



Scientific Committee on Consumer Products (SCCP) – Scientific Committee on Health and Environmental Risks (SCHER) – Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)

# Draft OPINION ON

# Use of the Threshold of Toxicological Concern (TTC) Approach for the Safety Assessment of Chemical Substances


**Preliminary report**

agreed by SCHER, SCCP and SCENIHR on 19 November 2008 by written procedure

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 Products (SCCP), 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 Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCHER

Questions relating to examinations of the toxicity and ecotoxicity of chemicals, biochemicals and biological compound whose use may have harmful consequences for human health and the environment.

In particular, the Committee addresses questions related to new and existing chemicals, the restriction and marketing of dangerous substances, biocides, waste, environmental contaminants, plastic and other materials used for water pipe work (e.g. new organics substances), drinking water, indoor and ambient air quality. It addresses questions relating to human exposure to mixtures of chemicals, sensitisation and identification of endocrine disrupters.

Scientific Committee members

Herman Autrup, Peter Calow, Wolfgang Dekant, Helmut Greim, Hanke Wojciech, Colin Janssen, Bo Jansson, Hannu Komulainen, Ole Ladefoged, Jan Linders, Inge Mangelsdorf, Marco Nuti, Anne Steenhout, Jose Tarazona, Emanuela Testai, Marco Vighi, Matti Viluksela

SCCP

Questions concerning the safety of consumer products (non-food products intended for the consumer).

In particular, the Committee addresses questions related to the safety and allergenic properties of cosmetic products and ingredients with respect to their impact on consumer health, toys, textiles, clothing, personal care products, domestic products such as detergents and consumer services such as tattooing.

Scientific Committee members

Claire Chambers, Gisela Degen, Ruta Dubakiene, Bozena Jazwiec-Kanyion, Vassilios Kapoulas, Jean Krutmann, Carola Lidén, Jean-Paul Marty, Thomas Platzek, Suresh Chandra Rastogi, Jean Revuz, Vera Rogiers, Tore Sanner, Günter Speit, Jacqueline van Engelen, Ian White

SCENIHR

Questions concerning emerging or newly-identified risks and on broad, complex or multidisciplinary issues requiring a comprehensive assessment of risks to consumer safety or public health and related issues not covered by other Community risk- assessment bodies

In particular, the Committee addresses questions related to potential risks associated with interaction of risk factors, synergic effects, cumulative effects, antimicrobial resistance, new technologies such as nanotechnologies, medical devices, tissue engineering, blood products, fertility reduction, cancer of endocrine organs, physical hazards such as noise and electromagnetic fields and methodologies for assessing new risks.

Scientific Committee members

Anders Ahlbom, James Bridges, Wim de Jong, Philippe Hartemann, Thomas Jung, Mats-Olof Mattsson, Jean-Marie Pagès, Konrad Rydzynski, Dorothea Stahl, Mogens Thomsen

Contact:

European Commission
Health & Consumer Protection DG
Directorate C: Public Health and Risk Assessment
Unit C7 - Risk Assessment
Office: B232 B-1049 Brussels

SCCP: Sanco-Sc6-Secretariat@ec.europa.eu

SCHER: Sanco-Sc8-Secretariat@ec.europa.eu

SCENIHR: Sanco-Sc1-Secretariat@ec.europa.eu

© European Commission 2008

(ISSN)

The opinions of the Scientific Committees present the views of the independent scientists who are members of the committees. They do not necessarily reflect the views of the European Commission. The opinions are published by the European Commission in their original language only.

http://ec.europa.eu/health/ph_risk/risk_en.htm

## ACKNOWLEDGMENTS

Members of the working group are acknowledged for their valuable contribution to this opinion:

Prof. J. Bridges – University of Surrey - UK
Dr. W.H. de Jong– National Institute for Public Health and the Environment - NL
Prof. B.O. Jansson – Institute of Applied Environmental Research - SE
Dr. O. Ladefoged – Institute of Food Safety and Nutrition - DK
Prof. T. Platzek - Bundesinstitut für Risikobewertung - DE
Dr. S.C. Rastogi - National Environmental Institute, DK
Prof. V. Rogiers – Vrije Universiteit Brussel - BE
Prof. T. Sanner - University of Oslo – NO
Dr. J. van Engelen – National Institute for Public Health and the Environment - NL

External experts

Dr. C. Fruijtier-Pölloth – CATS Consultants - DE
Dr. S. Kalweit - Bundesamt für Verbraucherschutz und Lebensmittelsicherheit - DE
Dr. P. Kasper - Bundesinstituts für Arzneimittel und Medizinprodukte - DE
Dr. J.R. Schlatter- Federal Office of Public Health - CH

Keywords: SCHER, SCCP, SCENIHR, scientific opinion, threshold of toxicological concern, TTC

Opinion to be cited as:
SCHER/SCCP/SCENIHR scientific opinion on the use of the Threshold of Toxicological Concern (TTC) approach for the safety assessment of chemical substances, date

## TABLE OF CONTENTS

## 1. BACKGROUND

The concept of TTC has its roots in the concept that 'safe levels of exposure' can be identified for individual chemicals with known toxicological profiles. TTC is an approach that aims to establish a human exposure threshold value below which there is a very low probability of an appreciable risk to human health also for chemicals for which toxicological data are not available, based on chemical structure and toxicity data of structurally related chemicals.

Starting with the generic approach ('exposure threshold') used by the US FDA in the 80s, the TTC concept has evolved over the years to take into account extensive analysis of available data on mainly the 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 (JECFA, EFSA), food contact materials (US FDA), genotoxic impurities in pharmaceuticals (EMEA) and for the risk assessment of chemicals (WHO IPCS). Recent publications have suggested that the TTC approach can also find uses in other categories of chemicals and more specifically on chemicals (or trace contaminants) in consumer products, food additives, pesticides and cosmetics.

Specifically for cosmetics, COLIPA, the European cosmetics industry association 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, 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*'.

## 2. TERMS OF REFERENCE

The SCCP/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 SCCP/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 SCCP/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.

   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 be

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 Threshold of Toxicological Concern approach and its usefulness for the human health risk assessment of chemical substances

## 3. SCIENTIFIC RATIONALE

### 3.1. Introduction

The Threshold of Toxicological Concern (TTC) approach is a risk assessment tool that is based on the principle of establishing a human exposure threshold value 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 structure and the known toxicity of chemicals which share similar structural characteristics.

The TTC might be used as substitute for substance-specific information in situations where there is limited or no information on toxicity of the compound, and where the human exposure is so low that adverse effects are not expected.

The TTC concept is currently used in relation to oral exposure to food contact materials and food flavourings and genotoxic impurities in pharmaceuticals. Application of TTC to dermal and inhalation exposures has received less attention. Recently, The European Cosmetic Toiletry and Perfumery Association (COLIPA) sponsored work by a group of experts to examine the potential use of the TTC concept in the safety evaluation of cosmetic ingredients (Kroes *et al*., 2007). In addition, other areas of application are being explored (e.g., medical devices, industrial chemicals, chemical compounds in the environment).

### 3.2. History and development of the TTC approach

Substances in food packaging materials were the first compounds for which a TTC-like approach was proposed. The US Federal Food, Drug and Cosmetic Act defined in 1958 that contact material and their components that might 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 that there was a need for a policy at the United States Food and Drug Administrations (US FDA) to handle low dose 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 the 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. Discussions went for several years concerning how to establish the level of a "Threshold of Regulation" (ToR). This represented the first practical application of the TTC-concept.

According to the interpretation of the Delaney Clause, a substance could not be added if it caused a lifetime cancer risk of more than 1 in a million ($1 \times 10^{-6}$). Thus, a distribution plot of the chronic dose rates was set up based on the analysis of 343 carcinogens from the carcinogenic potency database derived by Gold *et al.* (1984). By extrapolation to a distribution of $10^{-6}$ risk to develop cancer an estimated value of 0.5 ppb in food was derived and implemented by the US FDA in 1995 as the "Threshold of Regulation for food contact material" (US FDA, 1995). In addition, compounds with structural alerts for genotoxicity require case-by-case evaluation. Although US FDA had received a number of comments expressing the opinion that the 0.5 ppb threshold is more conservative and restrictive than is 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 of US FDA by incorporation of acute and short-term toxicity data, the results of genotoxicity testing, and structural alerts to identify potent and non-potent carcinogens. An evaluation of carcinogenic potency was performed on 709 rodent carcinogens in the carcinogen potency database of Gold *et al*.[1].Linear extrapolation to low dose was used to estimate the dose corresponding to an upper-bound

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

limit of lifetime risk of $10^{-6}$. This work confirmed the validity of a ToR 0.5 ppb in food for most carcinogens.

In order to evaluate non-cancer endpoints, Cheeseman *et al*. (1999) also analysed information from the Registry of Toxic Effects of Chemical Substances (RTECS) database on 3306 substances with oral reproductive toxicity data, and on 2542 substances for which there were data from other repeat-dose toxicity studies. Based on the results, Cheeseman *et al*. (1999) suggested the following tiered TTC approach in which structural alerts, genotoxicity test results and short-term toxicity data could be used to extend the US FDA's existing ToR approach:

- 1.5 µg/person/day (0.5 ppb): General threshold. Substances possessing positive Ames test results or certain structure alerts such as e.g. N-nitroso or benzidine-like chemicals should be evaluated on a case-by-case basis.
- 15 µg/person/day (5 ppb): Threshold for chemicals without structural alerts for carcinogenicity or with negative mutagenicity test (Ames test).
- 45 µg/person/day (15 ppb): Threshold for chemicals without structural alerts for carcinogenicity or with negative mutagenicity test (Ames test) and with an appropriate acute toxicity test with LD50 >1000 mg/kg bodyweight.

This tiered approach by Cheeseman *et al*. (1999) has not been adopted by US FDA.

The ToR/TTC used by US FDA concerned possible carcinogenic effects. Munro and co-workers (1996) evaluated the use of TTC related to other endpoints than carcinogenicity. They used structural information based on an algorithm developed in 1978 by Cramer *et al*. The chemicals were grouped into three structural classes based on a "decision tree" approach. This decision tree consisted of a total of 33 questions for which each is answered by "yes" or "no". Each answer led to another question or to a final classification into one of the three classes (I, II and III), reflecting a presumed low, moderate and significant toxicity. Human exposure thresholds of 1800, 540 and 90 µg/person/day were proposed for class I, II and III, respectively.

