European Commission

Scientific Committee on Consumer Safety
(SCCS)

Scientific Committee on Health and Environmental Risks
(SCHER)

Scientific Committee on Emerging and Newly Identified Health Risks
(SCENIHR)

OPINION ON

Use of the Threshold of Toxicological Concern (TTC) Approach for Human Safety Assessment of Chemical Substances with focus on Cosmetics and Consumer Products

The SCCS/SCHER/SCENIHR adopted this opinion by written procedure on 8 June 2012
after public consultation

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About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease Prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

Scientific Committee members

Jürgen Angerer, Ulrike Bernauer, Claire Chambers, Qasim Chaudhry, Gisela Degen, Elsa Nielsen, Thomas Platzek, Suresh Chandra Rastogi, Vera Rogiers, Christophe Rousselle, Tore Sanner, Jan van Benthem, Jacqueline van Engelen, Maria Vinardell, Rosemary Waring, Ian White

SCHER

Opinions on risks related to pollutants in the environmental media and other biological and physical factors or changing physical conditions which may have a negative impact on health and the environment, for example in relation to air quality, waters, waste and soils, as well as on life cycle environmental assessment. It shall also address health and safety issues related to the toxicity and eco-toxicity of biocides.

It may also address questions relating to examination of the toxicity and eco-toxicity of chemical, biochemical and biological compounds whose use may have harmful consequences for human health and the environment. In addition, the Committee will address questions relating to methodological aspects of the assessment of health and environmental risks of chemicals, including mixtures of chemicals, as necessary for providing sound and consistent advice in its own areas of competence as well as in order to contribute to the relevant issues in close cooperation with other European agencies.

Scientific Committee members

Ursula Ackermann-Liebrich, Rolf Altenburger, Herman Autrup, Denis Bard, Peter Calow, Stella Canna Michaelidou, John Davison, Wolfgang Dekant, Pim De Voogt, Arielle Gard, Helmut Greim, Ari Hirvonen, Colin Janssen, Renate Krätke, Jan Linders, Borut Peterlin, Jose Tarazona, Emanuela Testai, Marco Vighi

SCENIHR

This Committee deals with questions related to emerging or newly identified health and environmental risks and on broad, complex or multidisciplinary issues requiring a comprehensive assessment of risks to consumer safety or public health and related

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issues not covered by other Community risk assessment bodies. Examples of potential areas of activity include potential risks associated with interaction of risk factors, synergic effects, cumulative effects, antimicrobial resistance, new technologies such as nanotechnologies, medical devices including those incorporating substances of animal and/or human origin, tissue engineering, blood products, fertility reduction, cancer of endocrine organs, physical hazards such as noise and electromagnetic fields (from mobile phones, transmitters and electronically controlled home environments), and methodologies for assessing new risks. It may also be invited to address risks related to public health determinants and non-transmissible diseases.

Scientific Committee members
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ACKNOWLEDGMENTS

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EXECUTIVE SUMMARY

Introduction

The SCCP (now SCCS)/SCHER/SCHENIHR (SCs) were asked to evaluate potential applications of the Threshold of Toxicological Concern (TTC) approach for human health risk assessment of chemical substances. This opinion focuses on the potential applications of the TTC concept for cosmetics and other consumer products in relation to the mandates of the three SCs. It does not assess application of TTC in other areas, such as food, pharmaceuticals or EU chemical legislation (REACH), although such applications are described for completeness.

The SCs addressed the various product categories where the TTC approach was proposed and discussed a possible distinction between intentionally added ingredients and substances present as contaminants or impurities. Classes of chemicals, exposure situations, and toxicity endpoints which may be addressed by using the TTC concept were identified. The quantity and type of information (exposure, toxicity, QSAR, statistics, etc.) required for a particular class of chemicals and/or exposure situation before the TTC concept can be applied in the risk assessment were also discussed. Finally, additional research needed to strengthen the TTC approach and its usefulness was considered.

General considerations

The TTC approach is a risk assessment tool establishing human exposure threshold values for chemicals below which there is a very low probability of adverse effects to human health. According to the TTC concept, a "safe" level of exposure can be identified for many chemicals based on their chemical structure and the known toxicity of chemicals that share similar structural characteristics. The TTC approach is exclusively designed as a substitute for substance-specific information in situations where there is limited or no information on the toxicity of the compound and information on exposure indicates that human exposure is very low. All risk assessment approaches have some degree of uncertainty. When the TTC approach is applied, it is important for both risk assessors and risk managers to keep in mind that it is a probability-based screening tool and may have additional uncertainty. The derivation of the various TTC values is based on frequency distributions. The TTC values that have been proposed for use are not based on the lowest value in each of the distributions but on a point close to the lowest value.

Databases

The presently used TTC values are derived from two databases, one database containing carcinogenicity data from animal studies (Carcinogen Potency Database, CPDB) including 730 chemicals, and one database including 613 chemicals based on other toxicological endpoints (Munro database). Both are based on systemic effects after oral exposure. In addition, a database (RepDose) including toxicity data on 578 industrial chemicals based on oral and inhalation studies is available. Another independent dataset comprises 813 industrial chemicals that are selected from ELINCS. It is based on 28-day subacute oral toxicity tests (756 chemicals) and 90-day oral studies (57 chemicals) with adjusted NOAEL values using scaling factors of 6 and 2, respectively. Also, a data set of 232 substances, occurring in plastic food contact materials, was used to extend the Munro database. It is based on calculated NOAEL values adapted from derived TDIs multiplied with the usually applied safety factor of 100. Finally, a database combining RepDose, Munro, ToxRef and Toxbase using back-calculated NOEL and LOEL-values became recently available. Chemicals with complex chemical structures, however, are not adequately represented in the available databases.

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Exposure data

Exposure data are essential in any risk assessment. As the TTC approach introduces an additional level of uncertainty, the need for sound exposure data becomes even more important. When performing an exposure assessment, all routes and sources should be taken into account. In case of lacking information or insufficient scientific quality, worst case exposure scenarios have to be applied.

Conclusions and recommendations

The SCs consider the TTC approach, in general, scientifically acceptable for human health risk assessment of systemic toxic effects caused by chemicals present at very low levels, as based on sound exposure information.

It should be noted that the TTC concept is not intended to be applied to those chemicals which are regulated and for which specific requirements exist regarding toxicity testing.

All risk assessment approaches have some degree of uncertainty. However, when the TTC approach is used, it is important for both risk assessors and risk managers to keep in mind that it is a probability-based screening tool and may have additional uncertainty. The derivation of the various TTC values are based on frequency distributions and the TTC values that have been proposed for use are not based on the lowest value in each of the distributions but on a point close to the lowest value. Thus, when using either the cancer or non-cancer TTC values, there is a chance that a substance with an exposure below the relevant TTC value may still pose a potential risk for consumer health or a lifetime cancer risk $>10^{-6}$. This probability can be estimated to lie between zero and 5%.

Application of the TTC approach in risk assessment in any area requires a high level of confidence in 1) the quality and completeness of the toxicity databases, 2) the reliability of the exposure data for the intended use of the chemical and 3) the appropriateness of any extrapolations.

The application of the TTC should be done on a case-by-case basis and requires expert judgement and in-depth knowledge in both toxicology and exposure assessment. When using the TTC approach, any available information on the toxicity of the chemical and structurally related chemicals should be considered. This should also include structure activity relationship (SAR) and read-across analysis.

TTC approach relates only to systemic effects and, at present, cannot be used for the assessment of local effects. Allergy, hypersensitivity and intolerance are excluded due to uncertain dose-response data.

The TTC approach is not applicable to the following chemical classes:
• Aflatoxin-like, azoxy-, N-nitroso-compounds, benzidines and hydrazines are excluded due to their high carcinogenic potency.
• Metals and polyhalogenated dibenzo-*p*-dioxins, polyhalogenated dibenzofurans and polyhalogenated biphenyls, or other compounds known to accumulate in the body, e.g. Ochratoxin A are excluded because the safety factors used may not be high enough to account for differences between species in their elimination from the body.
• Potent hormones, such as steroids.
• Radioisotopes because their biological activity is radiation-specific
• High molecular weight chemicals, such as polymers, because such structures are not covered by the databases.
• Proteins are excluded because of potential for sensitisation or other biological activities.

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- Substances displaying pharmacological effects for which no readily accessible database is available.
- Insoluble particles and nanomaterials, because of their specific toxicokinetics properties compared to soluble materials.

Substances with complex chemical structures having several structural elements are not adequately represented in the available databases. Also chemicals with highly unique structures fall outside the databases. Such substances should be excluded from the TTC approach.

For substances with genotoxicity alerts and hence possible DNA reactive carcinogens, the default value of 0.15 µg/person/d corresponding to 2.5 ng/kg bw/d can be used for the moment, but its scientific basis should be strengthened. This could be achieved by e.g. extending the database by analysing all available carcinogenicity studies, using allometric adjustment factors and/or using the T25 or 1, 5 or 10% benchmark dose as points of departure for linear extrapolation.

Practical application of the TTC approach to chemicals with no structural alerts for genotoxicity is performed by analysing the structure and using Cramer classification as indicator of systemic toxicity. Recent analyses have revealed a number of misclassifications of chemicals when using the Cramer decision tree in its present form.
The SCs conclude that the TTC value of Cramer Class II is not adequately supported by the presently available databases. Therefore, chemicals suggested being Cramer class II by the structural analysis should be treated as Class III. The SCs accept in principle the division into Cramer Classes I and III. When assigning a chemical to the lowest toxicity class (Class I, 1800 µg /person/d corresponding to 30 µg /kg bw/d for substances without genotoxicity alerts), classification should be carefully considered and justified. If classification in Class I cannot be justified, the SCs recommend a general default value equivalent to Cramer Class III compounds (90 µg/person/d corresponding to 1.5 µg/kg bw/d for substances without genotoxicity alerts). All the scientific information available today should be used to define the various toxicity classes before expanding their number, i.e. the classification scheme should be modified based on up-to-date toxicological knowledge.

If there are data showing that a substance has endocrine activity, then the assessment should consider those data. The applicability/non-applicability of the TTC approach for such substances should be decided on a case-by-case basis. It should be noted that the EU intends to develop a systematic approach for the identification and assessment of endocrine disruptors which can be applied in the various fields of regulation.

The TTC, as discussed in this opinion, is not dealing with effects of mixtures of chemicals which are addressed elsewhere[1].

Usually, TTC is expressed in amount per person per day. In order to be applicable to the entire population, including all age groups, it is advised to express TTC values in amount per body weight per day and give special consideration to infants under the age of 6 months because of the potentially immature metabolism for some chemical structures, in particular when the estimated exposure is close to tolerable exposures defined by the TTC values.

Concerning application of the TTC concept and risk assessment of consumer products, limited information is available with regard to exposure to consumer products, where a large diversity of products and complex exposure scenarios, including multiple exposure routes, occur. High quality exposure data is lacking for many product categories. Substantial research is required on use frequency and amount used, duration of product

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[1] http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_155.pdf

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contact, concentration, emission or leaching of a substance from the product to the skin or air, and subsequent absorption via the skin, the lungs and by oral route.

From a scientific point of view, there is no distinction between toxicity induced by intentionally added ingredients or inadvertent contaminants. The applicability of the TTC concept for both types of substances is primarily dependent on exposure conditions and the quality of the databases available.

In relation to cosmetic ingredients, the current databases require further development and validation. For cosmetic ingredients, the TTC concept can only be used for those compounds which belong to a sufficiently represented structural class in the TTC database and where appropriate exposure data are available.

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BACKGROUND

"Safe levels of exposure" can be identified for non-genotoxic chemicals with known toxicological profiles. The "threshold of toxicological concern" (TTC) is an approach that defines a threshold for tolerable human exposures to specific chemicals without toxicological data. The TTC-derived exposure limits are based on toxicity predictions considering chemical structure of and toxicity data for structurally related chemicals. When exposures are below the TTC-based limits, there is a very low probability of an appreciable risk to human health.

Starting with the generic approach ("exposure threshold") used by the United States Food and Drug Administration (US FDA) in the 1980s, the TTC concept has evolved over the years to take into account extensive analysis of available data mainly on oral toxicity data of substances, intake/exposures to the substances, and on the basis of a structure-based decision tree to find applications mainly in the food area.

The TTC approach has been used to evaluate flavouring substances (Joint FAO/WHO Expert Committee on Food Additives (JECFA), EFSA), food contact materials (US FDA), genotoxic impurities in pharmaceuticals (EMA), and for the risk assessment of chemicals (World Health Organization International Programme on Chemical Safety, WHO IPCS). Recent publications have suggested that the TTC approach can also find uses in other categories of chemicals, e.g. for chemicals (or trace contaminants) in consumer products, food additives, pesticides and cosmetics.

Specifically for cosmetics, COLIPA, (the European Cosmetics Association, now Cosmetics Europe) sponsored work by a group of experts to examine the potential use of the TTC concept in the safety evaluation of cosmetic ingredients. In its report (Kroes *et al.,* 2007), the group concluded that *'overall the TTC approach provides a useful additional tool for the safety evaluation of cosmetic ingredients and impurities of known chemical structure in the absence of chemical-specific toxicology data'*. However, the group went on to conclude that *'the TTC approach relates to systemic effects, and use of the proposed procedure would not provide an assessment of any local effects at the site of application'*. In addition the Expert Group identified the need for the careful *'…consideration of whether route-dependent differences in first-pass metabolism could affect the applicability of TTC values derived from oral data to the topical route. Analysis has shown that the oral TTC values are valid for topical exposures and that the relationship between the external topical dose and the internal dose can be taken into account by conservative default adjustment factors'*.

1. TERMS OF REFERENCE

The SCCS/SCHER/SCHENIHR are requested to critically review the COLIPA Expert Group report on the use of the TTC concept in the safety evaluation of cosmetic products and the publicly available scientific literature on the concept of TTC and answer the following questions:

1. Does the SCCS/SCHER/SCENIHR consider the TTC approach appropriate for the human health risk assessment of chemical substances?

2. In elaborating their opinion(s), and if the available information allows it, the SCCS/SCHER/SCENIHR are asked to address the following:

    a) The various product categories including cosmetic products, consumer products, and other products where a significant exposure of consumers to chemical substances is likely to occur in normal use situations.

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b) The distinction between intentionally added ingredients and substances present in a particular product as inadvertent contaminants

c) Identification of classes of chemicals, exposure situations, toxicity end points for which the TTC concept may be appropriate and those for which it may not.

d) The quantity and type of data (exposure, toxicity, QSAR, statistics, etc) that will need to be available for a particular class of chemicals and/or exposure situation before the TTC concept can be applied in the risk assessment of chemicals.

e) Additional research needed to strengthen the TTC approach and its usefulness for the human health risk assessment of chemical substances.

PUBLIC CONSULTATION

A public consultation of the preliminary report of this opinion took place from 24 November 2008 to 2 January 2009. Twenty-one contributions were received during the consultation period.

In evaluating the responses from the consultation, submitted material was considered under the following conditions:
1. It concerned issues that are under the remit of the Scientific Committees
2. It referred directly to the content of the report and was related to the issues addressed in the report,
3. It contained specific comments and suggestions on the scientific basis of the opinion,
4. It has the potential to add to the preliminary opinion of Scientific Committees.

