The Threshold of Toxicological Concern (TTC) is a Pragmatic Risk Assessment Tool for the Safety Assessment of Cosmetic Ingredients with Low Consumer Exposure

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Cosmetics Europe
the personal care association

Introduction

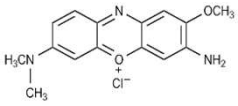
The Threshold of Toxicological Concern (TTC) is an internationally accepted pragmatic and conservative tool for the safety assessment of substances where no data regarding their systemic toxicity can be found. The TTC is based on the principle of establishing a human exposure threshold value for chemicals, below which there is a very low probability of risk to human health. Such threshold values may be identified for many substances based on their chemical structures and the known toxicity of chemicals sharing similar structural characteristics. The TTC approach utilizes human exposure threshold values (TTC values) that have been originally derived from oral toxicity data on cancer and non-cancer toxicity endpoints [1]. This database has been substantially enlarged by the COSMOS database, an enhanced oral non-cancer TTC dataset on a larger chemical domain, thereby resulting in a new, transparent and public TTC database which also includes 552 cosmetics-related chemicals [2]. The 5th percentile point of departure (POD) value for each Cramer Class was determined, from which human exposure TTC values have been derived. The combined COSMOS/Munro dataset provided TTC values of 46, 6.2 and 2.3 µg/kg bw/day for Cramer Class I, II and III, respectively. In order to demonstrate the diverse scope and successful application of the TTC concept to cosmetic ingredients including hair dyes, fragrances and plant-derived ingredients, Cosmetics Europe has prepared the following 3 case studies.

Case Study 1: Basic Blue 124 (Direct Hair Dye)

Can we safely use Basic Blue 124 up to 0.5% as direct hair dye?

Hair dyes are possible candidates for the TTC approach because of

- low use concentration
- low systemic exposure dose
- acute and intermittent exposure



Basic Blue 124 aka 3-Amino-7-(dimethylamino)-2-methoxyphenoxazin-5-ium chloride)

Assumption: No systemic toxicity data available

- Basic Blue 124 concentration in semi-permanent hair dye formulations up to 0.5%
- Consumer exposure per hair dying event at the max use concentration of 0.5% is 19.1 µg per application
- Consumer exposure every 2-3 weeks

Basic Blue 124

- was assigned to Cramer Class III based on structural profiling using the ToxTree tool (current version v3.1.0)
- has no genotoxic potential [3]
- In vitro skin penetration rate: 0.017 ± 0.016 µg/cm² → 0.033 µg/cm² (mean + 1 SD) x scalp surface 580 cm² → potential systemic exposure dose 0.019 mg per application = **19.1 µg per application < 140 µg per person/day** [2,3,4]

Estimated maximum exposure to Basic Blue 124 per hair dying event is about 7-fold below the TTC value for the structurally adequate Cramer class III
0.32µg/kg/d < 2.3 µg/kg/d

Conclusion: The TTC supports this very conservative exposure scenario. Additional refinement is possible due to the intermittent consumer exposure (consumer exposure at maximum every 2-3 weeks) [9]

Case Study 2: Trifolium pratense (Plant Extract)

Can we safely use 1 % of dried red clover flowers in a face cream?

- Complex mixture → tiered approach
- Absence of DNA-reactive mutagenicity confirmed based on experimental *in vitro* / *in silico* data
- Conservative assignment to Cramer class III using the Toxtree tool (current version v3.1.0)

Step 1: Analysis of known *Trifolium pratense* components
Over 50 distinct chemicals from *Trifolium pratense* (red clover flowers) were identified [5]

Step 2: Components not considered relevant to the safety evaluation of the extract

- high molecular weight material, e.g., proteins and sugars (44%)
- inert plant material, e.g., crude fibres (26.6%)
- polysaccharide-based gum (7.1%)
- mineral matter (about 7%)
- fat, maltol, ascorbic acid (reviewed by CIR, authorized in food, GRAS, etc.) (about 6%)
- water (4.9%)

Step 3: Justification for eliminating components present at a certain level

- Planned use level, e.g., 1% *of Trifolium pratense* extract in a face cream, would mean 1% in 1.54 g per day [4]
- At this use level, all components below 0.9% would have systemic exposure below the TTC value defined for Cramer class III with 140 µg/day (assuming 100% dermal absorption)

1540000 µg x 1.0/100 x 0.9/100 = 139 µg <140 µg/day

Step 4: Classification of any remaining components [1,5,6,7]

- For the remaining substances, i.e., typically few or even none, chemical structures are identified and classified according to the Cramer decision tree
- After the categorization into the respective Cramer Class, the skin penetration potential can be estimated based on the molecular weight and the calculated log Pow

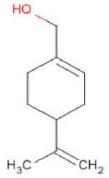
Conclusion: The TTC approach in its simple form (Cramer Class III, assumed 100% dermal absorption) is sufficiently conservative and adequate for plant extracts provided an absence of genotoxic activity is demonstrated [9]

Case Study 3: Perillyl alcohol (Fragrance)

Can we safely use perillyl alcohol as fragrance?

Perillyl alcohol (p-Mentha-1,8-dien-7-ol): [8]

- Assigned to Cramer Class I (low toxicity) using the Toxtree tool (current version v3.1.0)
- No genotoxic potential based on the available data



Maximum concentration in hydro-alcoholics: 0.000017%

- Inhalation exposure: 0.0033 µg/kg/day or 0.24 µg/day
- Total systemic exposure: 0.047 µg/kg bw/day
  - p95 calculated exposure derived from the Creme RIFM aggregate exposure model and concentration survey data from industry
  - assumes default 100% absorption for oral, dermal and inhalation exposure [8]

Estimated maximum consumer exposure to Perilla alcohol is about 1000x below the TTC value for the structurally adequate Cramer Class I, i.e., 46 µg/kg bw/day, derived from the COSMOS / Munro data set
0.047 µg/kg/d < 46 µg/kg/d [2]

Conclusion: TTC can support this exposure scenario. Overall, the TTC approach is an appropriate strategic component for many fragrances used in cosmetics due to the mostly very low use concentrations [9]

Conclusion

Overall, the case studies demonstrate that the TTC approach applied to cosmetic ingredients is an adequately conservative safety assessment tool to safeguard the consumer. Therefore, the TTC concept is considered useful to replace animal testing and to successfully evaluate the safety of cosmetic ingredients for which the consumer exposure is sufficiently low.

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