The use of the TTC concept for chemical substances present in the diet was discussed at two workshops (1999 and 2003) organized by the International Life Sciences Institute (ILSI). The deliberations of the Expert Group have been published by Kroes *et al.* (2000, 2004) and Barlow (2005). The group expanded the database for non-carcinogenic substances and concluded that endpoints such as effects on the nervous system, immune system, endocrine system and development were covered by the threshold previously proposed for the three Cramer classes, but that for organophosphates a specific TTC was needed. A TTC of 18 µg/person/day was derived (Kroes *et al.*, 2004). The carcinogenic potency database used by Cheeseman *et al.* (1999), comprising 709 compounds, was further expanded to 730 compounds and analysed in order to identify structural alerts that would give the highest calculated risks if present at very low concentrations in the diet.

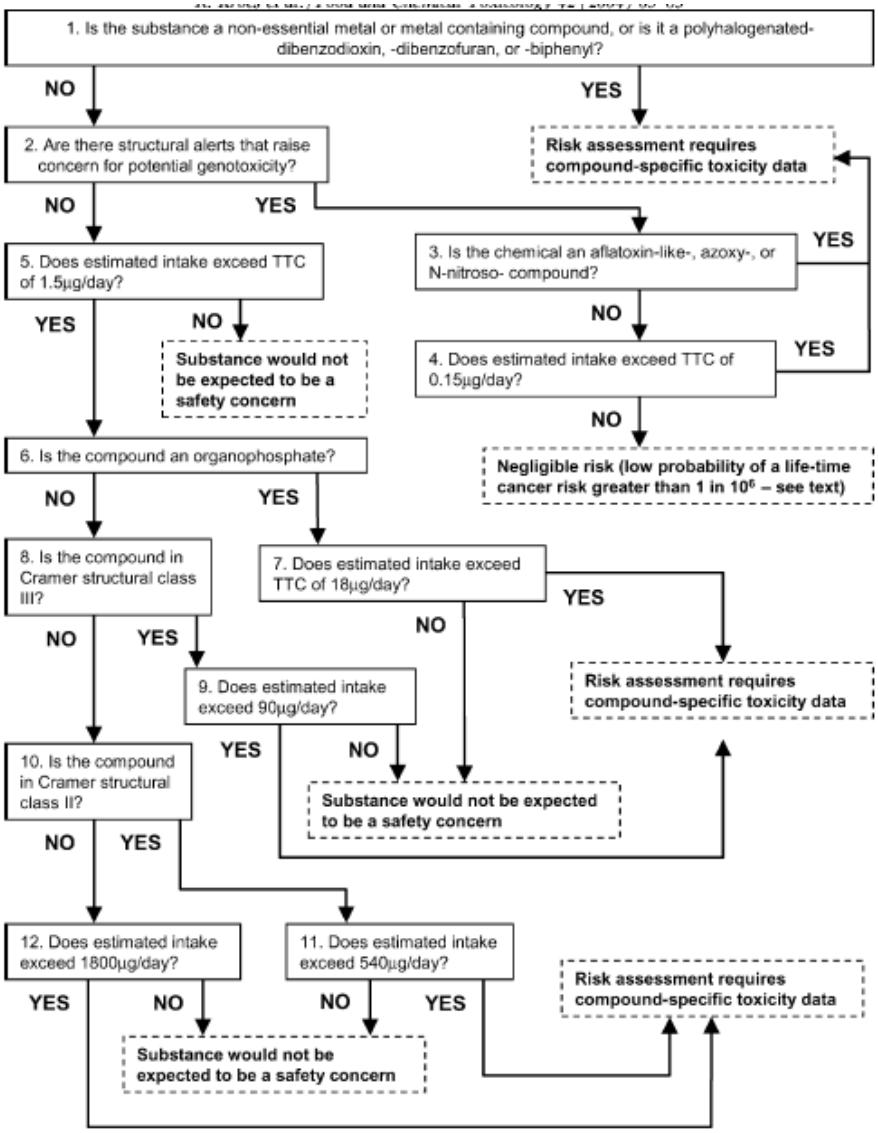


***Figure 1:*** *The TTC decision tree suggested by the ILSI Europe Expert group* (Kroes *et al*., 2004)**.**

The work of the Expert Group (Kroes *et al*., 2004) resulted in the construction of a decision tree (Fig. 1), based on a tiered approach, to act as guidance on how and when the TTC principle could be applied as a preliminary step in risk assessment of food. The questions are related to whether the chemical is suitable for assessment via the TTC concept according to defined exclusion criteria described above, the presence or absence of structural alerts for genotoxicity, and, depending on the chemical's structure, 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 will be reached: either, the substance would not be expected to be a safety concern, or, risk assessment requires compound-specific toxicity data. The decision tree is only applicable to chemicals of known structure, and with low molecular mass, as presented in the databases. Accordingly, it is not applicable to, for example, polymers. The ILSI Expert Group recommended that the TTC principle can be used for substances that are present in food in low concentrations, which lack toxicity data, but for which exposure assessment can provide reliable estimates (Kroes *et al*., 2004).

For risk assessment, a good estimate of exposure is critical, since this determines whether or not the TTC is exceeded.

Presently, the thresholds for human exposure to substances based on the structural Cramer classes are used in the procedure for the safety evaluation of chemically defined flavouring substances by the JECFA and in the European Union (JECFA 1996; SCF, 1999). In Europe, also the use of the TTC approach to define acceptable levels of genotoxic impurities in pharmaceuticals for human use has reached regulatory acceptance.

In addition, the application of TTC-based risk assessment strategies has recently been discussed in many areas where risk assessments are performed. These proposed uses are further described in chapter 3.6.

### 3.3. Toxicological databases

The establishment of a Threshold of Toxicological Concern is based on the analysis of toxicological data and chemical structures of a broad range of substances. The knowledge derived from this is used to substitute for substance specific information in situations where there are limited or no information on toxicity of a given substance to which the human exposure is so low that undertaking toxicity studies is considered not warranted.

As discussed in chapter 3.2, two major databases are available. One covers carcinogenic effects of chemicals and was developed in relation to the "Threshold of regulation" used by US FDA. The other covers a variety of non-cancer systemic effect endpoints. Both databases were developed for the use of the TTC concept in relation to food. This implies that for use of the TTC concept in other areas, it is necessary to assess whether the databases contain sufficient numbers of relevant chemicals in the area under consideration. It should also be noted that both databases only cover systemic effects after oral exposure.

*The carcinogenicity database* was originally based on 343 carcinogens from animal studies compiled in the Carcinogen Potency Database (CPDB) (Gold *et al*., 1984). Subsequently, the database has been expanded to 730 carcinogens taking into account the continuously updated CPDB (Cheeseman *et al*., 1999; Kroes *et al*. 2004; Barlow, 2005). Under the US FDA regulation, the use of a substance 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, the dose descriptor $TD_{50}$ (the daily dose rate required to halve the probability of an experimental animal of remaining without tumours at the end of its standard life-span) and extrapolation to a distribution of $10^{-6}$ risk to develop cancer. Assuming that a person consumes 1500 g of food and 1500 g of fluid daily and that the chemical is distributed evenly throughout the total diet, a level of 0.5 ppb of the chemical in the diet will correspond to 1.5 µg/person/day (0.025 µg/kg bw/day) and a lifetime cancer risk of less than $10^{-6}$ for most carcinogens. Five classes of chemicals were identified where a dietary exposure of 0.15 µg/person/day, which is 10-fold below the ToR figure, was of concern. Three of these groups of substances are genotoxic (aflatoxin-like, azoxy- and *N*-nitroso-compounds), while two groups were non-genotoxic (2,3,7,8-dibenzo-*p*-dioxin (TCDD) and its analogues, and steroids). The ILSI Work Group in 2003 concluded that compounds with these structural alerts for high carcinogenic potency require compound-specific toxicity data and should be excluded from any TTC approach (Kroes *et al.* 2004).

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 in oral toxicity tests. It included the chemical structures and the distribution of No Observed Effect Levels (NOEL) for chronic, subchronic, and reproductive toxicity after oral administration. The substances were grouped into three general classes (class I, II, and III), based on the chemical structure using the decision tree of Cramer *et al*. (1978). The reference database contained 137, 28 and 448 chemicals in class I, II and III, respectively. Carcinogenicity and mutagenicity were not considered.

**Class I**: Substances of simple chemical structure and efficient modes of metabolism that would suggest a low order of oral toxicity (e.g. L-glutamic acid, mannitol or propylene glycol).

**Class II**: Substances that are in a structural class in which there is less knowledge of the metabolism, pharmacology and toxicology, but for which there is no clear indication of toxicity (e.g. β-carotene, diallyl phthalate or maltol). Most substances in Class II belong to either of two categories; one includes substances with functional groups that are similar to, but somewhat more reactive than functional groups in Class I (e.g. allyl and alkyne); the other includes substances with more complex structures than substances in Class I, but that are common components of food.

**Class III**: Substances of a chemical structure that permit no strong initial presumption of safety, or that may even suggest significant toxicity (e.g. acetonitrile, 2,4-dinitrotoluene, chlorobenzene or p-aminophenol).

Human exposure thresholds of 1800, 540, and 90 µg/person/day (corresponding to 30, 9, and 1.5 µg/kg bw/d) were proposed for class I, II and III, respectively, using the 5th percentile of the lowest NOEL for each group of chemicals, a body weight of 60 kg, and a safety factor of 100 (Munro *et al*., 1996).