Each submission meeting these criteria was carefully considered by the Working Group.

A targeted hearing with the stakeholders who contributed to the public consultation took place on 24 September 2009. This hearing aimed to allow for a further exchange of views between the members of the Working Group and the stakeholders who contributed to the public consultation.

The comments received during the public consultation and the hearing have been considered in the finalisation of the revised opinion.

A joint meeting of the SCs with EFSA took place on 8 June 2011 in order to review opinion SCCP/1171/08 and EFSA's draft opinion on TTC, and eventually address potentially diverging views in line with the legal obligation of both bodies.

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2. SCIENTIFIC RATIONALE

This opinion of the three Scientific Committees (SCs) SCCS, SCHER and SCENIHR is limited to their mandates and focuses on potential applications of the TTC concept for cosmetics and other consumer products from which exposure of consumers to chemical substances is likely to occur in normal use situations. It does not assess the application of TTC in other areas, although such applications are described for completeness in this document.

2.1. Introduction

The Threshold of Toxicological Concern (TTC) approach is a risk assessment tool establishing human exposure threshold values for chemicals below which there is a very low probability of adverse effects to human health. According to this approach, a "safe" level of exposure can be identified for many chemicals based on their chemical structures and the known toxicity of chemicals sharing similar structural characteristics. The TTC is a probabilistic approach based on frequency distributions (5th percentile) of NOAELs (non-genotoxic chemicals) or "virtually safe doses" (predicted tumour risk of $1:10^6$) for genotoxic agents.

The TTC approach might be used as a substitute for substance-specific hazard information in situations where there is information on exposure which indicates that human exposure is very low and there is limited or no information on the toxicity of the chemical.
It should be noted that the TTC concept is not intended to be applied to those chemicals which are regulated and for which specific requirements exist regarding toxicity testing.

2.2. History and development of the TTC approach

A TTC-like approach was first proposed for chemicals in food contact materials in the US. According to the US Federal Food, Drug and Cosmetic Act, food contact materials that migrate unintentionally into food should be considered as food additives (US FD&C Act, 1958). This, in combination with the development of more sensitive analytical methods, implied a need for a policy at the United States Food and Drug Administration (US FDA) to handle putative toxicological risks of low exposures. The Food Additives Amendment included the Delaney Clause, which prohibits the approval of an additive "if it is found to induce cancer when ingested by people or animals". While still protecting public health, in the event that a substance turns out to be a carcinogen, the US FDA wanted to be able to waive requested tests in certain cases and to be consistent in this waiving procedure.

According to the interpretation of the Delaney Clause, a chemical could not be added to food if derived exposures caused a lifetime cancer risk of more than 1 in a million (10^{-6}). Under the US FDA regulation, the use of a chemical in food contact material resulting in a dietary level below 0.5 ppb can be exempted from further regulation. The value of 0.5 ppb was derived from a distribution plot of the chronic dose rates based on the dose descriptor TD_{50} (the daily dose rate required to induce a calculated 50% tumour incidence) based on the analysis of 343 chemicals from the Carcinogenic Potency Database (CPDB)[1] (Gold *et al.,* 1984), and linear extrapolation to a 10^{-6} risk. Assuming that a person (60 kg bw) consumes 1500 g of food and 1500 g of fluid daily and that the chemical is distributed evenly throughout the diet, a level of 0.5 ppb in the diet corresponds to a dose of 1.5 µg/person/d (25 ng/kg bw/d). The value of 0.5 ppb in food was implemented as the "Threshold of Regulation" (ToR) for food contact material (US FDA 1995). Although the US FDA subsequently received a number of comments expressing the opinion that the 0.5 ppb threshold is more conservative and restrictive

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[1] The Carcinogenic Potency Database (CPDB), http://potency.berkeley.edu/

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than necessary to adequately protect the public health, no data were submitted that
justified establishing a ToR at a higher dietary concentration level.

Cheeseman *et al.* (1999) extended the ToR concept by incorporating acute and short-
term toxicity data, results of genotoxicity testing, and structural alerts to identify potent
and less potent carcinogens. The evaluation of carcinogenic potency was expanded to
cover 709 rodent carcinogens in the CPDB. This work confirmed the validity of a ToR of
0.5 ppb in food (equivalent to 1.5 µg/person/d) for most carcinogens. Cheeseman
considered this value as a highly conservative assessment for the following reasons:

   - extrapolation was linear which is known to overestimate risks
   - the extrapolation process was based on response in the most sensitive species
   - potential carcinogens are overrepresented in the CPDB and therefore the frequency
   distribution is already biased towards higher potency compounds

In order to assess whether non-cancer endpoints impact the ToR, Cheeseman *et al*.
(1999) also analysed information from the Registry of Toxic Effects of Chemical
Substances (RTECS) database on 3 306 chemicals with oral reproductive toxicity data,
and on 2 542 chemicals with data from other repeat-dose toxicity studies. Based on the
results, a tiered TTC approach considering structural alerts, genotoxicity test results and
short-term toxicity data was suggested to extend the US FDA's existing ToR approach:

   • 1.5 µg/person/d: General threshold. Substances with positive Ames test results or
     structural alerts such as N-nitroso or benzidine-like chemicals should be evaluated
     on a case-by-case basis.
   • 15 µg/person/d: Threshold for chemicals without structural alerts for
     carcinogenicity or with negative mutagenicity test results (Ames test).
   • 45 µg/person/d: Threshold for chemicals without structural alerts for
     carcinogenicity or with negative mutagenicity test results (Ames test) and a
     LD_{50} (median lethal dose) >1,000 mg/kg bodyweight.

This tiered approach has not yet been adopted by the US FDA.

The ToR/TTC used by the US FDA focuses on carcinogenic effects. Munro *et al.* (1996)
evaluated the use of TTC related to endpoints other than carcinogenicity using structural
information based on an algorithm developed by Cramer *et al.* (1978). Chemicals were
grouped into three structural classes based on a "decision tree" approach. This decision
tree consists of 33 questions each of which is answered by "yes" or "no". Each answer
leads to another question or to a final classification into one of the three classes (I, II
and III), reflecting a presumed low, moderate or pronounced toxicity.

   Class I: Chemicals with simple structures indicating efficient metabolism and a
                  low order of oral toxicity.
   Class II: Chemicals in a structural class for which there is less knowledge of
                  metabolism, pharmacology and toxicology, but no clear indication of
                  toxicity. Most substances in Class II belong to one of the following two
                  categories: (i) chemicals with functional groups that are similar to, but
                  somewhat more reactive than functional groups in Class I; and (ii)
                  chemicals with more complex structures than in Class I, but that are
                  common components of food.
   Class III: Chemicals that permit no strong initial presumption of safety, or that
                  may even suggest significant toxicity.

The use of the TTC concept for chemicals present in the diet was discussed at two
workshops in 1999 and 2003 organized by the International Life Sciences Institute
(ILSI). The database for non-carcinogenic chemicals was expanded and it was concluded
that endpoints such as effects on the nervous system, immune system, endocrine system

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and development were also covered by the TTC values (Barlow *et al.,* 2001; Barlow 2005; Kroes *et al.,* 2000; Kroes *et al.,* 2004).

Human exposure thresholds of 1800, 540, and 90 µg/person/d (corresponding to 30, 9, and 1.5 µg/kg bw/d) were proposed for Cramer Class I, II and III, respectively, using the 5th percentile value of distribution of NOELs for each class of chemicals, a body weight of 60 kg, and a safety factor of 100 (Munro *et al*., 1996). When organophosphates were excluded from Class III, the human exposure threshold increased to 180 µg/person/d (3.0 µg/kg bw/d; Munro *et al*., 2008). Due to high potential toxicity, a specific TTC of 18 µg/person/d may be applicable for organophosphates.

The analysis by the ILSI working group included the 709 compounds used by Cheeseman *et al*. (1999) and evaluated an additional 21 compounds (total of 730), in order to identify structural alerts that would give the highest calculated risks if present at very low concentrations in the diet. It was concluded that chemicals with specific structural alerts for high carcinogenic potency require compound-specific toxicity data.
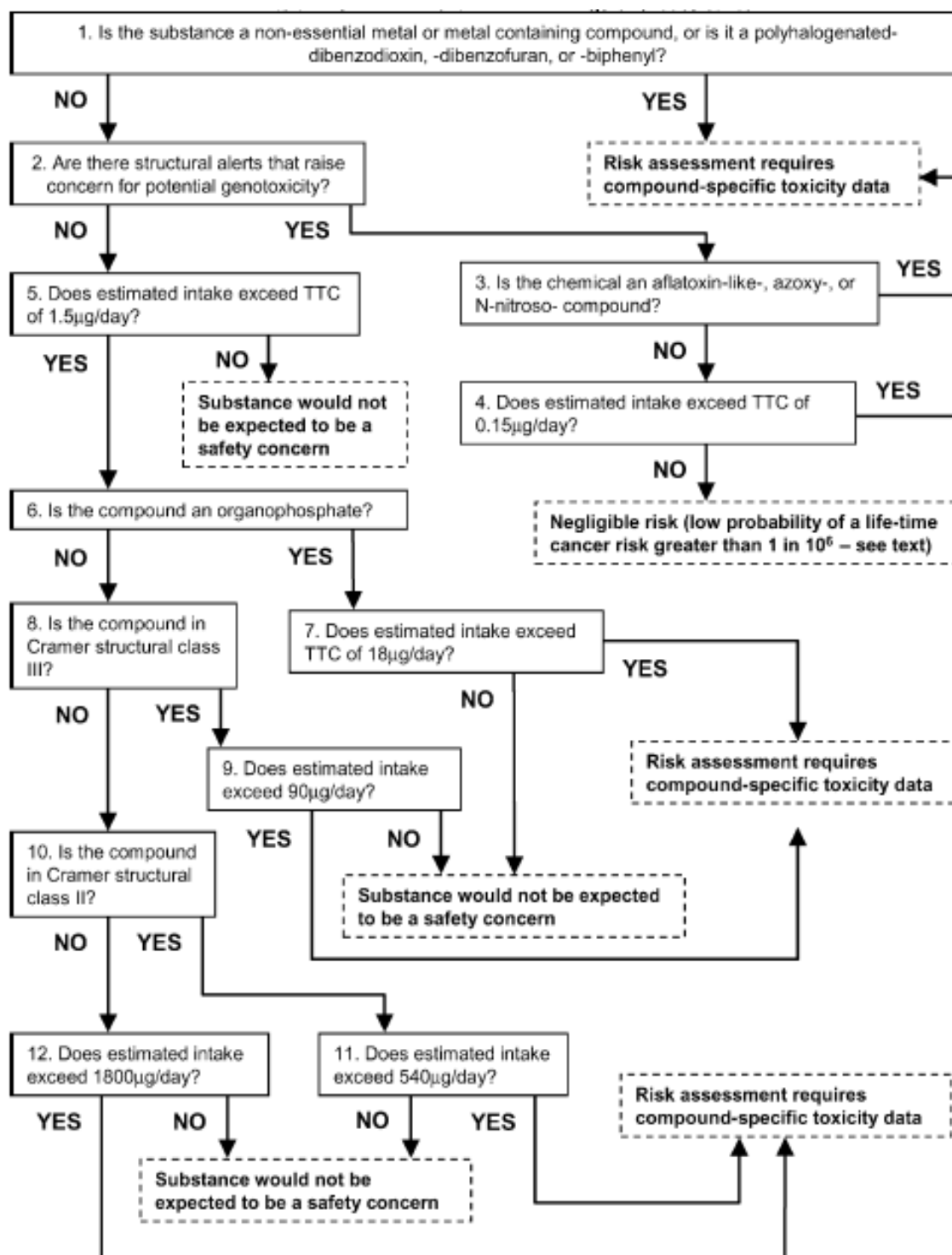
The ILSI Expert Group identified five classes of chemicals (the "cohort of concern"), where a significant proportion of their members may still be of concern at an intake of 0.15 µg/person/d, 10-fold below the ToR. Three of these classes of chemicals are highly potent genotoxins (aflatoxin-like, azoxy- and *N*-nitroso-compounds), while two classes are non-genotoxic (2,3,7,8-dibenzo-*p*-dioxin, TCDD, and its analogues, and steroids). In addition, heavy metals and other polyhalogenated dibenzo-*p*-dioxins, polyhalogenated dibenzofurans and polyhalogenated biphenyls, and other chemicals known to accumulate in the body, are excluded from the TTC approach. This is because i) the safety factors used may not be high enough to account for species differences in elimination kinetics, and ii) toxicity data on these chemicals were not included in the original databases used to develop the TTC principle.

To cover uncertainties in the derivation of the ToR, an additional factor of 10 was added to derive a TTC of 0.15 µg/person/d for chemicals with structural alerts for genotoxicity which are not part of the "cohort of concern" (Kroes *et al.,* 2004; Barlow, 2005).

The group also concluded that chemicals with hormonal activity, including steroids, should at present not be evaluated using the TTC principle, due to inconsistent data at lower doses. High molecular weight chemicals, such as polymers, were excluded because they were not included in the databases used to develop the TTC. Proteins should not be evaluated using the TTC approach because of the potential for allergenic or other biological activities, and because they were not included in the databases. At present, allergy, hypersensitivity and intolerance cannot be evaluated using the TTC principle, due to uncertain dose-response data, whereas other immunotoxic effects are covered.

A decision tree (Fig. 1) based on a tiered approach was developed to act as guidance for the application of the TTC. The responses to the questions define whether the chemical is suitable for assessment by the TTC concept according to exclusion criteria, the presence of structural alerts for genotoxicity, and, depending on the structure of the chemical, how the level of exposure is related to the relevant human exposure threshold. For any chemical taken through the decision tree process, one of two recommendations can be reached; either the chemical is not expected to be a safety concern, or risk assessment requires compound-specific toxicity data. The decision tree is structure-based and thus only applicable to chemicals with known structures represented in the databases. Finally, it was recommended that the TTC principle can be used for chemicals that are present in food in low concentrations, lacking toxicity data, but for which exposure assessment can provide reliable estimates (Kroes *et al*., 2004).

Recently, a modification of the decision tree was proposed. This included consideration of genotoxicity data as a way of refining the TTC limit for chemicals that have structural alerts for genotoxicity and also addresses duration of exposure (Felter *et al.,* 2009).

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Figure 1: *The TTC decision tree suggested by the ILSI Europe Expert group* (Kroes *et al*., 2004)**.**

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2.3. Toxicological databases

The establishment of a TTC is based on the analysis of the toxicity (potency) of a broad range of chemicals. Several databases correlating chemical structure and toxicity data have been used to derive the TTC values. They cover carcinogenic effects and a variety of non-cancer systemic toxicity endpoints. Most databases only contain toxicity data after oral exposure.

The *carcinogenicity database* was originally based on 343 rodent carcinogens from animal studies compiled in the Carcinogen Potency Database (CPDB) (Gold *et al*., 1984) and was later expanded to include 730 carcinogens (Kroes *et al*., 2004; Barlow, 2005). At present, the CPDB lists results from carcinogenicity studies on 1547 chemicals, including studies with negative results.

