Moda et al. 2007; Kumar et al. 2011). In case oral and dermal bioavailability are both  
288 low, it would strengthen the safety assessor's reasoning to omit the need to calculate the MoS,  
289 making at least for this type of ingredients *in vivo* repeated dose toxicity studies redundant and to  
290 focus on local toxicity (skin sensitisation and irritation) and mutagenicity/genotoxicity test results.  
291 Since most of the existing computational tools have been developed for pharmaceuticals, evidence  
292 should be provided for their applicability in the cosmetic sector.

293

294 To notice for the future is the possibility that when substantial evidence of low bioavailability is  
295 provided, the internal threshold of toxicological concern (TTC) concept might be applied. This  
296 probabilistic approach is used to identify human exposure thresholds below which the risk of  
297 toxicological concern is low by taking into account oral/dermal absorption of the compound (internal  
298 exposure) rather than external exposure (Partosch et al. 2015). For completeness, decisions relating  
299 to internal exposure following oral/dermal administration should include considerations of  
300 metabolism when one wants to omit the determination of the NOA(E)L, since it will then be  
301 important to consider the possibility of metabolic activation. Several *in vitro* and *in silico* models are  
302 available for predicting metabolism following oral exposure and there is increasing interest in the  
303 area of skin metabolism for which models are currently being developed (as reviewed recently by  
304 Dumont et al 2015). Though in the cosmetic sector the TTC concept has been accepted for the safety  
305 assessment of impurities for which the identity is known but toxicity data are lacking (Kroes et al.  
306 2007; SCCS/1564/15), more evidence is still needed to prove the applicability of the internal TTC for  
307 cosmetic ingredients.

308

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311

312 **References**

- 313 2009/1223/EC. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of  
314 30 November 2009 on cosmetic products. *Official Journal* 2009; L 342:59.
- 315 Chu KA, Yalkowsky SH. An interesting relationship between drug absorption and melting point.  
316 *International Journal of Pharmaceutics* 2009; 373(1-2):24-40. DOI: 10.1016/j.ijpharm.2009.01.026
- 317 Dumont C, Prieto P, Asturiol D, Worth A. Review of the availability of *in vitro* and *in silico* methods for  
318 assessing dermal bioavailability. *Applied in Vitro Toxicology* 2015; 1(2): 147-164. DOI:  
319 10.1089/aivt.2015.0003
- 320 Kroes R, Renwick AG, Feron V, Galli CL, Gibney M, Greim H, Guy RH, Lhuguenot JC, van de Sandt JIM.  
321 Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic  
322 ingredients. *Food and Chemical Toxicology* 2007; 45: 2533–62. DOI: 10.1016/j.fct.2007.06.021
- 323 Kumar R, Sharma A, Kumar Varadwaj P. A prediction model for oral bioavailability of drugs using  
324 physicochemical properties by support vector machine. *Journal of Natural Science, Biology and*  
325 *Medicine* 2011; 2(2): 168-73. DOI: 10.4103/0976-9668.92325
- 326 Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to  
327 estimate solubility and permeability in drug discovery and development settings. *Advanced Drug*  
328 *Delivery Reviews* 2001; 46(1-3):3-26. DOI: 10.1016/S0169-409X(00)00129-0
- 329 Magnusson BM, Anissimov YG, Cross SE, Roberts MS. Molecular size as the main determinant of  
330 solute maximum flux across the skin. *Journal of Investigative Dermatology* 2004; 122(4):993-9. DOI:  
331 10.1111/j.0022-202X.2004.22413.x
- 332 Moda TL, Montanari CA, Andricopulo AD. Hologram QSAR model for the prediction of human oral  
333 bioavailability. *Bioorganic and Medicinal Chemistry* 2007; 15(24): 7738-45. DOI:  
334 10.1016/j.bmc.2007.08.060
- 335 Newby D, Freitas AA, Ghafourian T. Decision trees to characterise the roles of permeability and  
336 solubility on the prediction of oral absorption. *European Journal of Medicinal Chemistry* 2015;  
337 90:751-65. DOI: 10.1016/j.ejmech.2014.12.006
- 338 Partosch F, Mielke H, Stahlmann R, Kleuser B, Barlow S, Gundert-Remy U. Internal threshold of  
339 toxicological concern values: enabling route-to-route extrapolation. *Archives of Toxicology* 2015;  
340 89:941-48. DOI: 10.1007/s00204-014-1287-6
- 341 Potts RO, Guy RH. Predicting skin permeability. *Pharmaceutical Research* 1992; 9:663-9.
- 342 Pugh WJ, Degim IT, Hadgraft J. Epidermal permeability-penetrant structure relationships: 4, QSAR of  
343 permeant diffusion across human stratum corneum in terms of molecular weight, H-bonding and  
344 electronic charge. *International Journal of Pharmaceutics* 2000; 197(1-2):203-11.
- 345 SCCS/1501/12. The SCCS's notes of guidance for the testing of cosmetic substances and their safety  
346 evaluation – 9<sup>th</sup> revision. 2015 Available through:  
347 [http://ec.europa.eu/health/scientific\\_committees/consumer\\_safety/docs/sccs\\_o\\_190.pdf](http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_190.pdf),  
348 consulted November 2015.

- 349 Steinmetz FP, Madden, JC, Cronin, MTD. Data Quality in the Human and Environmental Health  
350 Sciences: Using Statistical Confidence Scoring to Improve QSAR/QSPR Modeling. *Journal of Chemical*  
351 *Information and Modeling* 2015; **DOI:** 10.1021/acs.jcim.5b00294
- 352 Veber DF, Johnson SR, Cheng H-Y, Smith BR, Ward KW, Kopple, KD. Molecular properties that  
353 influence the oral bioavailability of drug candidates. *Journal of Medicinal Chemistry* 2002; 45(12):  
354 2615-2623. **DOI:** 10.1021/jm020017n