The ILSI workgroup in 2003 concluded that neurotoxicants, immunotoxicants, and teratogens would also be covered by the structure-based tiered TTC approach using the human exposure threshold of 1800, 540, and 90 µg/person/day for Cramer class I, II, and III respectively. For organophosphates, a human exposure threshold of 18 µg/person/day was derived (Kroes *et al.*, 2004). The TTC approach was considered not to be applicable to the following chemical groups/endpoints (Kroes *et al*, 2004; Barlow, 2005):

- **heavy metals** and **polyhalogenated dibenzo-*p*-dioxins**, **polyhalogenated dibenzofurans** and **polyhalogenated biphenyls**, or any other compound known to **accumulate** in the body, e.g. ochratoxin A, are excluded from the TTC approach, because the safety factors used may not be high enough to account for differences between species in their elimination from the body, or they were not included in the original databases used to develop the TTC principle, or toxicological data sufficient to perform a full chemical-specific evaluation is available
- **endocrine disrupting chemicals**, including **steroids,** should at present not be evaluated using the TTC principle, due to little and inconsistent data at lower doses
- **high molecular weight chemicals**, such as **polymers**, are excluded because they were not included in the databases used to develop TTC
- **proteins** are excluded from the TTC approach because of potential for allergenicity or other biological activities, and because they were not included in the original database used to develop the TTC principle.
- **allergy**, **hypersensitivity** and **intolerance** should at present not be evaluated using the TTC principle, due to too uncertain dose-response data, whereas other **immunotoxic effects** are included

Bitsch *et al*. (2006) have later published a database called RepDose consisting of chronic, subchronic and subacute toxicity data from studies after oral and inhalation exposure of 364 industrial chemicals. This database has recently been extended to include 578 chemical (Escher *et al*., 2008). About 100 chemicals are present in both the Munro and the RepDose databases. The RepDose database contains N(L)OEL from oral studies for 543 chemicals and N(L)OEL from inhalation studies for 255 chemicals.
Overall, very similar results were obtained for RepDose and the Munro database. For the oral route in the RepDose database LOELs and probably also NOELs (limited data) distributions are shifted to slightly lower values in RepDose compared to Munro. Accordingly, also mean and median values were lower for RepDose. The number of Cramer class II chemicals is very small in both databases, about 20 chemicals (ca 4% of the total number of chemicals in the databases). Within the RepDose database and in the Munro

database a major overlap of NOELs and LOELs between Cramer Class I, II and III was demonstrated. The authors pointed out that further refinement is needed to achieve a better separation of the classes.

## 3.4. Use of TTC in risk assessment

### 3.4.1 General considerations

In order to apply the TTC concept in risk assessment, information on human exposure (consumers, workers, general population exposed via environment) is of crucial importance. Thus, it is important to ensure that exposure estimates are as complete and accurate as possible, or that they are built on adequate conservatism to account for possible underestimates.

Humans are exposed to chemicals via ingestion, inhalation or dermal uptake, and it is the dose at 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. For all exposure routes, usually 100% absorption is assumed, unless chemical specific data indicating less absorption is available.

For a given substance, it is important to identify all exposure pathways to estimate the total exposure. For example, a substance present in a cosmetic product may also be used in a food package or in a building material. Moreover, while cosmetic products are mostly applied on the skin, ingestion of products applied on the lips or inhalation of a substance released from products may cause substantial exposure. Ingestion of indoor dust can also lead to exposure to chemicals, especially for children. For the latter group a major exposure pathway may also be sucking and chewing on articles containing the substance under consideration.

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. To extend the TTC approach to non-oral exposures, appropriate methodologies need to be developed to allow route-to-route extrapolation. It is also necessary to develop methodology to assess combined multi-route or multi-pathway exposures. Such methodology is not yet available. Advances in exposure modelling should also cover the need for assessments of such aggregate exposures. Combined exposures in terms of exposure to multiple chemicals with the same mode of action should be given attention. Chemicals which are assumed to accumulate in the body should *a priori* be excluded from the TTC approach.
Since particular groups in the population may use different amounts of specific foods and consumer products, exposure data may need to be sufficiently detailed to enable these groups to be examined separately, for example by age, gender or ethnicity.

Some aspects of current approaches for exposure assessment are briefly described in Annex I.

### 3.4.2 Exposure estimations

The assessment of exposure should be carried out in the most appropriate way in order to provide sound exposure estimates that are relevant to the exposed population and the particular uses of the chemical. If the substance in question is used uniquely for a specific purpose, e.g. in a particular food or cosmetic product, the exposure related to that purpose should be assessed. In case of exposure from various uses, aggregate exposure (multi-route/multi-pathway and/or several sources) has to be taken into account.

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.

**Food**

In the case of flavouring substances, the JECFA uses the Maximised Survey-derived Daily Intake (MSDI) method (also called *per capita times 10* method), which is derived from the annual production volume of flavourings as reported for USA (data from US National Academy of Science/National Research Council), Europe (data from International Organization of the Flavour Industry (IOFI)), and more recently from Japan, respectively. The estimates are based on the assumption that the surveys accounted for only 60% or 80% of the production in Europe or USA, respectively and that the entire amount produced was consumed by only 10% of the population. MSDI-based dietary exposure estimations are very crude, and the production data from Europe is old. New data for estimation of exposure is needed.

EFSA's former Scientific Panel on Food Additives, Flavouring Agents, Production Aids and Food Contact Materials (AFC Panel), in addition to the MSDI method, also performed exposure estimates using a modified theoretical anticipated maximum daily intake (mTAMDI) approach. Although both MSDI and mTAMDI are used in the opinions adopted by EFSA, the final evaluations are based on the MSDI method. However, if a calculated mTAMDI for a flavouring substance exceeds the relevant threshold for its structural class, more reliable exposure data are requested by which the substance will be re-evaluated (EFSA, 2004).

**Cosmetics**

In the case of cosmetic products which comprise a wide range of product types, a variety of exposure scenarios exist, e.g.:

- application in diluted form and rapidly washed off, e.g. soaps
- application over a large surface, skin contact for several hours, e.g. body lotions
- contact with the conjunctiva or mucosa, e.g. eye shadow, oral care products
- contact for prolonged time spans, used only periodically, e.g. sun screens
- products undergoing oxidative 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 secondary exposure by routes other than those resulting from direct application needs also to be considered (e.g. inhalation of spray products, ingestion of lip products). Finally, the usage pattern of cosmetic products may depend on some factors that will vary over time, such as age group, seasonal variations, local habits, fashion, disposable income, product innovation, etc.

For many years, SCCNFP/SCCP Notes of Guidance[1] have displayed the same set of existing cosmetic exposure data provided by the European Cosmetic Toiletry and Perfumery Association (COLIPA). Upon repeated request, more recent and robust data became available in 2005 (CREMe, 2005) for 6 product types (body lotion, deodorant, facial moisturizer, shampoo, lipstick and toothpaste), but for other product types such data does not exist.

Some cosmetic ingredients are used in a number of cosmetic products that could be applied by the same consumer. Therefore, the SCCNFP calculated a global daily exposure value for all cosmetic products that one person may daily apply on the skin. In a worst-case scenario, considering the consumer would use a set of cosmetic products containing the same preservative, the SCCNFP-value of 17.79 g/day is used in the calculation of the Systemic Exposure Dose (SED).

[1] The SCCP Notes Of Guidance For The Testing Of Cosmetic Ingredients And Their Safety Evaluation (6th Revision) http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_s_04.pdf

### Other consumer products

In contrast to the food and cosmetic areas, where at least some exposure information is available, the exposure information with respect to other consumer products such as toys and textiles is very poor. When considering exposure to consumer products in general, information is needed for the following steps: use frequency and amount used, duration of product contact, concentration, emission or leaching of a substance from the product to the skin or air, and subsequently, absorption via the skin, lungs and/or orally (food, drinking water, mouthing).

Information on product characteristics including substance concentrations, but especially on emission or leaching, is very scarce and scattered. For some product types, information about use frequency and amount can be found e.g. in HERA publications[1] or the Technical Guidance Document (TGD) for New and Existing Substances[2]. The Joint Research Centre (JRC) in Ispra has compiled information from the open literature and in-house industry experiments in a database, called the EISChemRisks database[3]. Assumptions about product use and other exposure factors needed in risk assessments are made searchable. The EISChemRisk database also contains some information about leaching and emission of chemicals from consumer products, but only to a limited extent. To assess emission or leaching from preparations or articles, specific experiments should be performed, or the emission/leaching should be estimated using an exposure model.

RIVM has developed an exposure model to assess emission from consumer products (mainly preparations) and calculates human exposure via the dermal, oral and inhalation route. The model includes a database, in which for a large number of consumer products (cleaning products, disinfectants, do-it-yourself products, cosmetics, pest control products) exposure scenarios are proposed, including an exposure model and the associated exposure parameters. All the parameters are justified in so-called factsheets[4].

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, information on exposure from such products is scarce.

### Industrial chemicals

For industrial chemicals the predominant exposure to workers and consumers is via inhalation or by skin contact. Workplace exposure is often rather high compared to contaminants in food and the applicability of the TTC concept is questionable (e.g. low level exposure not anticipated). However, experiences from the EU Risk Assessment Programme for Existing Substances show that it is very difficult to get sufficient information on the different uses and related exposure to make accurate exposure estimates. For substances for which only limited (or no) toxicological data is available, it is rather unlikely that high quality exposure data exists. Furthermore, in relation to industrial chemicals many different and changing uses of a substance make it very difficult to obtain a robust overall exposure estimate for the substance.

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

[2] http://ecb.jrc.ec.europa.eu/TGD/

[3] http://web.jrc.ec.europa.eu/eis%2Dchemrisks/action.cfm

[4] http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp

## 3.5. Current applications of the TTC approach

### 3.5.1 Food

#### *3.5.1.1 Food contact materials*

The US FDA Threshold of Regulation (ToR) for substances in food packaging was the first instance where a TTC-like approach was introduced by a regulatory body (US FDA 1995, for details see chapter 3.2).

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 0.5 ppb. The request should include a detailed discussion of how the dietary concentration was estimated as well as existing toxicological information on the substance and its impurities to determine whether a carcinogenicity study has been 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 currently not used in the approval process of food contact materials. In 1996, the European Commission requested that the former Scientific Committee on Food (SCF) provide an opinion on the scientific basis of the ToR concept. The Committee concluded that the ToR approach provided "reasonable assurance that no adverse effects would occur in man". However, further data would be needed for endpoints of concern such as neurotoxicity, developmental toxicity, immunotoxicity, and endocrine-active compounds (SCF 1996).

Although the TTC concept is not currently used, the European Food Safety Authority's Panel dealing with food contact materials (formerly the AFC Panel, now the Panel on food contact materials, enzymes, flavourings and processing aids (CEF)) applies a tiered approach to safety testing requirements that was first proposed and used by the SCF in 1990 and subsequently updated (Barlow, 1994; SCF, 1992, 2001). This tiered approach has some similarities with the philosophy of the TTC approach. For example, in the case of substances for which based on migration data the content in food is assumed not to 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 highest dietary exposures that may be encountered.

#### *3.5.1.2 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 for evaluation was discussed in a JECFA meeting in 1995 based on a paper prepared by Dr Munro. The procedure was endorsed with modifications in 1996 (JECFA 1996). It was based on empirical cumulative distributions of NOELS of compounds in the reference database grouped into the structural classes I, II and III according to Cramer *et al.* (1978).

Exposure estimation is an important part of the safety evaluation of flavouring substances. So far the JECFA has used the Maximised Survey-derived Daily Intake (MSDI) as reported for USA, Europe and Japan.