The *non-cancer toxicological endpoints database* of Munro *et al.* (1996) consists of 613 organic chemical substances tested for a variety of non-cancer endpoints in rodents and rabbits. It includes the chemical structures and the distribution of No Observed Effect Levels (NOEL) from chronic, subchronic, and reproductive toxicity studies. The reference database contains 137, 28 and 448 chemicals in Cramer Class I, II and III (see above), respectively. Carcinogenicity and mutagenicity endpoints were not considered for derivation of these values, although some of the chemicals in this database are carcinogenic and/or mutagenic.

Bitsch *et al*. (2006) reported the RepDose database, consisting of chronic, subchronic and subacute toxicity data from studies with 364 industrial chemicals after oral and inhalation exposure. Only 95 of these chemicals were also present in the Munro database. Data on organic chemicals with a limited number of functional groups were used; complex and multi-functional chemical structures like pharmaceuticals were excluded. This database was later expanded to cover 578 chemicals (Escher *et al*., 2008). The RepDose database contains N(L)OELs from oral studies for 543 chemicals and N(L)OECs from inhalation studies for 255 chemicals. Inhalation TTCs of industrial chemicals are derived in Escher *et al.* (2010).

Overall, the distributions of NOEL and LOEL values (5th, 95th percentiles, medians) and of chemicals in the three Cramer Classes are similar in the RepDose and the Munro databases. This supports the use of the TTC concept and indicates that the TTC values derived on the basis of the Munro database may be applicable to industrial chemicals. The number of Cramer Class II chemicals, however, is small in both databases (approximately 4% of the total number). Furthermore, a significant overlap of NOELs and LOELs between Cramer Classes I, II and III was demonstrated.

Bernauer *et al.* (2008) proposed an endpoint-specific TTC for reproductive toxicity by evaluating NOAELs from 58 fertility studies and 62 developmental toxicity studies from the EU existing chemicals programme. Oral TTC values for fertility and developmental toxicity of 1.5 and 1.0 µg/kg bw/d, respectively, were derived using a more conservative safety factor of 1000 due to the small database and because of dealing with serious health effects. These values were similar to the TTC value for these endpoints derived from 507 pharmaceuticals. Here, the 5th percentile of the NOAELs has been divided by a default factor of 100 resulting in a TTC value of 1 µg/kg bw/d. Similarly, based on the results of developmental toxicity studies of 93 chemicals tested by industry (van Ravenzwaay *et al.,* 2011), and authoritative reviews of reproductive and developmental toxicity studies of 283 chemicals (Laufersweiler *et al.,* 2012), the authors came to the conclusion that the TTC values protect against reproductive and developmental toxicity.

An independent dataset was utilised by Kalkhof *et al.* (2012) to evaluate the TTC values derived from the database of Munro *et al.* (1996). The dataset includes 861 new

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industrial chemicals registered in Europe between 1982 and 2008 selected from the European List of Notified Chemical Substances (ELINCS) because they have been tested in subacute or subchronic oral studies. This dataset does not overlap with the database of Munro *et al.* (1996). The analysis was based on the results of 28-day subacute oral tests conducted according to OECD 407 on 776 chemicals. Another 85 chemicals were tested according to OECD 408 in 90-day oral studies. The NOAELs were adjusted to obtain estimated chronic NOAEL values by scaling factors of 6 (28-day studies) and of 2 (ECETOC 1995; ECHA 2010a) for 90-day studies. The results of this study further support the conservative nature of the TTC values derived by Munro *et al.* (1996).

Another analysis included toxicity data of 232 substances used in food contact materials (FCMs) evaluated by EFSA or the former Scientific Committee on Food and allocated a Tolerable Daily Intake (TDI) based on oral toxicity data. For these substances "NOAELs" were "back-calculated" by multiplying the TDIs by the normally used safety factor of 100. These "NOAEL" values were then combined with the Munro *et al.* (1996) database. For both Cramer Class I and Cramer Class III substances, the NOELs for FCMs were higher than the lowest NOELs in the respective classes in the Munro *et al.* (1996) dataset. For the extended dataset, the ratios between the TDIs (i.e. Munro NOAELs or FCM NOAELs, divided by 100) and the relevant TTC values were determined to identify for which substances the TTC approach would indicate a higher value than the TDI. The TTC approach was found to be more conservative for 96% of the 845 substances included in the extended dataset. The chemical structures of the 35 substances for which the TTC approach was less conservative than the TDI were examined. From these 35 substances, 26 contained structures excluded from the TTC approach (Pinalli *et al.,* 2011).

Tluczkiewicz *et al.* (2011) combined four databases on repeated-dose oral toxicity studies (RepDose, Munro, ToxRef, and Toxbase) to increase the amount of data and the applicability/chemical domain of the derived thresholds. In compliance with the REACH guidance documents (ECHA 2010), time extrapolation factors of 2 or 6 were applied to NOEL values of subchronic/subacute exposure. For studies with only a LOEL value, an additional adjustment factor of 3 was applied (ECHA 2010). For interspecies differences, the allometric assessment factors of 4/7 for rat/mice extrapolation were applied, respectively. The resulting TTC RepDose database contains 521 compounds/*in vivo* studies. In their analysis, NOELs were analyzed on a molar basis using the metric mmol/kg bw/d. The molar TTC values were further multiplied with the median molecular weight of 220 g/mol of the TTC RepDose database. Groups of structurally similar compounds of high toxicity in Cramer Class I and of moderate to low toxicity in Cramer Class III were identified and reassigned to the appropriate Cramer Class according to their observed toxicological potency. This refinement resulted in a better discrimination of Cramer Classes I and III and an increased number of substances in Cramer Class II. The TTC values are 8.7 µmol/person/d (Class I), 6.72 µmol/person/d (Class II) and 0.28 µmol/person/d (Class III). Assuming a median molecular weight of 220 g/mol for the compounds in the TTC RepDose database, the corresponding TTC values were 1,930, 1,478 and 63 µg/person/d for Classes I, II and III respectively. The derived thresholds are close to the TTC values initially proposed by Munro with 1,800, 540 and 90 µg/person/d for Classes I, II and III, respectively.

2.4. Exposure estimations

As stated by Kroes *et al.* (2004), "*the TTC approach should be used only in cases where the available chemical-specific data are inadequate for normal risk characterisation. Any available information on the compound should be considered at the same time as the decision tree is applied, to ensure that any decision is compatible with the available data.*" This may include read-across, QSAR, preliminary testing results and other relevant information to be taken into consideration before the application of TTC.

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Similar to conventional risk assessment, information on human exposure (consumers, workers, general population exposed via the environment) is crucial in order to apply the TTC concept. Thus, it is important to ensure that exposure estimates are as complete and accurate as possible, or sufficiently conservative.

Humans are exposed to chemicals via ingestion, inhalation or dermal uptake. However, it is the dose to the target organ that is critical. In most cases, this is difficult to determine and has to be substituted with the internal or even the external exposure. If the chemical in question is used only for a specific purpose, e.g. in a particular food or cosmetic product, the exposure related to that purpose should be assessed. In cases of exposure from various uses, aggregate exposure (multi-route/multi-pathway and/or several sources) has to be taken into account.

For a given chemical, it is important to identify all exposure routes and sources when estimating the total exposure. For example, a chemical present in a cosmetic product may also be used in food packaging or in a building material. Moreover, while cosmetic products are mostly applied to the skin, ingestion of chemicals from products applied on the lips or inhalation of chemicals released from products may result in substantial exposure. Ingestion of indoor dust can also lead to oral exposure to chemicals, especially for children. For the latter group a major exposure pathway may also be mouthing of articles containing the chemical under consideration.

Since particular groups in the population may use different amounts of specific foods and consumer products, exposure data need to be sufficiently detailed to cover these groups, for example by age, gender or ethnicity.

If measured data are unavailable, other science-based methods should be used to estimate potential exposure. When a worst-case approach does not predict an exposure above a safe level, the use of more sophisticated methods may not be necessary. When respective exposure data are available, a probabilistic exposure assessment should be performed.

Cosmetics

Cosmetic products comprise a wide range of product types and a variety of exposure scenarios:

-   Application in diluted form and rapidly washed off, e.g. soaps (rinse-off);
-   Application over a large surface, skin contact for several hours, e.g. body lotions (leave-on);
-   Contact with the conjunctiva or mucosa, e.g. eye shadow, oral care products;
-   Contact for prolonged time spans, but only used periodically, e.g. sun screens;
-   Products undergoing reactions on the hair, used only once every 6 weeks, e.g. - oxidative hair dyes;
-   Products used primarily among certain groups such as children, pregnant women, etc.

The possibility of exposure by routes other than those resulting from direct application needs to be considered (e.g. inhalation of spray products, ingestion of lip products).

Recent exposure data for the most commonly used product types are based on two cosmetic exposure studies, commissioned by the European Cosmetic Toiletry and Perfumery Association COLIPA, now Cosmetics Europe, (Hall *et al.,* 2007, 2011; McNamara *et al.,* 2007). They can be found in the seventh revision of the SCCS Notes of Guidance (SCCS/1416/11). Figures for other product types have been updated based on earlier exposure data provided by COLIPA and literature data (Loretz *et al.,* 2005, 2006, 2008; Hall *et al.,* 2011).

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Cosmetic ingredients can be present in several cosmetic products used by the same consumer. For such ingredients, the "aggregate" daily exposure needs to be calculated. In order to do this, a representative set of cosmetic product types, reasonably expected to be concurrently used on a daily basis by the same consumer, has been identified. According to the SCCS Notes of Guidance, this aggregate value amounts to 17.4 g of finished cosmetic product/d, which is for example be used for the calculation of the Systemic Exposure Dosage (SED) of a cosmetic preservative.

Other consumer products

In contrast to cosmetic products and food, where at least some data are available, information on exposure from other consumer products such as toys and textiles is scarce. When considering exposure to consumer products in general, the following information is needed: frequency of use and amount used; duration of contact with the product; concentration; release or leaching of a substance from the product and subsequent absorption via the skin, lungs and/or GI tract (food, drinking water, mouthing of hands/fingers and/or objects).

Information on product characteristics e.g. concentrations of constituent chemicals, and particularly information on emission or leaching is scarce and scattered. For some product types, information about use frequency and amount can be found e.g. in HERA (Human Health and Environment Risk Assessment for Ingredients used in Household Products) publications[1] or the REACH guidance documents (ECHA 2010a; ECHA 2011). Information on product use and other exposure from the literature and industry reports is contained in a database (EISChemRisks)[2] which also contains limited information about leaching and emission of chemicals from consumer products. Assessment of release or leaching from preparations or articles requires specific studies, or estimation by using an exposure model.

The Dutch National Institute for Public Health and the Environment (RIVM) has developed an exposure model[3] to assess emissions from consumer products (mainly preparations) and calculates human exposure via the dermal, oral and inhalation route. Exposure scenarios are proposed for a large number of consumer products (cleaning products, disinfectants, do-it-yourself products, cosmetics, pest control products), including an exposure model and the associated exposure parameters.

In conclusion, exposure to consumer products other than cosmetics and food is even more complicated to assess, since human behaviour and product characteristics play an important role. In general, little information on exposure from such products is available. Furthermore, it should be noted that most existing information serving as a basis for TTC-evaluation is based on oral exposure, whereas for consumer products also other exposure routes (dermal, inhalation) are relevant.

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[1] http://www.heraproject.com/Initiative.cfm

[2] http://web.jrc.ec.europa.eu/eis-chemrisks/

[3] http://www.consexpo.com

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2.5. Current applications of the TTC approach

2.5.1 Food

2.5.1.1 Food contact materials

Under current US legislation, a request for exemption from regulation can be submitted to the US FDA if the use of a substance in food contact material results in a dietary concentration at or below the ToR of 0.5 ppb. Such a request should include a detailed discussion of how the dietary concentration was estimated and existing toxicological information on the chemical and its impurities, in order to determine whether a carcinogenicity study has to be carried out, or whether there are reasons for suspecting that the substance or its impurities are carcinogens or potent toxins (US FDA 2005).

In the EU, the TTC approach is not currently used in the approval process of food contact materials (see also section 2.6.1).

2.5.1.2 Flavouring substances

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has adopted the TTC principle in its evaluation of flavouring substances. The procedure was endorsed in 1996 (JECFA 1996).

The European Commission's Scientific Committee on Food (SCF) later considered the JECFA procedure and, whilst not formally endorsing the values for human exposure thresholds, concluded that it was a reasonable and pragmatic approach that could be used for chemically defined flavouring substances within the evaluation programme of the European Commission (SCF 1999). A slightly modified form of the JECFA procedure is used by EFSA since 2004 for the evaluation of about two thousand chemicals in the European Union Register of Flavouring Substances (EC 2002 and its subsequent amendments) (see Figure 2 below). EFSA has recently published a guidance document on the data requirement for assessing new flavouring substances (EFSA 2010).
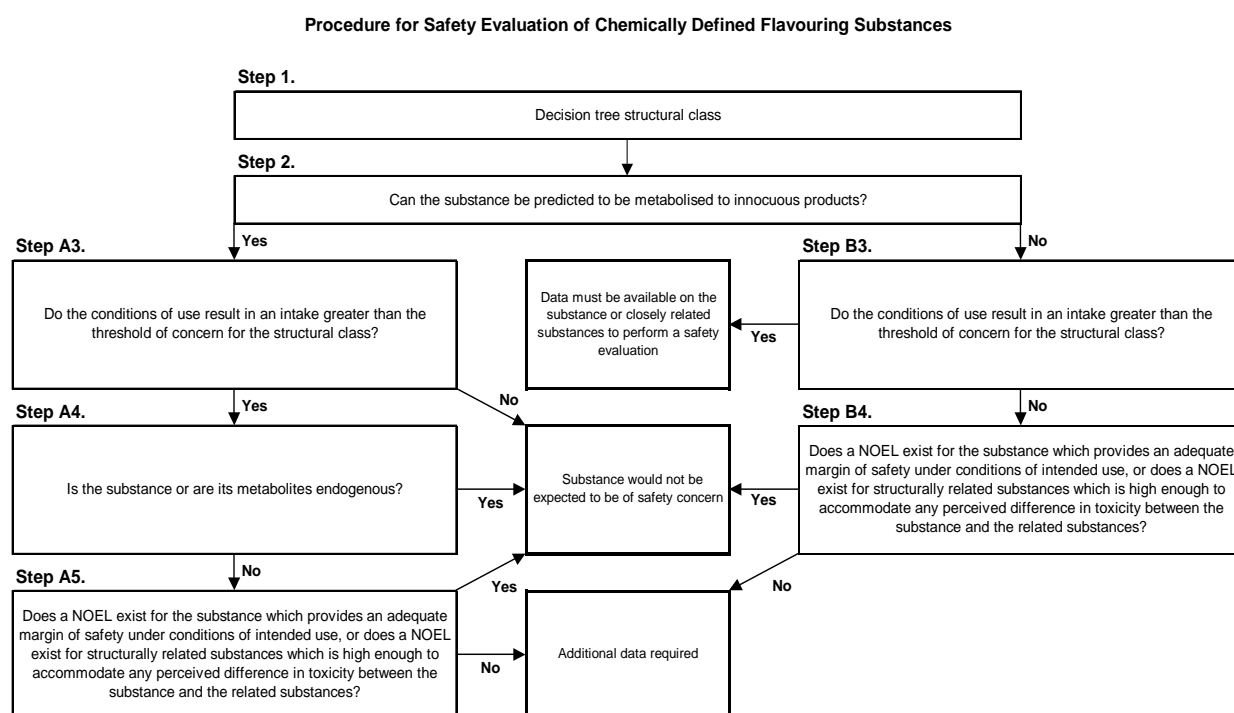
Figure 2: *Procedure for safety evaluation of chemically defined flavouring substances*

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The experience with the TTC concept for flavouring substances indicates that the TTC principle can be applied to a large number of chemicals with low exposure scenarios. However, it should be noted that the TTC for flavourings is applied to groups of structurally related chemicals. In addition, toxicity data are available for some of the compounds within each group and read-across is applied.

Many chemicals in flavourings are also used for other purposes, e.g. as fragrance materials or as preservatives in cosmetics. Such exposures are not considered in the evaluation of food flavourings. The exposures from fragrances may be higher compared to those from flavourings, for example from Eau de Toilette and perfumes, although the route of exposure is different.

2.5.2   Metabolites of plant protection products in groundwater

For metabolites of plant protection products in groundwater, the former EC Scientific Committee on Plants proposed a TTC approach[1]. The concentration of relevant metabolites (i.e. chemicals with comparable biological target activity as the active substance, or with unacceptable toxicological properties) should not exceed 0.1 µg/l. For metabolites considered to be "non-relevant" (i.e. no comparable biologic activity as the active ingredient), a TTC-based tolerable dose of 1.5 µg/person/d was proposed. At a consumption of 2 litres of water per day, the upper limit for the concentration of a "non-relevant" metabolite is 0.75 µg/l. For ''non-relevant metabolites" with drinking water concentration below 3.0 µg/l, no further toxicity testing was considered necessary if genotoxicity is excluded by testing.

Recent publications (Melching-Kollmuss *et al.*, 2010; Dekant *et al.,* 2010) have indicated that TTC may be a valid tool in risk assessment of metabolites of plant protection products, can provide an adequate margin of protection and a reliable evaluation of the need for a more complete risk assessment .

2.5.3   Pharmaceuticals

2.5.3.1   *Genotoxic impurities in pharmaceuticals*

The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) has released a "Guideline on the Limits of Genotoxic Impurities" (EMA 2006). The guideline recommends the application of the TTC to define acceptable limits of genotoxic impurities present in pharmaceuticals.

The synthesis of pharmaceuticals frequently involves the use of reactive starting materials and intermediates, which may remain as impurities in the final drug. Due to their reactive nature such impurities may be genotoxic. It has been estimated that 20 – 25% of all intermediates used in the synthesis of active pharmaceutical ingredients are mutagenic in the Ames test (Delaney, 2007).

Genotoxicity is a very broad term comprising a variety of direct and indirect mechanisms of DNA damage. In order to determine acceptable limits for genotoxic impurities the guideline discriminates between genotoxic compounds that induce mutations by direct interaction with DNA (DNA-reactive genotoxins) and those which operate via indirect mechanisms. A linear non-threshold model is applied to DNA-reactive impurities. For chemicals which do not directly interact with DNA such as mitotic spindle poisons, topoisomerase inhibitors or DNA synthesis inhibitors, a threshold is assumed. For such impurities, a Permitted Daily Exposure (PDE) derived from the NOEL in a relevant animal

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[1] SANCO/221/2000-rev. 10-final of 25 February 2003. Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC
http://ec.europa.eu/food/plant/protection/evaluation/guidance/wrkdoc21_en.pdf

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study with the use of uncertainty factors is calculated. It can be expected, however, that mechanistic data to decide whether a threshold mechanism is applicable to a genotoxic impurity are rarely available.

For other genotoxic compounds, the TTC is applied to determine acceptable levels of an impurity. Since the benefits of pharmaceuticals justify an acceptable lifetime risk of cancer of 10^{-5}, a 10-fold higher TTC level of 1.5 µg/person/d (compared to the TTC of 0.15 µg/person/d, corresponding to a 10^{-6} lifetime risk for genotoxic chemicals) is considered as the acceptable daily uptake for genotoxic impurities in pharmaceuticals. The concentration limits (in ppm) as the permitted impurity level in a drug substance derived from the TTC value can be calculated based on the expected maximum daily dose.

Depending on the clinical use, e.g. for pharmaceuticals for treatment of a life-threatening condition or when life expectancy of the patient population is limited, higher limits than 1.5 µg/person/d may also be acceptable, e.g. for less than 5 years. When the impurity is a known chemical and human exposure will be much greater from other sources, e.g. food, it might be inappropriate to limit the impurity at the TTC level.

As the TTC is calculated for a lifetime exposure, higher levels may be allowed for short-duration treatments. This issue is of relevance for drugs under development where acceptance criteria need to be adjusted taking into account phase-specific duration of clinical trials as well as the limited understanding of process chemistry in early development. Proposals for tolerable daily intakes for genotoxic impurities during clinical development are 5, 10, 20, and 60 µg/person/d for durations of exposure of 6-12 months, 3-6 months, 1-3 months, and less than 1 month, respectively. For a single dose, an exposure of up to 120 µg is considered acceptable.

As addressed earlier, some structural classes are excluded from the TTC approach based on their extremely high potency. Risk assessment of genotoxic impurities in pharmaceuticals belonging to such classes requires compound-specific toxicity data.

The guideline focuses on orally administered drugs when recommending the TTC as an acceptable limit and does not provide recommendations for other routes of administration. The document also includes a decision tree to assess the acceptability of genotoxic impurities. This decision tree suggests applying a policy of controlling levels to "As Low As Reasonably Practicable" (ALARP principle). This implies that every effort should be made to prevent the formation of such impurities during synthesis and, if this is not possible, to reduce them through technical efforts, e.g. purification steps. If the level of a mutagenic impurity is below the TTC-derived value it is not necessary to apply ALARP considerations (EMA 2007).

<u>What data are needed to apply TTC to genotoxic impurities in pharmaceuticals?</u>

Usually, impurities identified in pharmaceuticals are not subject to direct toxicological testing. An impurity of a new drug substance is considered qualified at the level present in the new drug substance batches used in non-clinical safety testing studies. If, for instance, a testing batch of a drug substance containing 0.05% of an impurity is found negative in the standard genotoxicity testing battery a qualification of this level with regard to genotoxicity is usually accepted. However, this qualification process is rather insensitive.

As an alternative approach for providing meaningful information on potential genotoxicity of impurities, a scientific expert review of the chemical reactions and the conditions involved may be performed to identify chemicals (starting materials, process impurities, reagents, intermediates) of potential concern. This review should include an evaluation of structure-activity relationships (SARs) for genotoxicity. Absence of a structural alert (e.g. through application of commonly used SAR assessment software including DEREK and

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MCASE) will be sufficient to conclude that the impurity is not of concern with respect to genotoxicity (EMA 2010).

Chemicals showing structural alerts not shared with the active substance are candidates for genotoxicity testing, preferably in a bacterial gene mutation test. If positive, it would need to be limited to the TTC level. A negative bacterial gene mutation test will overrule a structural alert and no further genotoxicity studies would be required. It is also acceptable to control impurities with a structural alert ensuring the level remains below the appropriate TTC value. The successful applicability of this structure-based assessment approach has been demonstrated for a range of structurally alerting compounds (Dobo *et al.,* 2006).

In conclusion, regulatory experiences with the TTC since the CHMP guideline came into force in January 2007 show that it can be used as a pragmatic tool for the regulation of genotoxic impurities in new medicinal products. It is noteworthy that the US FDA Center for Drug Evaluation and Research also considers the use of a TTC-based limit for regulation of genotoxic and carcinogenic impurities in pharmaceuticals (FDA 2008) and that recent work for a new ICH guideline on the assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals has started. One of the issues to be addressed is the question whether levels of genotoxic impurities should be regulated using a TTC approach (ICH 2010).

2.5.3.2 *Genotoxic constituents of herbal medicinal products/ preparations*

A TTC approach for the risk assessment of herbal preparations containing an identifiable genotoxic compound was introduced (EMA 2008). If an established risk assessment method cannot be applied because of the lack of data, the TTC concept is suggested for the assessment of genotoxic constituents in herbal preparations. Permitted levels of a genotoxic compound in herbal preparations can be calculated based on a TTC value of 1.5 µg/person/d. Higher limits could be justified under certain conditions such as short-term exposure, or if the applicant submits additional data and a toxicologically plausible argumentation.

2.6. Potential applications of the TTC approach

2.6.1 Food, food additives, contaminants and food contact materials

Food additives are chemicals that are added intentionally to foods to perform certain technological functions, for example to colour, sweeten, or preserve. In the EU, food additives are regulated by a framework regulation[1]. Only additives that have undergone a full toxicological evaluation are authorized. Therefore, the TTC principle is not considered relevant in the risk assessment of the major constituents of food additives.

However, the ILSI Expert Group recommended that the TTC principle could be used for chemicals present at low concentrations in food, for which there are no toxicity data but reliable exposure estimates (Kroes *et al*., 2004). Such chemicals might include impurities present at low concentrations in food additives, or degradation and reaction products of food additives formed in the food matrix. Similarly, it may be possible to apply the TTC principle to the evaluation of other chemicals of unknown toxicity, present at low concentrations in food, such as unexpected identifiable contaminants (environmental, man-made or naturally occurring), residues of processing aids or chemicals generated by food processing such as cooking, and pesticide metabolites, degradation products and reaction products.

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[1] Regulation (EC) No 1331/2008 of the European Parliament and of the Council of 16 December 2008 establishing a common authorisation procedure for food additives, food enzymes and food flavourings

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Although the TTC concept is not currently used in the EU for evaluation of chemicals migrating into food from food contact materials, EFSA applies a tiered approach to safety testing requirements that was first proposed by the SCF in 1990 and has been updated (Barlow 1994; SCF 1992; SCF 2001). This tiered approach has some similarities with the philosophy of the TTC approach. For example, in the case of chemicals for which migration into food does not exceed 50 ppb, only three *in vitro* genotoxicity tests are required. If these are negative, it is assumed that there will not be adverse health effects at the dietary exposures that may be encountered.

In order to further explore the application of the TTC concept for providing preliminary advice about possible human health risks of chemicals found in food, a Working Group of EFSA's Scientific Committee was established in 2008[1] to seek advice on the relevance and reliability of the TTC. In addition, the Working Group was asked to indicate any additional data needed to strengthen the underlying basis of the TTC concept and its practical use, and to look at a possible broader applicability of the TTC concept by EFSA. EFSA's Scientific Committee endorsed a draft opinion on TTC which was issued for public consultation in July 2011[2], and is anticipated to be adopted in a final form in 2012.

2.6.2   Medical devices

Medical devices comprise a large variety of products, ranging from wound dressings and bandages to catheters and implants, including pacemakers.

Residual chemicals from production and processing may be present in the final product. Tolerable limits can be determined according to EN ISO 10993-17 (2002). Application of the TTC concept for evaluation of chemical residues in medical devices is under discussion.

2.6.3   Residues from veterinary medicinal products

Residues of veterinary medicinal products in food commodities are assessed using a "classical" approach based on a NOEL from toxicity testing. Failure to identify a clear NOEL may mean that the assessment cannot be continued, even if residue concentrations are negligible. For chemicals with a low risk profile, TTC considerations are taken into account on a case-by-case basis, but the TTC approach has not been applied yet on a general basis.

An area of potential use of the TTC in veterinary medicinal products is the assessment of low level dietary exposures, in particular those resulting from residues in food-producing animals from the use of chemicals of botanical and homeopathic origin. In the past, the Committee for Medicinal Products for Veterinary Use (CVMP) applied an "exposure-driven" hazard characterization that is a pragmatic TTC-like approach based on the assumption that exposure to residues of individual constituents is too low to present a significant risk to consumers. Based on this, homeopathic preparations of D4 (dilution 1:10000) and higher are not subject to Maximum Residue Levels (MRL).

In addition, there is growing international interest in alternative concepts to address the question of risk assessment and management of residues of chemicals termed "substances without ADI/MRL" in imported food. The absence of risk based guidance values for this relatively large category of chemicals creates significant trade problems. Use of the TTC as reference point of action is currently under discussion[3].

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[1] Minutes of the 31th plenary meeting of the EFSA Scientific Committee, 2008
http://www.efsa.europa.eu/EFSA/Event_Meeting/sc_minutes_31st_plenmeet_adopted.pdf?ssbinary=true

[2] http://www.efsa.europa.eu/de/consultationsclosed/call/110712a.htm

[3] e.g. FAO/WHO Technical workshop on residues of veterinary drugs without ADI/MRL, 24 - 26 August 2004
Bangkok, Thailand, ftp://ftp.fao.org/docrep/fao/008/y5723e/y5723e00.pdf

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2.6.4   Industrial chemicals

The REACH Regulation[1] provides the possibility of waiving testing of a chemical based on the scenarios developed in the exposure assessment. The use of the TTC approach in REACH should be agreed upon by the relevant regulatory body, and it should be clearly indicated for which endpoints, routes and population it applies. The REACH guidance (ECHA 2008b) cautions that "independent of the approach used in risk assessment of industrial chemicals it is important to maintain a sufficient level of protection. In the striving for alternatives to animal testing one suggested approach is the use of generic threshold values. However, application of TTC would imply that limited data may be generated and thus, that the level of protection might be influenced. […] the possible application of TTC on industrial chemicals needs to be carefully considered."

With regard to exposure, the guidance document (ECHA 2008a) states specifically that, for human health aspects, the TTC approach is only applicable in cases with detailed information on all anticipated uses and use scenarios. Robust exposure estimates will require a significant effort, even in cases where the uses are well characterized. In the case of dispersive uses, it may not be feasible to generate an overall exposure estimate with the precision necessary for application of the TTC concept. Therefore, a TTC will in practice only be applicable in those cases with a limited number of exposure scenarios that allow good characterization.

Within REACH, the TTC concept may be of use for the safety assessment at tonnage levels demanding limited information on repeated dose toxicity and/or reproduction: REACH clearly indicates the need for non-testing methods and provides the opportunity of waiving testing based on exposure considerations. When clearly documented and justified the following options could apply:

a) When non-testing or *in vitro* methods are used, no quantitative threshold can be derived. In such cases, the TTC could be helpful in assessing the relevance of the exposure provided that SAR can be performed and relevant exposure routes can be calculated.
b) Certain tests (e.g. repeated dose and/or reproductive toxicity) can be waived when there is no significant human exposure anticipated. A TTC value could be helpful in assessing the relevance of the exposure provided that SAR can be performed and relevant exposure routes can be calculated.