The EFSA shares the burden with the JECFA on the evaluation of flavouring substances. The former AFC Panel and now the CEF Panel also uses the TTC approach for the assessment of flavouring substances in food (Larsen 2006). The procedure was already adopted by the Scientific Committee on Food (SCF) in 1999. The goal is to achieve an EU positive list of chemically defined flavouring substances. The procedure for the evaluation of flavouring substances is shown in fig 2.

The EU-Flavis Database as defined in Commission Regulation EC No 1565/2000 [1] is designed for automated transfer of data from existing databases to the Flavis database. This database contains 2800 flavouring substances claimed by industry to currently exist or be added to food and beverage in Europe and US. The majority of these compounds is structurally well characterized. In addition, about 400 of the 2800 are natural flavour complexes that already have been evaluated and are in use.

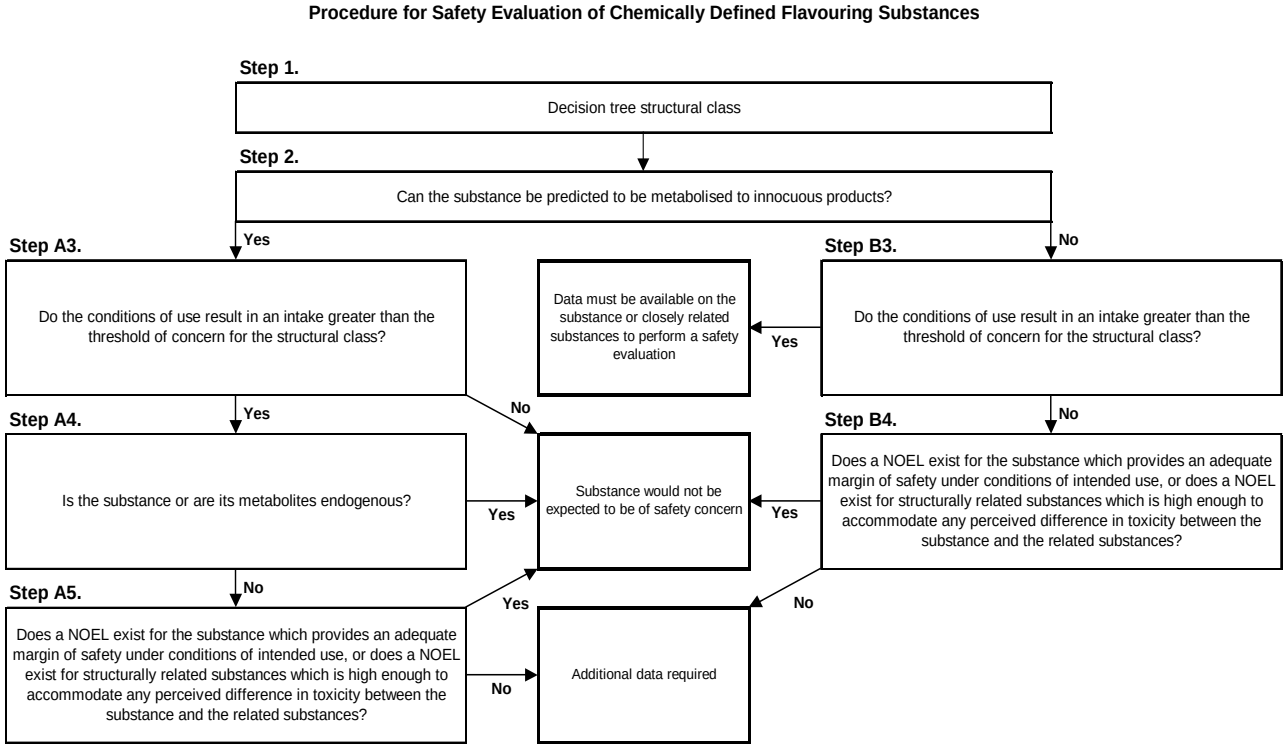


***Figure 2:*** *Procedure for safety evaluation of chemically defined flavouring substances*

According to SCF (1999), flavouring substances should be examined for structural alerts for genotoxicity and for test results that indicate that a substance is likely to be genotoxic. In case of evidence for genotoxicity of a substance, the procedure should not be used. As mentioned above, the AFC/CEF Panel also performs exposure estimates using the mTAMDI approach in addition to the MSDI.

In conclusion, the experience with the TTC concept for flavouring substances shows that the TTC principle can be used for a large number of chemical substances. The TTC methodology is used slightly differently by the EFSA and the JECFA.

It should be noted that many flavouring substances are also used for other purposes, e.g. as fragrance materials or preservatives. Such exposures are not considered in the evaluation of flavourings.

[1] Commission Regulation (EC) No 1565/2000 of 18 July 2000 laying down the measures necessary for the adoption of an evaluation programme in application of Regulation (EC) No 2232/96 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:180:0008:0016:EN:PDF

### 3.5.2 Pharmaceuticals

#### 3.5.2.1 Genotoxic impurities in pharmaceuticals

The European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP) has released a "Guideline on the Limits of Genotoxic Impurities" which came into effect on 1 January 2007 (EMEA, 2006). The guideline recommends the application of a TTC value for defining acceptable limits of genotoxic impurities present in drug substances.

The synthesis of pharmaceuticals frequently involves the use of reactive starting materials and intermediates, which may be present as impurities in the final drug substance or drug product. Due to their reactive nature such impurities may inherently possess potential genotoxic properties. It has been estimated that 20 – 25% of all intermediates used in the synthetic processes of active pharmaceutical ingredients would prove mutagenic in an Ames assay, since the reactivity that allows intermediates to be synthetically useful also renders them DNA-reactive (Delaney, 2007).

Regulations on how to control impurities in a drug substance are addressed in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Quality Guideline Q3A (ICH, 2002). Since this document does not specifically provide instructions for impurities with a genotoxic potential the CHMP has released in 2006 a "Guideline on the Limits of Genotoxic Impurities". More recently a Question and Answer (Q&A) document was published at the EMEA website (EMEA, 2007) which is intended to serve as a supplement of the guideline and addresses several aspects in relation to the practical implementation of the guideline's recommendations.

Genotoxicity is a very broad term comprising a variety of direct and indirect mechanisms related to DNA damage. For the purpose of determining acceptable limits for genotoxic impurities the guideline discriminates between genotoxic compounds that induce mutations by direct interaction with the DNA (DNA-reactive genotoxins) and those which operate via indirect mechanisms. Only for the former group a linear no-threshold model of the relationship between exposure and harm is applied. For chemicals (and their metabolites) which do not directly react with DNA but have initially non-DNA target such as mitotic spindle poisons, topoisomerase inhibitors or DNA synthesis inhibitors existence of a threshold can be assumed. Impurities which fall into this category would be regulated according to procedures outlined in the ICH Quality Guideline Q3C for Class 2 solvents (ICH, 1997). This method calculates a Permitted Daily Exposure (PDE) which is derived from the No-Observed-Effect-Level in the most relevant animal study with the use of uncertainty factors to relate the data to humans. It can be expected, however, that only in very rare cases mechanistic data may be available with which to decide whether a threshold mechanism is applicable to a genotoxic impurity.

For genotoxic compounds without sufficient evidence for a threshold-related mechanism the CHMP Guideline proposes the application of a TTC to determine acceptable impurity levels and reference is made to the paper of Kroes *et al.* (2004) where a TTC of 0.15 µg/day is proposed for those substances with structural alerts for genotoxicity corresponding to a $10^{-6}$ lifetime risk of cancer. Since it is generally agreed that existing benefits of pharmaceuticals would justify a lifetime risk of cancer of $10^{-5}$, a ten-fold higher TTC level of 1.5 µg/day was agreed as 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.

Dependent on aspects of the clinical use of a drug product there may also be circumstances to accept higher limits than 1.5 µg/day, e.g. for treatment of a life-threatening condition, or when life expectancy of the patient population is limited, e.g. less than 5 years. Also when the impurity is a known substance and human exposure will be much greater from other sources, e.g. food, it might be unproportional to limit the impurity at the TTC level.

As the TTC is calculated for a lifetime exposure, higher levels may be also 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 often limited understanding in process chemistry in early phases of development. Proposals for allowable daily intake for genotoxic impurities during clinical development according to this concept are provided in the Q&A document and are 5, 10, 20, and 60 µg/day for a duration 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 acceptable.

In agreement with the paper of Kroes *et al.* (2004) some structural groups such as aflatoxin-like, azoxy-, and N-nitroso-compounds are excluded from the TTC approach based on their extremely high potency, i.e. they induce tumours in rodent long-term studies in the ng/kg bw/day range. Risk assessment of genotoxic impurities belonging to such groups would require compound-specific toxicity data.

The guideline focuses on orally applied drugs when recommending the TTC as acceptable limit and does not provide any specific recommendations for other routes of drug administration.

The guideline 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 means, that every effort should be made to prevent the formation of such impurities during synthesis and, if not possible, to reduce them through technical efforts, e.g. purification steps. According to this decision tree approach the ALARP principles precede the recommended application of a TTC and it seems that ALARP should be applied even in cases where the concentration of a genotoxic impurity does not exceed the TTC level. This issue has been clarified in the Q&A document which clearly states that if the level of a mutagenic impurity is below the threshold of toxicological concern (equivalent to a clinical dose < 1.5 µg/day) it is not necessary to apply ALARP considerations (EMEA, 2007), i.e. a genotoxic impurity at TTC level would be acceptable even if its formation could be simply avoided by using a known and established alternative route of synthesis.

What data are needed to apply TTC to genotoxic impurities in pharmaceuticals?

Usually impurities identified in pharmaceuticals are not subject to direct toxicological testing with the isolated impurity. According to the recommendations of the ICH Q3A guideline an impurity would be 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 drug substance with an impurity at a level of 0.05% 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 since genotoxicity testing of a drug substance is very unlikely to detect even potent genotoxic impurities at levels usually present.

As an alternative approach for providing more meaningful information on potential genotoxicity of impurities the guideline recommends a scientific expert review of the synthetic route and the chemical reactions and conditions involved to identify compounds (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 based on a well-performed assessment (e.g. through application of commonly used SAR assessment software including DEREK and MCASE) will be sufficient to conclude that the impurity is of no concern with respect to genotoxicity and no further 'qualification' studies or justification will be required (EMEA, 2007).