2.6.5   Air pollutants

For the assessment of air contaminants, Drew and Frangos (2007) used the general TTC of 1.5 µg/person/d established for carcinogens by the US FDA (US FDA 1995), to calculate a "Concentration of No Toxicological Concern" (CoNTC) as a screening tool. Based on 50% of the FDA value, a body weight of 70 kg and inhalation of 20 m^3 of air per day, a general TTC for air contaminants was calculated as 0.03 µg/m^3. To validate the CoNTC value, it was compared with established air guideline values. Occupational exposure limits were divided by 42, consisting of a factor of 4.2 to convert occupational to continuous exposure (24 h/8 h x 7 d/5 d), and a factor of 10 to compensate for a greater sensitivity of the general population as compared to workers. Of 1857 values taken from air quality guidelines, only four were below the CoNTC. Evaluation of the toxicity data after inhalation of 203 industrial chemicals, when excluding local irritation, resulted in the definition of an inhalation TTC of 3.6×10^{-3} ppm for Cramer Class I and of 2.4×10^{-5} ppm for Cramer Class III chemicals (Escher *et al.,* 2010).

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[1] 1907/2006/EC, Regulation of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:141:0022:0022:EN:PDF

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2.6.6   Skin sensitising substances

The present TTC concept cannot be applied for establishing tolerable thresholds for the toxicological endpoint of sensitisation (see also 3.7.2.3). Recently, the use of the TTC approach for dermal sensitisation was proposed (Safford, 2008) based on a probabilistic analysis of available sensitisation data using the ELINCS data set and a compilation of data on the Local Lymph Node Assay (LLNA) in mice. Based on this analysis, a Dermal Sensitisation Threshold (DST) for humans was derived. Their approach further builds on the recently published method of the Quantitative Risk Assessment (QRA) for fragrances. Based on the results of the LLNA data, sensitisation thresholds for humans, No Expected Sensitization Induction Levels (NESILs), were derived and subsequently converted to an acceptable exposure level using several assessment factors (Api *et al.*, 2008).

The DST was then determined for each product type as a 95th percentile in the distribution. This implies that using this DST there is a 5% probability that an untested chemical would give an undue risk. It is also noted that the DST might be protective for induction of sensitisation, but not for the elicitation of contact dermatitis.

A further evaluation based on a meta-analysis of human sensitisation data for 53 fragrance allergens (Keller *et al.,* 2009) concluded that values for the Threshold of Sensitisation Concern (TSC) could be established which were similar to the Dermal Sensitisation Threshold (DST) values previously established using animal data (Safford, 2008). Since this time further work has been conducted to both expand and refine the DST process. The additional work consists of the following steps:

- Expansion of the LLNA dataset to 363 substances (271 sensitizers and 92 non-sensitizers);
- Investigation of whether classification of chemicals into mechanistic chemistry domains using chemical structure could be used to identify the most potent skin sensitisers;
- Benchmarking the refined DST process using fragrance allergens for which data are available on skin sensitisation potency in humans.

A DST of 900 $\mu g/cm^2$ was derived for chemicals classified as non-reactive and non-proreactive (Safford, 2011).

2.6.7   Cosmetic products

A cosmetic ingredient is any chemical substance or preparation of synthetic or natural origin that is used in the formulation of cosmetic products. Cosmetic ingredients may be chemically well-defined single chemicals with a known structure or complex preparations, requiring a clear definition and often corresponding to a mixture of substances of unknown or variable composition and biological nature (Directive 76/768/EEC as amended, SCCS Notes of Guidance[1]). In the new regulation No 1223/2009, a cosmetic product is defined as being composed of substances or mixtures of substances.

Proposal by COLIPA expert group for the use of TTC for cosmetic ingredients

The possible use of the TTC concept for the safety evaluation of cosmetic ingredients was discussed at a workshop organized by the European Cosmetics Association COLIPA and reported by Kroes *et al*. (2007).

The structural similarities between cosmetic ingredients and the chemicals on which the Cramer Classes for chemicals in food were based have been discussed by Kroes *et al.* (2007). The COLIPA Expert Group briefly considered the following classes of ingredients;

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[1] The SCCS Notes Of Guidance For The Testing Of Cosmetic Ingredients And Their Safety Evaluation (7th Revision) http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_004.pdf

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fragrances, dyes and colorants, food ingredients, low molecular weight organic chemicals with a variety of uses, metal salts, normal constituents of the human body, pharmaceutical-type compounds, plant and animal extracts, polymeric compounds and surfactants, emollients, humectants and emulsifying agents. The COLIPA Expert Group concluded that there is considerable potential for the TTC approach for many cosmetic ingredients, using an expanded decision tree.

The COLIPA Expert Group recognized that the TTC approach cannot be used for the assessment of local effects. They considered application to such effects potentially possible; however, the databases on local effects (e.g. skin irritation and contact allergies) and on chemicals producing these effects are too limited to be used as a basis for the derivation of TTC values for local endpoints.

Route of exposure and database

Both the comparability of the chemical structures of cosmetic ingredients and the chemicals in the database currently in use, and the possible impact of the route of administration are of importance when the TTC principle is applied to cosmetic ingredients.

Human exposure to cosmetic products occurs primarily via the topical route, although oral and inhalation exposures may also occur. The COLIPA Expert Group did not further explore exposure via the inhalation route.

With regard to the metabolism of chemical substances in the skin and in the gastrointestinal tract, including the liver, the COLIPA Expert Group did not attempt to review the different pathways of metabolism, but explored the basic principles in the context of applying the TTC concept to cosmetic ingredients. They concentrated on the influence of route-dependent differences in metabolism on systemic bioavailability of the chemical and its metabolites, because systemic effects are relevant to both dermal and oral administration.

The COLIPA Expert Group noted that topical application and oral ingestion may result in differences in systemic bioavailability due to:

(i)   More extensive first pass metabolism in the liver, compared with the skin, prior to reaching the general circulation,

(ii)   Slower and incomplete transfer across the skin compared with the intestinal wall, due to the physico-chemical properties of the chemical and different physiological properties of the tissues,

(iii)   The slower absorption after topical application may result in a different shape of the plasma concentration–time curve, even if the area under the curve is identical.

It was concluded that oral TTC values for Cramer Class III compounds would be likely to overestimate the potential toxicity of the same chemical following topical exposure, even if 100% of the topical dose entered the systemic circulation as the parent compound. Also the TTC values for Cramer Class II and Class I were considered relevant to topical exposures (Kroes *et al.,* 2007).

Default adjustment factors for percutaneous absorption

The safety evaluation of cosmetic ingredients and cosmetic products requires an estimate of the absorption across the skin. There are major differences in the rate and extent of transfer across the skin compared with the gastrointestinal tract. It was argued that exposure is determined by molecular characteristics, such as lipid solubility and molecular weight, which may predict the rate and extent of transfer across the skin and thus the extent of systemic exposure.

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The COLIPA Expert Group proposed that in the absence of experimental data on skin absorption (which can be obtained also with in vitro models according to the OECD Test Guideline n°428), the most appropriate method of estimating the systemic exposure to a cosmetic ingredient over a 24-hour period following single application should be based on calculation of Jmax (maximum flux). Based on the Jmax value for non-reactive chemicals with a molecular weight below 1000 Da, a fraction absorbed in the range of 10 to 80% (Kroes *et al.*, 2007) should be assigned as a default value. The absorption of chemicals with a molecular weight above 1000 Da was considered negligible.

<u>Default adjustment factors for rinse-off cosmetic products</u>

Rinse-off cosmetics are products that remain in contact with human skin for a limited time (<1 h) only and are subsequently washed off. Current EU Guidelines for cosmetic safety evaluation propose default retention factors of 0.01 or 0.1 (1% or 10%) for different rinse-off products (SCCNFP 2003). The COLIPA Expert Group noted that these factors would also be relevant for the safety evaluation of ingredients or their impurities present in cosmetic rinse-off products (shampoos, shower gels and hair dyes) using the TTC approach.

<u>Default adjustment factors for intermittent use of cosmetic products</u>

Intermittently used cosmetics are products that are used at intervals of > 1 week and include products such as self-tanning agents, depilatories (removers of body hair), hair dyes, permanent hair waving, hair straightening and bleaching agents. Some cosmetic products, such as hair dyes, result in consumer exposure at intervals of 2–3 weeks (direct hair dyes) to 6–8 weeks (oxidative hair dyes). Although the potential exposure per application is the same as for daily-used or intermittently-used products, the time-averaged (e.g. mean annual) consumer exposure from intermittent use of cosmetic products will be proportionately lower than that from a product used daily. The COLIPA Expert Group proposed to take into account intermittent use (time interval >7 days) of relevant cosmetic end products by the use of adjustment factors.

The COLIPA Expert Group noted that there are 3–10 fold differences in NOAEL values between oral acute and sub-chronic animal studies and between oral sub-chronic and chronic studies. Therefore, similar adjustment factors could be applied to cosmetic ingredients where the pattern of exposure is intermittent rather than daily, and when exposure on the day of use is compared with TTC values derived from chronic daily treatment. They proposed that the estimated exposure should be decreased by default adjustment factors of 3-fold for ingredients used only once per week and 10-fold for ingredients used less frequently.

<u>Conclusion of the Colipa expert group</u>

The COLIPA Expert Group concluded that it is scientifically justifiable to use the TTC approach and the database underlying the TTC values established for food chemicals for the safety evaluation of cosmetic ingredients and impurities. Regarding the potential systemic toxicity arising from dermal exposure, the COLIPA Expert Group agreed that substances such as proteins, heavy metals, and chemicals that may have or are suspected to have pharmacological properties, in addition to substances with specific structural alerts of concern, should be excluded for application of the TTC.

2.6.8   Consumer products, including household care products

If there are no specific national rules, the safety of a consumer product is assessed in accordance with European standards, Community technical specifications, codes of good practice and the state of the art.

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The applicability of the TTC database to ingredients in cosmetic and household care products has been evaluated (Blackburn *et al.,* 2005) based on repeated dose toxicity data for 248 substances used in cosmetic or household care products, 29 of which were already in the Munro database. Of the remaining 219 chemicals, 145 could be assigned to a Cramer Class (the rest could not be classified, e.g. because they were polymers, inorganic salts, or materials with undefined structures). Of these, many chemicals had repeated dose toxicity data by dermal or inhalation routes, to reflect the consumer route of exposure. However, only 45 chemicals had suitable oral NOAELs to be compared with the Munro database; 21 were assigned to Cramer Class I, 3 to Cramer Class II and 21 to Cramer Class III. These chemicals were compared to the chemicals in the Munro data base; the highest and mean NOELs were similar for the two sets, but the lowest NOELs were lower.

2.7. Discussion of potential applications

2.7.1 General aspects

The application of the TTC approach has recently been discussed in various areas of risk assessment which are of relevance for the SCs.

For the acceptance of the TTC approach for a specific application or product category it is required to evaluate whether the chemical domains relevant for this application or product category are covered in the available databases.

According to Kroes *et al.* (2004) and Barlow (2005), several chemical classes should be excluded from the general TTC approach (see Section 3.2). The application of TTC to endpoints like allergic reactions, intolerance and local effects needs more analysis. The SCs considers that, in the addition to these chemical classes and endpoints, the TTC is also not applicable to:

- Hydrazines and benzidines due to their high carcinogenic potency
- Insoluble particles and nanomaterials, because of their specific toxicokinetic properties compared to soluble materials.
- Chemicals displaying pharmacological effects for which no readily accessible database is available.

Substances with endocrine-related toxicity can cause a wide range of endocrine-mediated adverse effects, including reproductive and developmental toxicity as well as, for example, thyroid and adrenal toxicity. Such effects have been assessed in hazard identification and risk assessment procedures that were in place when the Munro *et al.* (1996) database was compiled. Recent analyses of data on reproductive and developmental toxicity (see 2.3), based on studies using harmonised test protocols, also showed that the TTC values are adequately protective. Steroids may be an exception to this, since they can have potent endocrine activity; it is therefore recommended that the TTC approach is not applied to substances with steroid structures.

If there are data showing that a substance has endocrine activity, then the assessment should consider those data. The applicability/non-applicability of the TTC approach for such substances should be decided on a case-by-case basis. The EU intends to develop a systematic approach for the identification and assessment of endocrine disruptors which can be applied in the various fields of regulation.

Usually the TTC values are expressed in amount per person per day. In order to be applicable to the entire population, including different age groups, it is advised to express the TTC in amount per body weight per day. Special consideration should be given to infants under the age of 6 months due to the potentially immature metabolism, in

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particular when the estimated exposure is in the range of the TTC value (Renwick *et al*., 2000; Ginsberg *et al*., 2004).

In all databases used to derive TTC values, the doses are based on mass units (mg/kg bw/day). Comparison of toxicity of chemicals might be better addressed by expressing doses (potencies) on a molar basis (mmol/kg bw/day).

In order to perform any risk assessment, complete and accurate information on human exposure is desirable. This information is available in the case of pharmaceuticals, and for food flavouring substances conservative estimates can be made. Much less information exists in the area of consumer products, where there is a diverse range of products and more complex exposure scenarios, including multiple routes. Therefore, in this area, the uncertainties are higher and methodology is less developed. Significant exposure is likely for products that are frequently used and where exposure by multiple routes (oral exposure, skin contact and/or inhalation) and from many sources, e.g. cleaning products, cosmetics and toys, may occur. For many of these consumer products, however, exposure data are limited or absent.

TTC values for toxicity endpoints

In the present TTC approach 2 databases are used: one carcinogenicity database containing 730 chemicals (Cheeseman *et al*., 1999; Kroes *et al*., 2004; Barlow, 2005) and one based on other systemic toxicological endpoints containing 613 chemicals (Munro *et al.,* 1996) (see Section 3.3 for description). Both databases are exclusively based on systemic toxic effects after oral exposure.

The TTC carcinogenicity database, including 730 chemicals, was developed on the basis of The Carcinogenic Potency Database (CPDB)[1] which now contains 1547 chemicals (positive and negative carcinogenicity results). In contrast, by the end of 2009 IARC had classified 174 agents/exposures as human carcinogens or probably human carcinogens[2] and the US EPA IRIS database contained 98 substances classified as human carcinogens, likely or probably human carcinogens[3].

The TTC values of 0.15 and 1.5 µg/person/d for substances with and without a structural alert for genotoxicity, respectively, were derived from animal carcinogenicity studies in the CPDB.

The SCs evaluated whether a TTC value of 0.15 µg/person/d (2.5 ng/kg bw/d) for substances with genotoxicity alerts, and hence possibly DNA reactive carcinogens, is sufficiently protective when compared to an evaluation based on the potency of the chemicals classified in the IRIS database. A 10^{-6} lifetime cancer risk after oral exposure was extrapolated based on US EPA slope factors[4] and compared with the TTC value. The analysis was based on quantitative risk characterisation data that were available from the US EPA IRIS database (for details see Annex, Table 1). Substances excluded from the TTC approach (including hydrazines and benzidines) were also excluded from this analysis.

For established human carcinogens, doses resulting in a lifetime cancer risk of 10^{-6} were less than 2.5 ng/kg bw/d (the proposed TTC value) in 2 out of 4 cases (bis(chloromethyl)ether and vinyl chloride; substances highlighted in yellow in Annex, Table 1). For substances classified as probable, likely or suggestive human carcinogens, the TTC value gave calculated risks of $>10^{-6}$ for 10 out of 29 substances (34%).