Substances showing alerting structures which are not shared with the active substance would be candidates for genotoxicity testing, preferably in a bacterial gene mutation test, and if found positive would need to be limited to the TTC level as specified in the guideline. It is also acceptable to control impurities with a structural alert by assuming they will be positive (without resorting to any testing) and ensuring the level remains below the appropriate TTC value. A negative bacterial gene mutation test will overrule a structural alert and no further genotoxicity studies would be required. The successful applicability of this structure-based assessment approach in industry practice has been demonstrated for a range of structurally alerting compounds that are used as starting materials or are present as intermediates in the synthetic process of pharmaceuticals (Dobo *et al*, 2006).

The TTC concept should not be applied to genotoxic impurities for which adequate carcinogenicity data from rodent long-term studies are available and allow for a compound-specific risk assessment.

In conclusion, regulatory experiences with the TTC since coming into force of the CHMP guideline in January 2007 show that this concept can be used as a pragmatic and very helpful tool for the regulation of genotoxic impurities in new drug substances. It is noteworthy that also the US FDA's Center for Drug Evaluation and Research is considering the use of a TTC-based limit for regulation of genotoxic and carcinogenic impurities in drug substances (McGovern and Jacobson-Kram, 2006).

#### 3.5.2.2 Genotoxic constituents of herbal medicinal products / preparations

Recently, a guideline on the assessment of genotoxicity of herbal medicinal products/ preparations was published by the EMEA Committee on Herbal Medicinal Products (EMEA, 2008a). This guideline will come into force on 1 December 2008 and allows using a TTC approach for the risk assessment of herbal preparations containing an identifiable genotoxic compound.

If an established risk assessment method cannot be applied because of the lack of pertinent data, the HMPC suggests using the TTC concept as an option for the assessment of genotoxic constituents in herbal preparations. The HMPC proposes to use the same TTC approach as currently described in the CHMP guideline on genotoxic impurities in medicinal products (EMEA, 2006), though it is specifically noted by the HMPC that genotoxic constituents in herbal preparations are not considered to be impurities. With the approach described in the CHMP guideline permitted levels of a genotoxic compound in herbal preparations could be calculated based on a TTC value of 1.5 µg/day – the amount considered to be associated with an acceptable risk for most pharmaceuticals (excess cancer risk of <1 in 100,000 over a lifetime), and taking into account the expected daily dose. 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.

It should be noted that the TTC concept as currently applied is not validated for mixtures and preparations with often variable composition and for which a complete chemical characterisation is often not available. Plant extracts were not part of the databases used in the derivation of the TTC concept. However, because of limited experience in the risk assessment of genotoxicity of herbal medicinal products a "lot of latitude in argumentation and justification has been allowed to the applicant" by the HMPC (EMEA, 2008b).

### 3.5.3 Industrial chemicals

The REACH Regulation 1907/2006/EC[1] provides in Annex XI ("Substance-tailored exposure-driven testing") the possibility to waive testing of a substance based on the scenarios developed in the exposure assessment. Adequate justification and documentation shall be provided. However, there is no reference to any thresholds. The Commission will amend the legislation by 1 December 2008 to set the criteria defining what constitutes adequate justification.

In the guidance document for the implementation of REACH (ECHA, 2008) information on criteria for waiving certain studies is provided. According to Chapter R.7C ("Endpoint Specific Guidance"), Appendix R.7-1 "Threshold of Toxicological Concern (TTC)", the use of the TTC approach in relation to REACH should be agreed upon by the relevant regulatory body before use, and it should be clearly indicated for which endpoints, routes and population they apply.
The document points out limitations of the approach with respect to applicability of database, excluded classes of chemicals and extrapolation to other exposure routes than oral exposure.

With regard to exposure, the guidance document states specifically that, for human health aspects, the TTC approach is only applicable in case there is detailed information available on all anticipated uses and use scenarios for which the risk assessment is provided. Based on the experience of the EU Risk Assessment Programme for Existing Substances, robust exposure estimates will require a significant effort, even in cases where the uses were well characterized. In case of a multitude of (dispersive) uses and applications, it may not be feasible to generate overall exposure estimate with detail and precision necessary for use in a risk assessment relying on the thresholds based on the TTC concept. Therefore, a TTC will in practice only be applicable in those cases where there are only a few number of exposure scenarios that allow good characterization. Furthermore, the use of the TTC approach does not provide information on classification and labelling of a chemical, or on its potency for a specific effect.

The guidance document considers that it is feasible that within REACH the TTC concept may be of use for the chemical safety assessment at tonnage levels triggering 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 that case a TTC value could be helpful to assess the significance of the exposure
b) certain tests (eg. repeated dose and/or reproductive toxicity) can be waived when it can be demonstrated that there is no significant human exposure. Also in this case a TTC value could be helpful to assess the significance of the exposure

The guidance concludes 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 TTC concept is considered a helpful tool under REACH, especially in the case of waiving certain studies.

It should be noted that when using the TTC approach under REACH no information on classification and labelling of a chemical or on its potency for a certain effect is provided.

[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

## 3.6. Potential applications of the TTC approach

### 3.6.1 Food

#### 3.6.1.1 Food additives

Food additives are substances 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 directive[1] and three specific directives on colours[2], sweeteners[3] and the remaining food additives[4]. Prior to their authorization, food additives were evaluated for their safety by the SCF and from 2003 by EFSA.

Guidance on submissions for food additive evaluations covering core studies and other additional tests has been given by the EC Scientific Committee on Food (SCF 2001). The studies required would depend on the chemical structure of the additive, its proposed use and levels of use in food, and whether it is a new additive or a reexamination of an existing additive. According to the regulation only additives that have undergone a full toxicological evaluation are authorized. Therefore, the TTC principle is not considered relevant so far in the risk assessment of the food additives.

However, the ILSI Expert Group which evaluated the TTC concept for chemical substances present in the diet recommended that the TTC principle can be used for substances that are present in food in low concentrations, which lack toxicity data, but for which exposure assessment can provide reliable exposure estimates (Kroes *et al*., 2004).

The EFSA TTC Working Group was adopted at the 31st plenary meeting of the EFSA Scientific Committee[5]. The draft mandate for TTC concept refers to the establishment of a generic human exposure threshold value below which there would be no appreciable risk to human health. This concept has been used by the EFSA's former ACP Panel for the safety assessment of food flavourings. The purpose of this new mandate is to look at a possible broader applicability of the TTC concept in other areas of risk assessment performed by EFSA Scientific Panels.

In principle, the TTC principle can be used by JECFA to evaluate *indirect* (contaminants in small concentration present in food additives) food additives (JECFA 1995, JECFA 1996). However, so far no examples have been described in the literature.

In conclusion, the TTC approach may possibly be used if an unsuspected chemical or impurity be detected in a food additive. In future other areas of risk assessment may be included.

[1] Council Directive 89/107/EEC of 21 December 1988 on the approximation of the laws of the Member States concerning food additives authorized for use in foodstuffs intended for human consumption http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31989L0107:EN:HTML

[2] European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31994L0036:EN:HTML

[3] European Parliament and Council Directive 94/35/EC of 30 June 1994 on sweeteners for use in foodstuffs http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31994L0035:EN:HTML

[4] European Parliament and Council Directive No 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0002:EN:HTML

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

#### 3.6.1.2 Residues from Veterinary medicinal products

Residues of veterinary medicinal product in food commodities are assessed in accordance with Commission Regulation (EEC) 2377/901. A risk assessment is carried out using a "classical" approach based on a No Observed Effect Level (NOEL) which is converted into an ADI (Acceptable Daily Intake) for humans. The ADI is the reference value for the exposure assessment. Failure to identify a clear NOEL and ADI may mean that the assessment cannot be continued, even if residue concentrations are expected to be negligible. For certain substances with a relatively low risk profile, TTC-like consideration have been taken into account on a case by case basis, but the TTC, as a scientific concept, has not been applied yet. The Scientific Committee of Veterinary Medicinal Products (CVMP) has, however, already identified some scenarios where the TTC concept may be appropriate.

An area of potential use is the assessment of low level dietary exposure scenarios, in particular those resulting from residues in food producing animals from use of substances of botanical and homeopathic origin. In the past, CVMP has applied an "exposure-driven" hazard characterization; a pragmatic TTC-like approach based on the assumption that exposure to residues of individual constituents would be too low to present a significant risk to consumers. Based on this, homeopathic preparations of D4 (dilution 1:10000) and higher got an entry in CR (EEC) 2377/90 Annex II ("List of substances not subject to maximum residue levels (MRL)") without further in-depth toxicological evaluation of residues.

The TTC may also be of benefit in the evaluation of potential health risks from certain impurities in pharmaceutical formulations. For human medicinal products a TTC has been adopted for genotoxic impurities. There is ongoing discussion to introduce such a limit for veterinary medicinal products.

In addition, there is growing international interest in alternative concepts to address the complex question of risk assessment and management of residues of substances termed "substances without ADI/MRL" in imported food. The absence of risk based guidance values for this relatively large category of compounds has been shown to create significant trade problems since some member countries may ban, and others may tolerate a certain level of detectable residue. Use of the TTC as science based reference point of action is currently discussed within the EU Commission (e.g., revision of CR (EEC) Nr. 2377/90) but also at an international level within Committees of the Codex Alimentarius[2].

The CVMP noted in its discussions, however, that TTCs do not exist for all relevant toxicological endpoints and that several TTCs are still at an exploratory stage requiring further in-depth examination. In addition, it was emphasized that in the further development of the TTC concept adequate attention needs to be given to those aspects that are specific to active compounds as those used in veterinary medicines. In this area endpoints for pharmacological and microbiological effects play a quantitative important role in the evaluation of exposure scenarios. It appears that none of these endpoints currently fit into the effect categories for which TTCs have already been elaborated.

The TTC concept is currently not used in the assessment of consumer safety of residues of veterinary medicinal products in food. The TTC might offer an appropriate option in the assessment of substances that have no ADI/MRL and certain impurities/trace level residue concentrations. It should be noted that endpoints like pharmacological or microbiological effects are not addressed in the currently available databases.

[1] Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31990R2377:EN:HTML

[2] 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

#### 3.6.1.3 Drinking water contaminants and materials intended for contact with drinking water

According to the EU Drinking Water directive[1], Member States shall lay down the parametric values corresponding at least to the values set out in the Directive. Where parameters are not set out in the Directive limit values must be laid down by the Member States if necessary to protect health.

A number of Member States operate very different national acceptance schemes for products and/or materials used in contact with drinking water. Development of a common system for approval of materials intended for use in contact with drinking water within the EU, called the European Acceptance Scheme (EAS), started in 1999. This work is based on Council Directive for drinking water (98/83/EC) and the directive on construction products[2] (89/106/EC). The Commission intends to revise the Drinking Water directive in 2008 and in the Directive refer to other relevant product directives.
Within EAS, a list for plastic food contact materials developed by SCF/EFSA, has been used as a starting point for making a positive list of plastic materials that can be used in contact with drinking water.

For pesticide metabolites in groundwater, the former EC Scientific Committee on Plants proposed a TTC approach in its opinion regarding the draft guidance document on relevant metabolites[3]. The concentration of relevant metabolites (i.e. for which there is reason to assume that they have comparable intrinsic properties as the active substance in terms of its biological target activity, or that it has certain toxicological properties that are considered severe and unacceptable) must not exceed 0.1 µg/l. For metabolites considered to be not relevant, a threshold of concern should be followed. If the structure is unknown, the Committee has proposed a TTC value of 1.5 µg/person/day (0.02 µg/kg bw/day) for an adult person with a body weight of 75 kg. If a consumption of 2 litres of water per day is assumed, the acceptable upper limit for the concentration of the metabolite is 0.75 µg/l.

The EC Scientific Committee on Plants has concluded that TTC is a valid tool to be used in the process of risk assessment of metabolites and, under the proposed conditions of use, can provide an adequate margin of protection and a reliable evaluation of the need for a more complete risk assessment of metabolites of plant protection products.

### 3.6.2 Cosmetic products

According to the Cosmetics Directive[4] (76/768/EEC as amended), a cosmetic product is defined as *any substance or preparation intended to be placed in contact with the various parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition*

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

[1] Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:330:0032:0054:EN:PDF

[2] Council Directive 89/106/EEC of 21 December 1988 on the approximation of laws, regulations and administrative provisions of the Member States relating to construction products http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31989L0106:EN:HTML

[3] SANCO/221/2000-rev. 7b of 3 July 2002. 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

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

chemically well-defined single substances with a molecular and structural formula or complex preparations, requiring a clear definition and often corresponding to a mixture of substances of unknown or variable composition and biological nature (76/768/EEC as amended, SCCP Notes of Guidance[1])

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 SCCP 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 SCCP, some advice is also given in the Notes of Guidance including mineral, animal, botanical and biotechnological ingredients. Here, too, the requirement is expressed for external contamination data and toxic components. As the Notes of Guidance only give advice and are no legislation, the content of dossiers submitted to the SCCP and even more those treated by individual safety assessors is quite heterogeneous with respect to the degree to which impurities are identified and quantified.

Human exposure to cosmetic products is primarily via the topical route, although oral and inhalation exposures also occurs.

**COLIPA proposal for 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 COLIPA and reported by Kroes *et al*. (2007).

The Expert Group (Kroes *et al.*, 2007) recognized that the TTC approach can presently not be used to evaluate local effects. They considered application to such effects potentially possible; however, the databases on local effects, such as sensitization or irritation, and on substances producing these effects, are currently too limited to be used as a basis for the derivation of valid TTC values for local endpoints.

Route of exposure and database

Both comparability of the chemical structures of cosmetic ingredients and chemicals in the currently used database, and the possible impact of the route of administration are of great 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 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 and liver, the Expert Group did not attempt to review the different pathways of metabolism, but explored the basic principles in the context of applying the TTC values to cosmetic ingredients. The Group concentrated on the influence of route-dependent

[1] The SCCP Notes Of Guidance For The Testing Of Cosmetic Ingredients And Their Safety Evaluation (6th Revision) http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_s_04.pdf

differences in metabolism on systemic exposure to the chemical and its metabolites, because systemic effects would be relevant to both dermal and oral administration.

The Expert Group noted that topical application and oral ingestion can result in different proportions of the applied dose entering the body and that difference in bioavailability may arise from:

(i) More extensive metabolism in the intestine and liver, compared with the skin, prior to reaching the general circulation, or

(ii) Slower and incomplete transfer across the skin compared with the intestinal wall, due to the physicochemical properties of the compound.

Moreover, the slower absorption after topical application results in a different shape of the plasma concentration–time curve even if the same total fraction of the dose is absorbed.

It was concluded that the TTC values for Cramer class III compounds would be likely to overestimate the potential toxicity of the same compounds following topical exposure, even if 100% of the topical dose entered the general 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 TTC concept in the safety evaluation of cosmetic ingredients and cosmetic products requires an estimate of the absorption across the skin. There are major differences in the rates and extents of transfer across the skin compared with those across the gastrointestinal tract. For application of the TTC approach to cosmetic ingredients it was argued that exposure is determined by molecular characteristics, such as lipid solubility and molecular weight, which predict the rate and extent of transfer across the skin and thus the extent of systemic exposure.

The Expert Group proposed that in the absence of experimental data, the most appropriate method to estimate the systemic exposure over 24 h to a cosmetic ingredient, following a single application, should be based on calculation of Jmax (maximum flux) and a default fraction absorbed for non-reactive chemicals with a molecular weight below 1000 Da in the range 10 to 80% depending on Jmax (Kroes et *al*., 2007) should be assigned. The absorption of chemicals with a molecular weight above 1000 Da should be considered negligible.

Default adjustment factors for rinse-off cosmetic products

Rinse-off cosmetics are products that remain in contact with human skin only for a limited time (<1 h) and are subsequently washed off. Current EU Guidelines of cosmetic safety evaluation propose default retention factors of 0.01 or 0.1 (1% or 10%) for different rinse-off products (SCCNFP, 2003). The 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.

Default adjustment factors for intermittent use of cosmetic products

Intermittently used cosmetics are products that are used in intervals of > 1 week and include products such as self-tanning agents, depilatories (removers of body hair), hair dyes, permanent hair waiving, hair straightening and bleaching agents. Some cosmetic products, such as hair dyes, produce consumer exposure at intervals of 2–3 (direct hair dyes) to 6–8 (oxidative hair dyes) weeks, respectively. Although the potential exposure per event 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 Expert Group proposed to take into account intermittent use (time interval >7days) of relevant cosmetic end products by the use of adjustment factors.

The 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. The Expert Group 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 (Kroes *et al.*, 2007).

Procedure to apply the TTC approach to the safety evaluation of cosmetic ingredients
The Group concluded (Kroes *et al*., 2007) that it is scientifically justified 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 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.

This proposal will be discussed in section 3.7.2.

### 3.6.3 Allergic contact dermatitis

In the present form, the TTC concept refers to systemic toxicity, in which allergic contact dermatitis is not considered as an endpoint. Recently a proposal was published to use the TTC approach for dermal sensitisation as well (Safford, 2008). A probabilistic analysis of available sensitisation data was performed using the ELINCS data set and a compilation of Local Lymph Node Assay (LLNA) data. Based on this analysis a Dermal Sensitisation Threshold (DST) was derived.

The approach further built 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 (NESILs) were derived and these are subsequently converted to an acceptable exposure level using a number of assessment factors (see publication of Api et al. 2007).

The DST was then determined for each product type as a 95$^{th}$ percentile in the distribution. This implies that using this DST there is a 5% probability that an untested chemical would give an undue risk. The author indicates that the choice of the percentile is certainly a matter of risk management and can be debated. He also notes that the DST will be protective for induction, but not for the elicitation of sensitisation.

### 3.6.4 Genotoxic impurities in veterinary medicinal products

For human medicinal products, a TTC has been adopted for genotoxic impurities. There is ongoing discussion to introduce such a limit for veterinary medicinal products as well, not only in relation to animal safety but also as reference point for user safety and possibly consumer safety evaluations. However, these discussions are at a preliminary stage.

### 3.6.5 Medical devices

Medical devices comprise a large variety of products ranging from wound dressings and bandages to catheters and implants, including pacemakers. Medical devices are regulated by the Medical Device Directive[1], the Active Implantable Medical Devices Directive[2], and the

[1] Council Directive 93/42/EEC of 14 June 1993 concerning medical devices
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31993L0042:EN:HTML

[2] Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31990L0385:EN:HTML

*In vitro* Diagnostic Devices Directive[1] (IVDD, Directive 98/79/EEC) and their amendments. Essential Requirements are included in the directives for medical devices to guarantee safe and reliable products on the European market. In order to fulfil these manufacturers can choose to make use of European Standards. A risk management strategy is used according to the standard EN ISO 14971 (2007 in which both risks and benefits for users and patients are considered. For the biological safety evaluation, the EN ISO 10993 series of standards "Biological evaluation of medical devices" (CEN, Brussels, Belgium, ISO, Geneva, Switzerland) has been developed. Both the final product (the medical device itself) and the components of the product may be evaluated. Depending on the type of product and the duration of patient contact a more rigorous safety evaluation may be needed (EN ISO 10993-1:2003).

In the production and processing of the materials into a final product several chemical residues may be present. For the chemicals and possible residues allowable limits can be determined according to EN ISO 10993-17 (2002). Currently, the TTC concept is not used for evaluation of medical devices. However, the TTC concept is attractive for the use in the medical device area for chemical residues of production processes. Within the ISO Technical Committee 194 "Biological Evaluation of Medical Devices" the TTC concept has recently become a subject of discussion for possible application in the medical device area.

### 3.6.6 Consumer products, including Household care products

The General Product Safety Directive (GPSD)[2] is intended to ensure a high level of product safety throughout the EU for consumer products that are not covered by specific sector legislation (e.g. toys, chemicals, cosmetics, machinery). The Directive provides a generic definition of a safe product. Products must comply with this definition. If there are no specific national rules, the safety of a product is assessed in accordance with European standards, Community technical specifications, codes of good practice, the state of the art and the expectations of consumers. In addition, the EU chemical legislation applies. Some substances and preparations are not considered dangerous and circulate freely on the European market without any particular rules. Others are classified as dangerous and can circulate freely only when packaged and labelled in accordance with Directive 67/548/EEC[3] (for dangerous substances) or Directive 1999/45/EC[4] (for dangerous preparations). Also, the Limitations Directive 76/769/EEC[5], in which the use of certain hazardous chemicals is restricted, applies [for details see Annex II].

Currently, for chemicals used in consumer products the TTC concept is not used. This might change in the future according to a possible broader use of the TTC concept within the REACH process (see 3.4.3).