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[1] http://potency.berkeley.edu/cpdb.html

[2] http://monographs.iarc.fr/ENG/Classification/crthall.php

[3] http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList

[4] http://www.epa.gov/iris/carcino.htm

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It is noted that there are a number of methodological differences in EPA's cancer risk assessments versus those used to calculate the potency distributions for the TTC from the Gold database. The TTC lifetime cancer risk of 10^{-6} was calculated from animal data in the Gold database by dividing the TD_{50} by 500 000 (linear extrapolation). No scaling factors were used for converting the animal dose into a corresponding human dose, introducing as such already a shift in the TTC value towards a higher value. Indeed, a comparison of the 12 substances from the IRIS database that do not meet any TTC exclusion criteria and that have slope factors > 0.4 $(mg/kg\ bw/d)^{-1}$, i.e., those substances with a potency exceeding the TTC limit of 0.15 µg/person/d, with the TD_{50}s of those substances in the CPDB database (see Annex, Table 2), shows that:

- 11 of the 12 IRIS carcinogens are also listed on the CPDB; only one is not (quinoline);
- 8 of these 12 have a TD_{50} in the CPDB with a potency lower than that one resulting in the TTC limit of 0.15 µg/person/d, i.e. a TD_{50} > 1.25 mg/kg bw/d;
- Of the 4 with a higher potency (highlighted in yellow), 3 are within 3-fold and one (bis(chloromethyl)ether) appears to be associated with a much higher potency.

Taken together, the analysis (Annex, tables 1 and 2) reveals that a TTC value of 0.15 µg/person/d was associated with a higher than 10^{-6} lifetime cancer risk in 33% (4/12) to 36% (12/33) of known or suspected human carcinogens, depending on the database used for the analysis (CPDB or IRIS database, respectively).

With regard to the development of the CPDB database, it is important to note that it contains data on chemicals prioritised for carcinogenicity testing, for example on the basis of their genotoxicity. In the IRIS database, only chemicals with high concern regarding potency as carcinogens and human exposure are listed and an evaluation will thus be skewed. In the context of the TTC approach, it was noted at an early stage that some potent carcinogens have "virtually safe doses" (VSD, predicted lifetime risk of 10^{-6} based on linear extrapolation) lower than the ToR of 1.5 µg/person/d (Munro, 1990; Cheeseman *et al.,* 1999). Kroes *et al.* (2004) later identified that for 86 out of 730 of these substances, the VSDs were also below 0.15 µg/person/d and that a number of them fell within certain structural groups. The structural features of those groups containing the highest proportion of substances with VSDs below 0.15 µg/person/d were identified as aflatoxin-like (5 substances), azoxy (4 substances), and N-nitroso moieties (47 substances). These three structural groups were excluded from the TTC approach. However, it is noted that after removing those 56 compounds, 30 out of 730 (4.1%) remained where the TTC value may be associated with a risk of > 10^{-6}.

Furthermore, it is worth mentioning that in 2009 the SCs have published an opinion on risk assessment methodologies and approaches for genotoxic and carcinogenic substances. According to this opinion, the "Margin of Exposure" (MOE) and linear extrapolation from the T25 (calculated dose giving a tumour incidence of 25% in an animal experiment) to a risk of 10^{-5} can be used in risk assessment of genotoxic carcinogens. In the MOE-approach, potency is represented by the benchmark dose or the T25 derived from animal carcinogenicity studies. MOEs of > 10 000 when using $BMDL_{10}$ or 25 000 when using T25 are considered to be of low concern. Depending on the quality of the animal carcinogenicity data and the number of dose levels used in these studies, the dose-descriptors T_{25} or the BMD(L) are used as points of departure for risk estimation in the low dose region. The 'linearised' approach (T25 method) results in a lifetime cancer risk considered being of low concern while the MOE approach results in dose values representing a low concern. It is recommended that a BMDL (LED) is selected that is representative of the lower end of the observed range. In most cases that would be $BMDL_{10}$ (LED_{10}), but in some cases even $BMDL_{01}$ may be used (SCHER/SCCP/SCENIHR 2009).

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Although there is at present no scientific consensus with regard to the best method to predict cancer risks in humans from animal data, the above analysis, based on a limited number of substances, indicates that there is a need to further elaborate on an appropriate TTC value for substances that might be carcinogenic in humans.

For the moment, the default value of 0.15 µg/person/d corresponding to 2.5 ng/kg bw/d can be used for substances with genotoxicity alerts and hence possible DNA reactive carcinogens, but its scientific basis should be strengthened.
This could be achieved by e.g. extending the database, analysing all available carcinogenicity studies, using allometric adjustment factors and/or using the T25 or 1, 5 or 10% benchmark dose as points of departure for linear extrapolation.

The non-cancer toxicological endpoints database of Munro *et al*. (1996) subdivides chemicals according to the Cramer classification in high, medium and low toxicity categories. Practical application of the TTC approach is usually done by analysing the chemical structure and using Cramer classification as indicator of systemic toxicity. Significant overlaps of NOELs and LOELs between the three Cramer Classes have been demonstrated and there is only a low number of entries in the Cramer Class II category. Recent analyses have revealed a number of misclassification of compounds when using the Cramer decision tree in its present form. Use of the actually available software tool for classification may also result into misclassification (see Patlewicz *et al.*, 2008).

The SCs conclude that the TTC value of Cramer Class II is not supported by the presently available databases and these substances should be treated as Class III substances.

The SCs accept in principle the division into Class I and Class III. For the lowest toxicity class (Class I, 1800 µg/person/d corresponding to 30 µg/kg bw/d for substances without genotoxicity alerts), classification should be carefully considered and justified. If classification in Class I cannot be justified the SCs recommend a general default value equivalent to Cramer Class III compounds (90 µg/person/d corresponding to 1.5 µg/kg bw/d for substances without genotoxicity alerts). All the scientific information available should be used to define the various toxicity classes before expanding the number of classes, i.e. the classification scheme should be modified based on up-to-date toxicological knowledge and recent developments e.g. QSAR evaluations.

2.7.2 Cosmetics

Several questions need to be considered in relation to the suggested use of the TTC approach for application to cosmetics:

- To what extent are the available databases relevant for cosmetic ingredients considering structural similarities/dissimilarities between cosmetic ingredients and substances in the existing databases?
- What are the differences in metabolism between dermal and oral routes of application?
- How should external and internal exposure be assessed?
- Should intentionally added or formed ingredients in cosmetic products and inadvertent contaminants and impurities be considered differently?

Each of the above topics is analysed and discussed in the following sections.

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2.7.2.1   Potential applicability of available data bases to cosmetic ingredients

The similarity between cosmetic ingredients and the chemicals used to derive the Cramer classes was discussed by Kroes *et al.* (2007). However, in spite of the number of ingredient categories evaluated, the documentation of this evaluation was not sufficiently detailed and cannot be used as a basis for the general application of the TTC for cosmetic ingredients. An evaluation of available data on cosmetic ingredients by the SCs is presented below.

The EU database (CosIng[1]) contains approximately 19 000 cosmetic ingredients as well as substances regulated for use in cosmetic products, including chemicals explicitly banned in Annex II of the Cosmetics Directive. In a preliminary search in the CosIng database using CAS numbers (September 2008), 247 chemicals were identified that are also present in the database of Munro *et al.* (1996) (Table 1). Of these, 96 are banned from use in cosmetics. Of the remaining 151 cosmetic ingredients, 101, 17 and 33 are present in Cramer Class I, II and III, respectively. These 151 chemicals can be grouped in approximately 25 of the 92 chemical categories considered by Blackburn *et al.* (2005) for categorising the chemicals in the Munro database; and some chemicals may appear in multiple categories. Among the 96 chemicals that are not permitted for the use in cosmetics, 6 substances are Cramer Class I chemicals [(bis(2-ethylhexyl) phthalate, benzylbutyl phthalate, dibutyl phthalate, 2,6-dimethyl-1,3-dioxan-4-yl acetate, ethyl acrylate, ethylene glycol monomethyl ether], 2 substances are Cramer Class II chemicals [isophorone and propargyl alcohol] and 88 substances are Cramer Class III chemicals [many pesticides, some dyes, some chlorinated solvents, bisphenol A, vinyl chloride etc.].

Table 1:   *The cosmetic ingredients which are common in the database of Munro et al. (1996) and* CosIng *(September 2008)*

Cramer Class	Number of chemicals		Number of cosmetic ingredients common to CosIng and Munro database	Number of banned Chemicals common to Annex II of EU Cosmetic Directive and Munro database
	in Munro database	Checked*		
I	137	131	101	6
II	28	27	17	2
III	448	441	33	88
Total	613	599	151	96

*Due to the lack of CAS No. some chemicals could not be checked

Substances with complex chemical structures as found in e.g. UV-filters and oxidative hair dye reaction products are not covered in the Munro database and were specifically excluded from RepDose since effects of different functional groups may interact, thus making the derivation of (Q)SAR impossible. The analysis of different QSAR programmes has shown that predictivity was very low for molecules with complex structures (Pölloth and Mangelsdorf, 1997) and chemicals with unique structures that would be considered to fall outside the domain of the hundreds of chemicals in the databases that were used to establish the tiered TTC values should be excluded (Felter *et al.,* 2009).

Comparison of "safe doses" obtained by SCCNFP/SCCP risk assessments with values obtained by the TTC approach for these chemicals

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[1] http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.simple

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In a separate analysis the SCs compared 250 chemicals evaluated by SCCNFP/SCCP in the period 1997 – 2007 with the Munro data base. Of these 250 chemicals, 19 chemicals (7.6%) were found in the Munro database. Eleven of these were classified as Cramer Class I, one as Cramer Class II, and seven as Cramer Class III. With the exception of the category "Other substances" the number of cosmetic ingredients evaluated by the SCs and included in the Munro database was rather limited (Table 2). It should also be noted that among the 10 chemicals in the category "Other substances", 6 chemicals are included in Annex II of the Cosmetics Directive[1] and are banned from use in cosmetic products.

Table 2:   *Number of chemicals in the different categories of cosmetic ingredients evaluated by SCCNFP/SCCP in the period 1997 – 2007 which are included in the Munro database*

Category	Number of chemicals	Cramer class			Total (% in Munro database)
		I	II	III	
Fragrances	30		1	2	3 (10%)
Hair dyes	122	1		3	4 (3.3%)
Preservatives	25	2			2 (8%)
UV-filters	22				0 (0%)
Other substances	51	8		2	10 (20%)
Total	**250**	**11**	**1**	**7**	**19 (7.6%)**

Of the 19 chemicals of the Munro database also evaluated by SCCNFP/SCCP, NO(A)ELs are available for 13 substances. For these, a comparison can be made between acceptable values derived from the toxicological data (NO(A)EL) and exposure limits according to the TTC approach (Table 3). For these substances, it can be concluded that the TTC approach gives a reasonable protection. However, for a general application in cosmetics, more evaluations are needed.

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[1] Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products, as amended
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31976L0768:EN:HTML

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Table 3: *The cosmetic ingredients evaluated by SCCNFP/SCCP in the period 1997 – 2007 which are included in the Munro database*

Category	Name	CAS No.	Cramer Class / Geno- toxic alert	Acceptable value µg/kg bw/d		Ref
				TTC	**Risk assessment**	
Fragrances	Furfural[1]	98-01-1	II / GA	0.0025	1	1
	Coumarin[2]	91-64-5	III	1.5	-	2
	Methyl-N-methylanthranilate[3]	85-91-6	III	1.5	-	3
Hair dyes	Acid Blue 9 (INCI)	3844-45-9	I	30	6300	4
	HC Blue n° 2	33229-34-4	III	1.5	1000	5
	Acid Red 18	2611-82-7	III	1.5	10000	6
	Para-Aminophenol	123-30-8	III	1.5	100	7
Preservatives	Benzoic acid	65-85-0	I	30	5000	8
	Formaldehyde[4]	50-00-0	I	30	-	9
Other substances	Diethylene glycol monoethyl ether	111-90-0	I	30	2000	10
	Ethylene glycol monomethyl ether[5, 6]	109-86-4	I	30	-	11
	Diethylphthalate	84-66-2	I	30	1500	12
	Dibutyl phthalate[5, 7]	84-74-2	I	30	20[8]	13,14
	Benzylbutylphthalate[5, 9]	85-68-7	I	30	500	14
	Diethylhexylphthalate[5, 6]	117-81-7	I	30	48	14
	Toluene[10]	108-88-3	I	30	-	15
	Hydroquinone[11]	123-31-9	I / GA	0.0025	5	16,17
	Acetonitrile[5]	75-05-8	III	1.5	-	18
	Acrylamide[5, 12]	79-06-1	III / GA	0.0025	0.01[13]	19

The references are listed at the end of the Opinion
[1] Carcinogen category 2; H351
[2] Opinion on sensitisation only
[3] Opinion on photo-toxicity only
[4] Carcinogen category 2; H351. Used as a preservative with a maximum concentration of 0.2%.
[5] Banned in cosmetic products
[6] Reprotox. category 1B; H360
[7] Reprotox. category 1B; H360. TDI for DBP of 0.01 mg/kg bw/d defined by EFSA
[8] LOAEL
[9] Reprotox. category 1B; H360
[10] Reprotox. category 2; H361. Opinion on use as a solvent in nail cosmetics only
[11] Carcinogen category 2; H351, mutagen category 2; H341
[12] Carcinogen category 1B; H350, mutagen category 1B; H340, reprotox.category 2; H361
[13] Represents a lifetime cancer risk of 10^{-5} (according to opinion "on acrylamide" (ref.: 19)

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The COSMOS project

The COSMOS project is part of the FP7 SEURAT cluster of research projects, running from 2011-2015. A recent report by the EC Joint Research Centre and other COSMOS partners describes the application of chemoinformatic methods to explore the applicability of the Threshold of Toxicological Concern (TTC) approach to cosmetic ingredients (Worth *et al.*, 2012). The chemical space of the Munro non-cancer dataset was characterised to assess whether this underlying TTC dataset is representative of the "world" of cosmetic ingredients, as represented by the COSMOS Cosmetics Inventory (4460 chemicals). In addition, the commonly used Munro threshold values based on Cramer classification were applied to a toxicological dataset of cosmetic ingredients, the COSMOS TTC dataset (558 substances with well defined structures), to assess the degree of protectiveness resulting from the application of the Cramer classification scheme. This analysis is considered preliminary, since the COSMOS TTC dataset and Cosmetics Inventory are subject to an ongoing process of extension and quality control within the COSMOS project. According to the authors, the results of this preliminary analysis show that the Munro dataset is broadly representative of the chemical space of cosmetics, although certain structural classes are missing, notably organometallics, silicon-containing compounds, and certain types of surfactants (non-ionic and cationic classes). Furthermore, compared with the Cosmetics Inventory, the Munro dataset has a higher prevalence of reactive chemicals and a lower prevalence of larger, long linear chain structures. The COSMOS TTC dataset, comprising repeat dose toxicity data for cosmetics ingredients, shows a good representation of the Cosmetics Inventory, both in terms of physico-chemical property ranges, structural features and chemical use categories. Thus, this dataset is considered to be suitable for investigating the applicability of the TTC approach to cosmetics.