---

[1] Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:331:0001:0037:EN:PDF

[2] Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on general product safety
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:011:0004:0017:EN:PDF

[3] Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31967L0548:EN:HTML

[4] Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1999:200:0001:0068:EN:PDF

[5] Council Directive 76/769/EEC of 27 July 1976 on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31976L0769:EN:HTML

**Household products**

The applicability of the TTC database to ingredients in personal and household care products has been evaluated recently (Blackburn *et al*, 2005). From databases at Proctor and Gamble, repeat dose toxicity data were obtained for 248 substances used in personal care or household care products, but NOAELs could only be identified for 45 of them. Of these, 21 fall into Cramer class I, only 2 in Cramer class II and 21 into Cramer class III. These product chemicals were compared to the substances in the Munro data base and highest and mean NOELs were similar for the two sets, but the lowest NOELs were lower in the Munro base.

It is not possible to extrapolate the results from the Blackburn *et al.* study to other types of consumer products where quite different substances may be used.

### 3.6.7 Air pollutants

For air toxics Drew and Frangos (2007) used the TTC of 0.02 µg/kg bw/day established for carcinogens by FDA 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 an inhalation rate of 20 $m^3$/day the threshold for air toxics becomes 0.03 µg/$m^3$. To validate the CoNTC value it was compared with established air guideline values from reputable sources all over the world. Occupational exposure limits were divided by 42 (24h/8h x 7d/5d x10) where a factor of 10 is used to compensate for a greater sensitivity of the general population as compared to healthy workers. Of 1857 values taken from air guideline from several agencies, only 4 are below the CoNTC.

## 3.7. Discussion of potential applications

### 3.7.1 General aspects

The Threshold of Toxicological Concern (TTC) is a risk assessment tool establishing a human exposure threshold value for chemicals below which there is a very low probability of adverse effects to human health. The concept is based on extrapolation of toxicity data from an available database to a chemical compound for which the chemical structure is known, but no toxicity data is available. The concept has reached regulatory acceptance for the safety evaluation of food constituents present in low concentrations (food contact materials, flavourings) and to define acceptable levels of genotoxic impurities in pharmaceutical for human use.

The application of the TTC approach has recently been discussed in various areas of risk assessment which are of relevance for SCCP, SCHER and SCENIHR.

However, the acceptance of this principle for hazard evaluation and use in risk assessment of a chemical will have to dependent on the quality, quantity, and relevance of the underlying toxicity database, and a reliable estimation of the exposure to the chemical.

According to Kroes *et al*, 2004 and Barlow, 2005, the following chemical groups should be excluded from the general TTC approach

- heavy metals and polyhalogenated dibenzo-*p*-dioxins, polyhalogenated dibenzofurans and polyhalogenated biphenyls, or any other compound known to accumulate in the body
- endocrine disrupting chemicals, including steroids
- high molecular weight chemicals, such as polymers
- organophosphates
- proteins

No database is available that would allow application of TTC to endpoints like allergic reactions, hypersensitivity, intolerance and local effects.

The SCCP/SCHER/SCENIHR Working Group (SC WG) considers that the TTC is also not applicable to

- particulate matters including nano-materials since the knowledge is limited
- the endpoints pharmacological or microbiological effects since no database is available

It should also be noted that when using the TTC approach under REACH no information on classification and labelling of a chemical or on its potency for a certain effects is provided.

Database

At present one carcinogenicity database containing 709 carcinogens (Cheeseman *et al*., 1999) and one based on other systemic toxicological endpoints containing 613 chemicals (Munro *et al.*, 1996) are available. Both are exclusively based on systemic effects after oral exposure. In addition, preliminary information has been presented on a database (RepDose) containing 578 industrial chemicals based on both oral and inhalation exposure (Escher *et al.*, 2008). For acceptance of the TTC for a specific area, it will be necessary to make an evaluation whether the chemical classes relevant for this area are covered by these databases. It is obvious that when there is no database containing certain groups of chemicals or certain endpoints the TTC concept can not be used for these chemicals or endpoints.

For the oral route the RepDose database gives lower values than the Munro database for all 3 Cramer classes. The number of Cramer class II chemicals is very small in both databases, about 20 chemicals (ca 4% of the total number of chemicals in the databases). It was found that all derived inhalation TTCs are lower than those for oral exposure. According to the authors, this might be due to the inclusion of local effects [e.g. irritation] in addition to systemic effect within the RepDose database a major overlap of NOELs and LOELs between Cramer Class I, II and III was demonstrated. A better separation of the Cramer classes is needed.

Exposure

In order to apply the TTC concept in risk assessment, complete and accurate information on human exposure is essential. In the case of pharmaceuticals and food, where TTC is already in use, the available information is good. Much less knowledge 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 via multiple routes (oral exposure, skin contact and/or inhalation) and sources takes place e.g. cleaning products, cosmetics and toys. For many of these product categories, however, exposure data are limited or completely lacking.

### 3.7.2 Cosmetics

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

- to what extent can the available databases be used in the case of cosmetic ingredients considering structural similarities/dissimilarities between cosmetic ingredients and substances in the existing databases?
- What are the differences in metabolism between dermal and per oral routes of application?
- How to address skin contact allergies and other topical effects?
- how should exposure be assessed?
- should intentionally added or formed ingredients in cosmetic products and inadvertent contaminants and impurities be considered differently?

Each the above parameters is analysed and discussed in the following sections.

#### 3.7.2.1 Potential applicability of available data bases to Cosmetic ingredients

In the EU there exists a data base (CosIng[1]) of about 15,000 cosmetic ingredients. In a preliminary search by the SC WG in the CosIng database using CAS numbers (September 2008), 251 chemicals that are also present in the database of Munro *et al.* (1996) were identified (Table 1). Of these, 96 are banned from the use in cosmetic products. Of the remaining 155 cosmetic ingredients, 101, 17 and 37 are in Cramer Classes I, II and III, respectively. These 155 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.

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

| Cramer Class | No. of chemicals | | No. of cosmetic ingredients common to CosIng and Munro database | No. 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 | 37 | 88 |
| **Total** | **613** | **599** | **155** | **96** |

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

In a separate analysis the SC WG compared the 250 chemicals that have been evaluated by SCCNFP/SCCP in the period 1997 – 2007 with the Munro data base. Of the 250 chemicals, only 19 chemicals (7.6%) were found in the Munro database. Eleven of these were classified as Cramer Class I, 1 as Cramer Class II, and 7 as Cramer Class III. With the exception of the group "Other substances" the number of cosmetic ingredients included in the Munro database were rather limited (Table 2). It should also be noted that among the 10 chemicals in the group "Other substances", 6 chemicals are banned in cosmetic products.

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

| Group | No. 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 for which also SCCNFP/SCCP assessment reports are available, NO(A)ELs are available for 13 substances. For these, a comparison can be made between acceptable doses derived from the toxicological data (NO(A)EL) and exposure limits according to the TTC approach (Table 3). For 4 of these ingredients, the

[1] http://ec.europa.eu/enterprise/cosmetics/cosing/

acceptable levels according to TTC are higher than the maximum doses determined by conventional risk assessments.

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

| Group | Name | CAS No. | Cramer class | Acceptable dose µg/kg bw/d | | Ref |
|---|---|---|---|---|---|---|
| | | | | TTC | Risk assessment | |
| Fragrances | Furfural[1] | 98-01-1 | II | 9 | 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 | 30 | 5 | 16,17 |
| | Acetonitrile[5] | 75-05-8 | III | 1.5 | - | 18 |
| | Acrylamide[5,12] | 79-06-1 | III | 1.5 | 0.01[13] | 19 |

*The references are listed at the end of the Opinion
[1] Carcinogen EU category 3
[2] Opinion on sensitisation only
[3] Opinion on photo-toxicity only
[4] Carcinogen EU category 3. Used as a preservative with a maximum concentration of 0.2%.
[5] Banned in cosmetic products
[6] Reprotox EU category 2; R60-61
[7] Reprotox. EU category 2; R61 and category 3; R62. TDI for DBP of 0.01 mg/kg bw/day defined by EFSA
[8] LOAEL
[9] Reprotox. category 2; R61, and category 3; R62
[10] Reprotox EU category 3. R63. Opinion on use as a solvent in nail cosmetics only
[11] Carcinogen EU category 3, mutagen category 3
[12] Carcinogen EU category 2, mutagen category 2, reprotox category 3; R62
[13] Represent a lifetime cancer risk of $10^{-5}$

When comparing the substances used in cosmetics with the chemicals present in the Munro database, it becomes apparent that the database available does only to a limited extent cover the ingredients used in cosmetic products. Cramer classes and NO(A)EL/calculated NOEL of only 155 cosmetic ingredients (belonging to approximately 25 chemical categories based on chemical structure) and of 96 substances banned in cosmetic products are known. This appears to be a very small number compared to the more than 15.000 ingredients that are included in the Inventory of Cosmetic Ingredients and may be potentially in use in cosmetic products.

Moreover, only 19 substances out of the 250 for which detailed safety evaluations have been performed by SCCNFP/SCCP in the period 1997 – 2007 are included in the database of Munro *et al. (1996).* Most strikingly, in this small sample four substances have acceptable doses derived from conventional risk assessment which are below the TTC values. This does not give confidence that the application of the TTC approach would ensure appropriate protection of the consumers.

Taking the above together, the SCs conclude that a revised and adequate toxicity database of relevance to cosmetic ingredients of various chemical categories, within all three Cramer Classes, and with reliable NO(A)EL will be required before the safety evaluation of ingredients in cosmetic products employing the TTC approach can be conducted with confidence.

#### 3.7.2.2 Differences in metabolism between dermal and per oral routes of application

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 structure with barrier function, there is growing evidence that metabolizing enzymes and transport proteins are involved in the regulation of transport processes through the skin, functioning as a quasi biochemical barrier of the skin (Baron and Merk, 2001, Merk et *al*., 2004, Merk et *al*., 2007).

A more detailed description of skin metabolism is given in Annex I. In summary, the major enzymes found in the liver may also be present in the skin, but at lower activity levels compared to other tissues. This activity is inducible by xenobiotics. Numerous enzyme activities have already been identified in the skin. There are examples that only small percentages of absorbed substances are metabolized. On the other hand, in some cases complete biotransformation during dermal absorption was observed. Detoxification capacity (phase II enzymes) may be even more pronounced in the skin. Oxidative bioactivation of prohaptens to haptens in the skin is considered a hazard of xenobiotics applied topically. To date, the fate of chemicals in the skin with regard to type and degree of metabolism remains a matter of uncertainty.

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. To extend the TTC approach to non-oral exposures, appropriate methodologies need to be developed to allow route-to-route extrapolation taking into account the potential for skin metabolism and/or biotranformation/bioactivation.