Analysis of the data in the COSMOS TTC dataset revealed that the 5th percentile in the cumulative probability distribution of NOEL values for Cramer Class I cosmetic ingredients is approximately two-fold lower than the corresponding 5th percentile in the Munro dataset (1362 vs 3000 µg/kg bw/d). More specifically, 19 out of 201 (9.5%) Cramer Class I cosmetic ingredients were identified with NOEL values lower than the Munro threshold of 3000 µg/kg bw/d. These were considered as false (problematic) negatives for Cramer Class I. The authors noted that 14 of the 19 false negatives for Cramer Class I were taken from the US FDA's PAFA (Priority-based Assessment of Food Additives) database, which is based on a wide range of study types, species and exposure durations, and includes a high percentage (around 45%) of free-standing NOELs (only one dose tested), which are therefore likely to be conservative. Within Cramer Class II, there were no false negatives, and within Cramer Class III, there were only 2 out of 150 (both vitamins). The prevalence of these "false (problematic) negatives" within Cramer Class III was 1.3%, which is less than the prevalence of 5% expected by chance resulting from the use of the 5th percentile of cumulative probability distribution of NOELs in the derivation of TTC values.

It was also observed that the majority of these "false negatives" do not arise when structural alerts for DNA-binding are used to identify potential genotoxicants. Based on these preliminary results, the authors concluded that the current TTC approach is applicable to cosmetics, although a number of improvements can be made, through the quality control of the underlying TTC datasets, modest revisions/extensions of the Cramer classification scheme, and the development of explicit guidance on how to apply the TTC approach.
The COSMOS TTC database is still being developed but the SCs conclude that there are too few substances in Class II to be able to draw firm conclusions about the adequacy of Cramer Class II. Furthermore, the 5th percentile for Class I is lower than the 5th percentile for the Munro non-carcinogen dataset (with a factor >2). This is not the case for Cramer Class III. These observations therefore support the conservative approach (see also under 3.7.1) to start with the default values equivalent to Cramer Class III compounds (90 microgram/person/day for substances without genotoxicity alerts).

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2.7.2.2   Metabolism by the skin

Skin is both a physical and a biochemical barrier to the absorption of chemicals. Besides the role of the stratum corneum as the most critical barrier, there is growing evidence that enzymes of biotransformation and transport proteins are involved in the regulation of flux through the skin (Baron and Merk 2001; Merk *et al*., 2004; Merk *et al*., 2007).

The major biotransformation enzymes found in the liver may also be present in the skin, but at lower activity levels compared to other tissues. There are examples where only small percentages of absorbed substances are metabolized; in any case this process is not rate limiting in terms of actual absorbed dose, although it may affect the nature of the material entering the bloodstream._Indeed, in some cases complete biotransformation during dermal absorption was observed (e.g. p-aminophenol and p-phenylenediamine (Nohynek *et al.,* 2005, 2010)). Detoxification capacity (phase II enzymes) may be even more pronounced in the skin. Oxidative bioactivation of pro-haptens to haptens in the skin is considered a hazard of xenobiotics applied topically. To date, the fate of chemicals in the skin regarding the type and degree of metabolism remains a matter of uncertainty.

The databases used to develop the TTC principle cover experiments with oral administration of the chemicals. Both risk assessment and the TTC approach have to rely on oral toxicity data and route-to route extrapolation. For a sound risk assessment percutaneous absorption data and information on skin metabolism are necessary.

2.7.2.3   Skin contact allergy and topical effects

According to Kroes *et al.* (2007), the TTC concept is not applicable to assess risk of contact dermatitis and other local effects (e.g. contact allergies, irritation, phototoxicity), which are important endpoints for the safety assessment of cosmetic ingredients.

The proposal to use the TTC approach for dermal sensitisation (Safford, 2008 and 2011, described in section 2.6.6) is based on the dermal sensitisation QRA method published by Api *et al*. (2008). This method was reviewed by the SCCP (now SCCS) (SCCP 2008). The main conclusion of this opinion was that after refinement and validation, models such as the dermal sensitization QRA approach may be applicable for risk assessment of new substances to suggest a safe level of exposure prior to incorporation into products. However, aggregated exposures must be incorporated in the dermal sensitization QRA model and validation must be performed employing a broad range of different chemicals and data from substantial clinical investigations. In addition, there is at present no scientific consensus on the methodology of translation of hazardous doses identified in the LLNA to safe human exposure doses.

2.7.2.4   External and internal exposure assessment of cosmetics and TTC

When a cosmetic ingredient is evaluated by the SCCS as safe for use in a well-defined exposure scenario, the evaluation of systemic toxicity is based on chemical-specific information including:

-   The oral NOAEL (subacute, subchronic, reproductive study in rodents)
-   Internal exposure/bioavailability) from oral exposures is taken into consideration to adjust NOAEL derived from oral toxicity studies
-   Dermal absorption (*in vitro* dermal absorption study on skin from human or animal (pig) sources).

When no dermal absorption study is available, a default value of 100% is applied. In addition, local effects, sensitisation and genotoxicity/mutagenicity are taken into account for safety assessment.

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Concerning exposure assessment of chemicals used in cosmetics, the COLIPA Expert Group (Kroes *et al.*, 2007) made a number of recommendations on the use of default adjustment factors for percutaneous absorption, rinse off cosmetic products, and the intermittent use of cosmetic products (section 3.6.2). A detailed discussion of these proposals goes beyond the scope of this opinion, since it concerns the safety evaluation of cosmetic ingredients in general.

The use of an adjustment factor for percutaneous absorption needs further elaboration based on a broad systematic comparison of predicted and experimentally obtained percutaneous absorption values.

In the proposal from Kroes *et al.* (2007), an external exposure value was converted to an internal exposure value. The latter value is then compared to the TTC value as if the TTC value is also an internal exposure value. This is the case under the assumption of 100% oral bioavailability, which in many cases does not hold true. For proper route-to-route extrapolation, the NOAELs from the Munro database need to be corrected for oral absorption. If applying the TTC approach for cosmetics, an adjusted internal TTC value has to be defined considering both dermal and oral absorption. It should be mentioned that in only few cases quantitative information on absorption after oral administration is available.

2.7.2.5   Potential application of the TTC approach to intentionally added ingredients and impurities in cosmetic ingredients

The cosmetic legislation does not particularly address impurities. Indirectly, however, the 6th Amendment to the Directive (93/35/EEC) introduced the requirement to provide qualitative and quantitative composition of the product, the physical and chemical and microbiological specifications of the raw materials and the finished product, and the purity and microbiological control criteria of the cosmetic product.

In the case of substances that require evaluation for inclusion in a positive list in the Annexes of the Directive, the SCCS, in its Notes of Guidance, explicitly demands data on the characterization and purity of cosmetic ingredients and on the characterization of impurities or accompanying contaminants. Significant impurities must be identified and their concentrations given. It is further mentioned that the results of safety studies on ingredients are only relevant when they refer to the substances used with their own specific purity and impurity patterns.

In the case of cosmetic ingredients evaluated by individual safety assessors and not by the SCCS, some advice is also given in the Notes of Guidance including mineral, animal, botanical and biotechnological ingredients. Here, too, the requirement is expressed for data on external contamination and toxic components. As the Notes of Guidance give advice but are not binding, the content of dossiers submitted to the SCCS and even more those treated by individual safety assessors is quite heterogeneous with respect to the degree to which impurities are identified and quantified.

In relation to cosmetic ingredients, the databases currently in use require further development. From a scientific point of view, there is no distinction between intentionally added ingredients or inadvertent contaminants. The applicability of the TTC concept for both types of substances is primarily dependent on exposure conditions, chemical structure and the databases available. For cosmetic ingredients, the TTC concept can only be used for those compounds which belong to a sufficiently represented structural class in the TTC database and where appropriate exposure data are available.

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2.7.2.6 Proposal for TTC application on oxidative hair dye reaction products

In a submission concerning reaction products of oxidative hair dye ingredients, COLIPA suggested that the TTC approach should be applied for such reaction products. However, dermal absorption data have only been provided for a fraction of the relevant compounds. Therefore, the SCCP (2009) concluded that the proposal to use the TTC approach for the risk assessment of oxidative hair dyes cannot be considered at this stage since the knowledge of dermal absorption is a prerequisite. In cases where data on dermal absorption are not available, 100% absorption should be assumed. In addition, the available toxicity database of chemical compounds does not contain compounds similar to reaction products of oxidative hair dyes with regard to structural elements and complexity. Such a database should be established first. Furthermore, a detailed discussion of the structural elements of the hair dye reaction products with regard to structural alerts of genotoxicity and systemic toxicity is needed before the application of the TTC approach could be envisaged.

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3. OPINION

The Threshold of Toxicological Concern (TTC) approach is a risk assessment tool to evaluate safety with regard to systemic toxicity of chemicals that occur at very low levels. It is based on the principle of establishing a generic human exposure threshold value for chemicals, below which there is a low probability of systemic adverse effects to human health. In this approach toxicity data from an available database are extrapolated to a chemical compound for which the chemical structure is known, but no or limited toxicity data are available. Currently, it is being used for food contact materials (only in the USA), food flavourings, genotoxic impurities in pharmaceuticals and for pesticide metabolites in ground water. The use of this approach has been suggested for a number of other areas of application. It should be noted that the TTC concept is not intended to be applied to those chemicals which are regulated and for which specific requirements exist regarding toxicity testing.

The Scientific Committees (SCs) consider that the TTC approach in itself is scientifically acceptable. All risk assessment approaches have some degree of uncertainty. However, when the TTC approach is used, it is important for both risk assessors and risk managers to keep in mind that it is a probability-based screening tool and may have additional uncertainty. The derivation of the various TTC values are based on frequency distributions and the TTC values that have been proposed for use are not based on the lowest value in each of the distributions but on a point close to the lowest value. Thus, when using either the cancer or non-cancer TTC values, there is a chance that a substance with an exposure below the relevant TTC value may still pose a potential risk for consumer health or a lifetime cancer risk $>10^{-6}$. This probability can be estimated to lie between zero and 5%.

When using the TTC approach, all available information on the compound should be considered. This should also include SAR and read-across analysis. Moreover, the application of this principle for risk assessment of a chemical is dependent on the reliability, adequacy and relevance of the underlying toxicity database. Many complex chemical structures are not adequately represented in the available databases. The influence of individual functional groups is unknown and e.g. any receptor-mediated effects of the parent compounds or metabolites are difficult to assess. Endpoints not included in the databases used for the extrapolation of a TTC need to be considered separately, e.g. local effects.

Appropriate exposure assessment is essential for all risk assessments, including application of the TTC. In the case of food flavourings and genotoxic impurities in pharmaceuticals, where the TTC is already in use, the available exposure information has been considered adequate or, in the case of food flavourings, has allowed a conservative estimate of exposure to be made. Limited knowledge exists in other areas, e.g. for consumer products, where a large diversity of products exists and complex exposure scenarios have to be considered including multiple exposure routes.

The answers to the specific questions are:

1.   *Does the SCCS/SCHER/SCENIHR consider the TTC approach appropriate for the human health risk assessment of chemical substances?*

The SCs consider the TTC approach, in general, scientifically acceptable for human health risk assessment of systemic toxic effects caused by chemicals present at very low levels. The application of the TTC should be done on a case-by-case basis and requires expert judgement.

Practical application of the TTC approach to chemicals with no genotoxicity alert is usually done by analysing the chemical structure and using Cramer classification as

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indicator of systemic toxicity. Recent analyses have revealed a number of misclassification of compounds when using the Cramer decision tree in its present form. The SCs conclude that the TTC value of Cramer Class II is not supported by the presently available databases and these substances should be treated as Class III substances.

The SCs accept in principle the division into Cramer Classes I and III. When assigning a chemical to the lowest toxicity class (Class I, 1800 µg/person/d corresponding to 30 µg/kg bw/d for substances with no genotoxicity alert), classification should be carefully considered and justified. If classification in Class I cannot be justified, the SCs recommend a general default value equivalent to Cramer Class III compounds (90 µg/person/d corresponding to 1.5 µg/kg bw/d for substances without genotoxicity alerts). All the scientific information available today should be used to define the various toxicity classes before expanding their number, i.e. the classification scheme should be modified based on up-to-date toxicological knowledge.

For the moment, the default value of 0.15 µg/person/d corresponding to 2.5 ng/kg bw/d can be used for chemicals with genotoxicity alerts and hence possible DNA reactive carcinogens, but its scientific basis should be strengthened.
This could be achieved by e.g. extending the database, analysing all available carcinogenicity studies, using allometric adjustment factors and/or using the T25 or 1, 5 or 10% benchmark dose as points of departure for linear extrapolation.

Usually, TTC values are expressed as an amount per person per day. In order to be applicable to the entire population, including all age groups, it is advised to express TTC values in an amount per body weight per day and give special consideration to infants under the age of 6 months because of the potentially immature metabolism for some chemicals structures, in particular when the estimated exposure is close to tolerable exposures defined by the TTC values.

2. *In elaborating their opinion(s), and if the available information allows it, the SCCS/SCHER/SCENIHR are asked to address the following:*

   a) *The various product categories including cosmetic products, consumer products, and others where a significant exposure of consumers to chemical substances is likely to occur in normal use situations.*

In a regulatory context, the TTC concept is presently applied only in very low exposure situations. The evaluation presented in the opinion indicated that from a scientific perspective the TTC approach can be applied to cosmetics, other consumer products and chemicals to which consumers may be exposed. However, the provisions as mentioned in the answer to Question 1, apply.

In relation to cosmetic ingredients, the databases currently in use require further development and validation. From a scientific point of view, there is no distinction between intentionally added ingredients or inadvertent contaminants. The applicability of the TTC concept for both types of substances is primarily dependent on exposure conditions, chemical structure and the databases available. For cosmetic ingredients, the TTC concept can only be used for those compounds which belong to a sufficiently represented structural class in the TTC database and where appropriate exposure data are available.

In addition, it should be noted that an appropriate exposure assessment is essential for all risk assessments, including application of TTC. Significant exposure is likely for consumer products, especially when they are frequently used. This may involve oral exposure (e.g. mouthing), skin contact and/or exposure via inhalation by using e.g. toys, cosmetics or cleaning products. For many of these product categories, however, exposure information/data are limited or lacking. Only limited information is available in

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particular in the field of exposure to consumer products, where a large diversity of products exists and complex exposure scenarios have to be considered including multiple exposure routes. In this area, methodologies are less developed and therefore, the uncertainties are higher.

> b) *The distinction between intentionally added ingredients and substances present in a particular product as inadvertent contaminants.*

Taking the above into consideration there is no distinction between toxicity induced either by intentionally added ingredients or inadvertent contaminants. The applicability of the TTC concept for both categories of substances is primarily dependent on exposure conditions and the databases available.

> c) *Identification of classes of chemicals, exposure situations, and toxicity end points for which the TTC concept may be appropriate and those for which it may not be*

The answer to the first part of the question is given in the reply to Questions 1 and 2a. The TTC approach relates only to systemic effects and, at present, cannot be used for the assessment of local effects. Allergy, hypersensitivity and intolerance are excluded due to uncertain dose-response relationship.

The TTC approach is not applicable to the following chemical classes:

- Aflatoxin-like, azoxy-, N-nitroso-compounds, benzidines and hydrazines are excluded due to their high carcinogenic potency.
- Metals and polyhalogenated dibenzo-*p*-dioxins, polyhalogenated dibenzofurans and polyhalogenated biphenyls, or other compounds known to accumulate in the body, e.g. Ochratoxin A are excluded because the safety factors used may not be high enough to account for differences between species in their elimination from the body.
- Potent hormones, such as steroids.
- Radioisotopes because of their radiation-specific biological activity
- High molecular weight chemicals, such as polymers, because such structures are not covered by the databases.
- Proteins are excluded because of potential for sensitisation or other biological activities.
- Substances displaying pharmacological effects for which no readily accessible database is available.
- Insoluble particles and nanomaterials, because of their specific toxicokinetic properties compared to soluble materials.

Substances with complex chemical structures having several structural elements are not adequately represented in the available databases. It is also important to note that chemicals with highly unique structures fall outside the databases. Such substances should be excluded from the TTC approach.

If there are data showing that a substance has endocrine activity, then the assessment should consider those data. The applicability/non-applicability of the TTC approach for such substances should be decided on a case-by-case basis. It should be noted that the EU intends to develop a systematic approach for the identification and assessment of endocrine disruptors which can be applied in the various fields of regulation.

The TTC, as discussed in this opinion, is not dealing with effects of mixtures of chemicals which are addressed elsewhere[1].

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[1] http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_155.pdf

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d) The quantity and type of data (exposure, toxicity, QSAR, statistics, etc.) that will need to be available for a particular class of chemicals and/or exposure situation before the TTC concept can be applied in the risk assessment of chemicals

When using the TTC approach, any available information on the compound should be considered. This approach should also include SAR and read-across analysis. However, the application of this principle in terms of risk assessment for safety evaluation of a chemical is dependent on the reliability, adequacy and relevance of the underlying toxicity database, and a reliable estimation of the exposure to the chemical in the respective field of application.

Significant exposure is expected from a large number of consumer products. To assess exposure, information is required on a number of aspects; use frequency and amount used, duration of product contact, concentration, emission or leaching of a substance from the product, and subsequent absorption from the skin, lungs and/or the gastro-intestinal tract. Therefore, exposure to consumer products other than cosmetics is even more complicated to assess, since human behaviour and product characteristics play an important role. In general, information on exposure from such products is scarce.

e) Additional research needed to strengthen the Threshold of Toxicological Concern approach and its usefulness for the human health risk assessment of chemical substances

The TTC concept could be strengthened by further expansion and refinement of the existing databases. The present decision tree for Cramer classification should be refined based on up-to-date toxicological knowledge. Furthermore, specific decision trees for the application of the TTC approach have to be developed for the various potential fields. The TTC value for chemicals with structural alerts for genotoxicity should be strengthened by an expanded analysis of carcinogenicity studies and application of up-to-date extrapolation procedures.

Chemicals with complex structures are not adequately covered in existing databases. It is necessary to include toxicity data on these compounds.

4. RECOMMENDATIONS

Application of the TTC approach in risk assessment in any area requires a high level of confidence in: 1) the quality and completeness of the databases; 2) the reliability of the exposure data for the intended uses of the compound under study; and 3) the appropriateness of any extrapolations. It is the opinion of the Scientific Committees that in each of these areas further research is needed.

4.1. Databases

Since the original data sets used for the TTC approach were compiled some time ago, expansion is possible with more recent data. Additional structural alerts and complex structures may be identified which may be introduced into or excluded from the TTC approach. Furthermore, specific decision trees for the application of the TTC approach should be developed for the various potential fields of application.

Regarding the non-carcinogen database the following points need to be addressed:

- The databases must contain up-to-date/peer-reviewed data or data produced under GLP and following toxicity testing guidelines.
- When new data are introduced, they need to be displayed in the same form as the existing data, meaning that they need to be the same type of result of the same

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type of test (e.g. NOAEL/NOEL/LOAEL/LOAEL from 28-day/90-day/chronic studies with rodents and rabbits). Furthermore, assessment/adjustment factors (e.g. regarding allometry, study duration and study outcome) should be considered.

The SCs encourage industry to disclose their high quality GLP-reports of systemic toxicity studies for the expansion of existing databases or the construction of new databases on additional end points.

Chemicals with complex structures are not adequately covered in the Munro database. It is necessary to include toxicity data on these compounds into databases to be used for derivation of TTCs.

The scientific basis of the TTC value for compounds with genotoxicity alerts (0.15 µg/person/d corresponding to 2.5 ng/kg bw/d) needs to be strengthened. This could be achieved by e.g. extending the database to cover all available carcinogenicity studies, using allometric adjustment factors and/or using the T25 or 1, 5 or 10% benchmark dose as reference dose for linear extrapolation.

4.2. Cramer classification

Practical application of the TTC approach is usually done by analysing the chemical structure and using Cramer classification as indicator of systemic toxicity. Several recent analyses have revealed a number of misclassification of compounds when using the Cramer decision tree in its present form. All scientific information available today should be used to define the various toxicity classes before expanding the number of classes, i.e. the classification scheme should be modified based on up-to-date toxicological knowledge and recent developments e.g. QSAR evaluations.

4.3. Exposure assessment

For application of the TTC concept and risk assessment of consumer products, the generation of high quality exposure data is needed and substantial research in this area is required. In the following areas, research is needed for consumer products: use frequency and amount used, duration of product contact, concentration, leaching or release of a substance from the product to the skin or air, and subsequently, absorption via the skin and/or the lungs or via oral route.

When performing an exposure assessment, all routes and sources of exposure should be taken into account.

Possible combined exposures to multiple chemicals with the same mode of action need to be evaluated in order to decide to which extent the TTC concept can be applied to mixtures.

4.4. Route-to-route extrapolation

The databases used to develop the TTC principle comprise experiments with oral administration of the chemicals, i.e. by gavage or in diet or drinking water. The assessment of products that result in topical (e.g. cosmetics) or inhalation exposure requires route-to-route extrapolation. In such cases, also the extent of oral bioavailability is an important factor. For route-to-route extrapolation, assuming 100% oral absorption is considered by the SCs as a best case and not a worst case estimate. Therefore, when oral data are used as a source for deriving TTC values for other than oral exposures, the NOAELs of the studies should be corrected for oral bioavailability. It is recommended that when applying the TTC approach for cosmetics, an adjusted internal TTC value is defined considering both dermal and oral absorption.

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5. MINORITY OPINION

None

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6. List of Abbreviations

ADI — Acceptable daily intake

ALARP — As low as reasonably practicable

BMD(L) — Benchmark dose (lower confidence limit)

bw — Body weight

CAS — Chemical Abstracts Service

CHMP — Committee for Medicinal Products for Human Use

Colipa — European Cosmetic, Toiletry and Perfumery Association (renamed Cosmetics Europe in 2012)

CoNTC — Concentration of no toxicological concern

CPDB — Cancer Potency Data Base

CVMP — Committee for Medicinal Products for Veterinary Use

d — Day

DST — Dermal sensitisation threshold

ECETOC — European Centre for Ecotoxicology and Toxicology of Chemicals

ECHA — European Chemicals Agency

EFSA — European Food Safety Authority

ELINCS — European List of Notified Chemical Substances

EMA — European Medicines Agency

FCM — Food contact materials

GLP — Good laboratory practice

IARC — International Agency for Research on Cancer

ICH — International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ILSI — International Life Sciences Institute

JECFA — Joint FAO/WHO Expert Committee on Food Additives

LED — Lowest estimated dose

LLNA — Local lymph node assay

MOE — Margin of exposure

MRL — Maximum residue limit

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NESIL	No expected sensitization induction levels
NOAEL	No observed adverse effect level
N(L)OEL	No (Lowest) observed effect level
N(L)OEC	No (Lowest) observed effect concentration
OECD	Organisation for Economic Co-operation and Development
ppb	Parts per billion
QRA	Quantitative risk assessment
(Q)SAR	(Quantitative) Structure-activity relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RIVM	National Institute for Public Health and the Environment, The Netherlands
RTECS	Registry of Toxic Effects of Chemical Substances
SCCP	Scientific Committee on Consumer Protection
SCCS	Scientific Committee on Consumer Safety
SCF	Scientific Committee on Food
SCHER	Scientific Committee on Health and Environmental Risks
SCENIHR	Scientific Committee on Newly Identified and Emerging Health Risks
SCs	Scientific Committees (SCCS, SCHER, SCENIHR)
SED	Systemic exposure dosage
SF	Safety factor
T25	Dose giving a tumour incidence of 25% in experimental animals after correction for the spontaneous incidence
TD50	Median toxic dose
TDI	Tolerable daily intake
ToR	Threshold of regulation
TSC	Threshold of sensitisation concern
TTC	Threshold of toxicological concern
US EPA	United States Environmental Protection Agency
US FDA	United States Food and Drug Administration
VSD	Virtually safe dose
WHO IPCS	World Health Organization International Programme on Chemical Safety

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ANNEX

The following calculations are considered as conservative. They are in part based on US EPA slope factors derived for compounds of high concern and high potency and thus do not represent the range of potencies that a frequency distribution approach such as the TTC is based on. Moreover, the slope factors are derived using highly conservative assumptions. The database for the US FDAs ToR is already considered conservative (see above), the derived TTC for chemicals with structural alerts for carcinogenicity has added an additional safety factor of 10 to the ToR.

Table 1: Calculated lifetime cancer risk after oral administration.

The lifetime cancer risks have been calculated from the Slope factor (Taken from EPA IRIS database: http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList).

Substances excluded from the TTC approach, such as metals, polyhalogenated dibenzo-p-dioxins and furans, polyhalogenated biphenyls,benzidines, hydrazines and N-nitroso-compounds as well as bioaccumulative substances were excluded from this analysis.

Substances that would not be covered by the 0.15 µg/person/d TTC value are highlighted.

Name	CAS no	Classifi-cation*	Slope factor (mg/kg bw/d)$^{-1}$	Lifetime cancer risk 10^{-6} (ng/kg bw/d)
Human carcinogens				
Benzene	71-43-2	A	0.015 -0.055	18 – 67
Bis(chloromethyl)-ether	542-88-1	A	220	0.0045
Trichloroethylene	79-01-6	Carcinogenic	0.046	21.7
Vinyl chloride	75-01-4	A	0.72	1.4
Probable or likely human carcinogens or substances with suggestive evidence of carcinogenic potential				
Acrylamide	79-06-1	Likely	0.5	2.0
Acrylonitrile	107-13-1	B1	0.54	1.9
Aniline	62-53-3	B2	5.7×10^{-3}	180
Aramite	140-57-8	B2	2.5×10^{-2}	40
Azobenzene	103-33-3	B2	1.1×10^{-1}	9
Benzo(a)pyrene	50-32-8	B2	7.3	0.137
Benzotrichloride	98-07-7	B2	13	0.077
Benzyl chloride	100-44-7	B2	0.17	5.9
Bis(chloroethyl)ether	111-44-4	B2	1.1	0.91
Bromate	15541-45-4	B2	0.7	1.4
Bromodichloro-methane	75-27-4	B2	6.2×10^{-2}	16
Bromoform	75-25-2	B2	7.9×10^{-3}	130
Carbon tetrachloride	56-23-5	Likely	0.07	14.3
Di (2-ethylhexyl)-phthalate	117-81-7	B2	1.4×10^{-2}	67
1,2-Dibromoethane	106-93-4	Likely	2	0.5
1,2-Dichloroethane	107-06-2	B2	9.1×10^{-2}	11
Dichloromethane	75-09-2	Likely	0.002	500
1,3-Dichloropropene	542-75-6	B2	1×10^{-1}	10
2,4-/2,6-Dinitro-toluene mixture		B2	0.68	1.5
1,4-Dioxane	123-91-1	Likely	0.1	10
Epichlorohydrin	106-89-8	B2	9.9×10^{-3}	100
Furmecyclox	60568-05-0	B2	3.0×10^{-2}	33
Hexachloroethane	67-72-1	Likely	0.04	25
4,4'-Methylene bis-(N,N'-dimethyl)aniline	101-61-1	B2	4.6×10^{-2}	22
Propylene oxide	75-56-9	B2	0.24	4.2
Quinoline	91-22-5	B2	3	0.33
1,1,2,2-Tetrachloroethane	79-34-5	Likely	0.2	5
Trichloroacetic acid	76-03-9	Suggestive	0.07	14.3
1,2,3-Trichloropropane	96-18-4	Likely	30	0.03

* Classification according to US EPA:

A - Human carcinogen,

B1 - Probable human carcinogen - based on limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals,

B2 - Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals,

Likely - Likely to be carcinogenic to humans.

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Table 2. Carcinogens in the IRIS database with potencies exceeding the TTC limit of 0.15 µg/person/d and how these compare to TD50s for the same compounds in the CPDB database

Substances excluded from the TTC approach, such as metals, polyhalogenated dibenzo-p-dioxins and furans, polyhalogenated biphenyls, benzidines, hydrazines and N-nitroso-compounds as well as bioaccumulative substances were excluded from this analysis. TD-50s highlighted are those that are also associated with a potency exceeding the TTC limit.

Chemical	EPA Oral Slope Factor * (mg/kg bw/d)$^{-1}$	CPDB TD-50** (mg/kg bw/d)	Equivalent TTC in µg/person/d (0.12 x TD$_{50}$ value)
Potency figure equivalent to TTC***	**0.4**	**1.25^{1}**	**0.15**
Acrylamide	(1) 0.5	(2) 3.75	0.450
Acrylonitrile	0.54	6.32	0.758
Benzo[a]pyrene	7.3	0.956	0.115
Benzotrichloride	13	0.396	0.048
Bis(chloroethyl)ether	1.1	11.7	1.404
Bis(chloromethyl)ether	220	0.00357	0.0004
Bromate	0.7	9.82	1.178
1,2-Dibromomethane	2	1.52	0.182
2,4-/2,6-Dinitrotoluene	0.68	6.21	0.745
Quinoline	3	Not Listed	--
1,2,3-Trichloropropane	30	0.875	0.105
Vinyl chloride	0.72	6.11	0.733

*   see table 1
**   TD50s were taken from summary tables of the online version of the CPDB
*** The following values are equivalent to high potency. The proposed TTC of 0.15 µg/person/d is
     not sufficiently protective (too high) for: EPA oral SF > 0.4 (mg/kg bw/d)-1
                                                        TD50< 1.25 mg/kg bw/d1

[1] A TD$_{50}$ of 1.25 mg/kg bw/d is equivalent to a TTC value of 0.15 µg/person/d (assuming 60 kg body weight):

$$\frac{\text{Risk}}{\text{Dose}} = \frac{1\,E\text{-}6}{0.15\ \mu g/d} = \frac{1\,E\text{-}6}{0.0025\ \mu g/kg/d} = \frac{1}{2.5\ mg/kg/d} = \frac{0.5\ (TD_{50})}{\textbf{1.25 mg/kg/d}}$$

Lower TD$_{50}$s are associated with a higher potency, such that any substance with a TD$_{50}$< 1.25 mg/kg bw/d would not be considered to be protected by a TTC of 0.15 µg/person/d.