#### 3.7.2.3 Skin contact allergy (sensitisation) and other topical effects

As mentioned in sections 3.6.2 and 3.7 the expert Group (Kroes *et al.*, 2007) recognized that the TTC approach cannot at present be used to evaluate local effects. They considered application to such effects potentially possible; however, the databases on local effects, such as sensitization or irritation, and on substances producing these effects, are currently too limited to be used as a basis for the derivation of valid TTC values for local endpoints.

The SC WG agrees with the conclusion that the TTC concept is not applicable for the safety evaluation of allergic contact dermatitis and of other local effects at the site of application (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, described in section 3.6.3) is based on the dermal sensitisation QRA method published by Api et al. (2007). This method was recently reviewed by the SCCP (SCCP, 2008). The main conclusion of this opinion was that from a scientific point of view, models like the dermal sensitization QRA approach may, after refinement and validation, in the future 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 scientific consensus must be obtained, especially concerning the choice of safety factors in the model.

As a consequence, the concerns stated by the SCCP for the dermal sensitization QRA also refer to the TTC concept for allergic contact dermatitis and make, at this time, the TTC concept not applicable for this endpoint.

#### 3.7.2.4 Exposure assessment of cosmetics and TTC

When a cosmetic ingredient is evaluated by the SCCP as safe for use in a well-defined exposure scenario, the evaluation of systemic toxicity is based upon the availability of experimentally determined values of that particular compound, including:

- the NOAEL (subacute, subchronic, reproductive study in rodents)
- dermal absorption (*in vitro* dermal absorption study on pig/human skin). 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.

Concerning exposure assessment of chemicals used in cosmetics, the industry Expert Group (Kroes *et al*., 2007) made a number of recommendations concerning the use of default adjustment factors for percutaneous absorption, rinse off cosmetic products, and the intermittent use of cosmetic products (section 3.6.2 above). A detailed discussion of these proposals would go beyond the scope of this opinion, since it concerns the safety evaluation of cosmetic ingredients in general, not only the application of the TTC approach. However, some critical points of the proposal of default adjustment factors for percutaneous absorption are discussed below.
The Expert Group (Kroes et al 2007) proposed that in the absence of experimental data the most appropriate method to estimate the systemic exposure over 24 h to a cosmetic ingredient should be based on calculation of $J_{max}$ (maximum flux) and a default fraction absorbed for non-reactive chemicals with molecular weight less than 1000 dalton in the range 10 to 80% depending on $J_{max}$ should be assigned as so called default adjustment factors for percutaneous absorption. It was argued that the rate and extent of transfer across the skin is determined by molecular characteristics, such as lipid solubility and molecular weight and thus the extent of systemic exposure can be predicted.

A comparison was made by Kroes *et al*. with skin absorption data of 15 cosmetic ingredients. The following drawbacks are obvious:
Six of the given examples are hair dyes. However, hair dyes are not representative for all cosmetics because of their short contact time. In 4 of 6 studies (Acid Yellow 3, tetrabromophenol blue, Acid Yellow 23, Pigment Red 57) the amount of formulation used was considerably higher than stipulated in the SCCP Notes of Guidance. Excessive amounts are known to influence skin absorption rates. In addition, in the case of oxidative hair dyes the amount absorbed strongly depends on the presence of reaction partners (p-phenylenediamine, catechol). This kind of studies is not suited to derive general rules for percutaneous absorption of cosmetic ingredients. Moreover, the use of calculated values for log $P_{O/W}$ bear a considerable uncertainty.
Although the use of an adjustment factor for percutaneous absorption in the absence of experimental data is promising, the SC WG considers that this proposal is far from being sufficiently developed and should be further validated based on a broad systematic comparison of predicted and experimentally obtained percutaneous absorption values

#### 3.7.2.5 Potential application of the TTC approach to intentionally added ingredients and/or impurities.

Based on the above considerations and limitations concerning the available data bases, the skin to oral route extrapolation, and the exposure assessments the Scientific Committees conclude that the TTC approach as proposed by Kroes *et al.* 2007 is at present in general not applicable for risk assessment of intentionally added or formed ingredients present in cosmetic products. The same conclusion can be reached for impurities in cosmetic ingredients. In the future with validated extended databases and percutaneous absorption

default factors and adequate knowledge on skin-oral route metabolism and biotransformation differences, the application for cosmetic ingredients and impurities could be further considered.

### 3.8. Research needs

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 upon which the decision tree is based and 2) the reliability of the exposure data for the intended use of the compound under study. It is the opinion of the Scientific Committees that in both of these areas further research is needed

**Further development and validation of toxicological databases:**
The carcinogenicity database of Gold et al. (1984) was originally developed nearly 25 years ago and expanded in 1999 by Cheeseman *et al*. This database of more than 700 substances should be reviewed with regards to the quality of the data included. It should also be established to what extent the substances in the database can be considered to be carcinogenic according the current guidelines for classification of carcinogens.

The non-cancer toxicological endpoints database (Munro *et al.* 1996) is based upon data from the Registry of Toxic Effects of Chemical Substances (RTECS). Since this database is known to include data without a preliminary in depth quality check, the data used in the non-cancer database also require an in-depth quality control.

An evaluation of more recent toxicity data is also needed. In case the TTC approach would acquire general use, the carcinogenic and non-cancer database should be continuously updated with newly available information on the substances they contain. This would involve monitoring of published literature and database searches.

The following aspects with regard to data entry need to be addressed:
- the databases must contain up to date and peer-reviewed data
- when new data are introduced, they need to be displayed under the same form as the existing data, meaning that they need to be the same type of result of the same type of test (e.g. NOAEL/NOEL/LOAEL/LOAEL from 28-day/90-day/chronic studies with rats/mice/dogs). Furthermore, correction factors (e.g. regarding allometry, study duration and study outcome) should be considered.
- the database must contain a sufficient number of structure analogues to the compounds under study

Since the original data set was built for substances to be used in food contact materials, it is possible that in other sectors additional structural alerts could be identified which also need exclusion from the approach. It is also possible that for each sector, a specific decision tree will need to developed and applied, especially in view of the diverging exposure scenarios.

Once the approach has been optimised for application in a sector, it could be challenged by performing a number of tests with known substances, as the one performed under 3.7.2.1 for the cosmetic area.

Since there is a major overlap of NOELs and LOELs between Cramer Class I, II and III, it would be desirable to achieve a better separation of the classes and consequently the TTCs based on them. The Cramer classification was developed in 1978 on theoretical considerations and might be improved by analysis of outliers in the Classes and the incorporating recent experience on QSAR and modes of action into the decision tree.

**Exposure data**

As stated in previous scientific committee opinions, exposure data are essential in any risk assessment procedure. In case they are lacking or are of insufficient scientific quality, worst case scenarios are regularly applied. As the TTC approach introduces an additional level of uncertainty in the hazard assessment by deriving the expected hazard, the need for sound exposure data becomes even more imminent. Therefore, for each sector, research efforts are needed to determine exposure, including aggregate exposure.

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. This also includes research on systemic exposure after dermal and inhalation exposure. In the following areas research is needed for consumer products: use frequency and amount used, duration of product contact, concentration, emission or leaching 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.

## 4. OPINION

The Threshold of Toxicological Concern (TTC) approach is a risk assessment tool that is at present used to evaluate safety of chemicals that occur at low levels. Currently it has been used for food contact materials, flavouring agents and genotoxic contaminants in pharmaceuticals. The approach has been suggested for a number of other application areas.

The TTC concept 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. The concept is based on extrapolation of toxicity data from an available database to a chemical compound for which the chemical structure is known, but no or limited toxicity data is available. From a scientific point of view, in principle, the TTC approach is applicable to any substance be it an intentionally added ingredient or a substance present in a particular product as inadvertent contaminant or impurity.

The principle of the TTC approach in itself is scientifically acceptable. However, the application of this principle in terms of risk assessment for safety evaluation of a chemical is dependent on the quality, quantity, and relevance of the underlying toxicity database, and a reliable estimation of the exposure to the chemical in the respective field of application.

One carcinogenicity database (Cheeseman et al., 1999) containing 709 carcinogens and one (Munro *et al*., 1996) based on other toxicological endpoints containing 613 chemicals have been used for derivation of the TTC values. Both are exclusively based on systemic effects after oral exposure. Several classes of chemicals have been identified, for which the TTC concept can not be applied (link to list). Also for certain endpoints, like allergic reactions, intolerance, local effects and pharmacological effects, the approach can presently not be applied. Additional limitations exist with regard to extrapolation to other exposure routes (inhalation and dermal). Recently published preliminary data on the RepDose database suggest that there is some doubt about the classification system by Cramer and that refinements are needed.

Appropriate exposure assessment is essential for TTC. In the case of genotoxic contaminants in pharmaceuticals, and food flavourings, where TTC is already in use, the available information has been considered adequate. 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. In this area, the uncertainties are higher and methodology is less developed. Significant exposure is likely for products that are frequently used. This may involve oral exposure or skin contact or exposure via inhalation by using e.g. cleaning products, cosmetics or toys. For many of these product categories, however, exposure data are limited or lacking.

In relation to cosmetic ingredients, the current database is considered inadequate. Therefore, the TTC approach is at present in general not applicable for intentionally added or formed ingredients present in cosmetic products. The same conclusion can be reached for impurities in cosmetic ingredients. In the future with validated extended databases and more experience, the application for chemicals in cosmetics and possibly other consumer products could be further considered.

Further research is needed in the development and validation of the current toxicity databases particularly in the areas where an insufficient number of representative chemicals is included. In addition, the methodology for assessing systemic exposure needs to be improved and appropriate data on exposure need to be generated for the various exposure scenarios.

## 5. MINORITY OPINION

Not applicable

## 6. REFERENCES

Api AM, Basketter DA, Cadby PA, Cano MF, Ellis G, Gerberick GF, Griem P, McNamee PM, Ryan CA, Safford R. (2007). Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. Regul Toxicol Pharmacol. 2007 Oct 24. [Epub ahead of print]

Bando H, Mohri S, Yamashita F, Takakura Y, Hashida M. (1997) Effects of skin metabolism on percutaneous penetration of lipophilic drugs. J Pharm Sci **86**: 759-761.

Barlow S.M. (1994). The role of the Scientific Committee for Food in evaluating plastics for packaging. Food Additives and Contaminants **11**:249-259

Barlow S (2005). Threshold of toxicological concern (TTC). A tool for assessing substances of unknown toxicity present at low levels in the diet, ILSI Europe Concise Monograph Series, The International Life Sciences Institute (ILSI) Europe.

Baron JM, Merk HF. Drug metabolism in the skin. Curr Opin Allergy Clin Immunol. 2001; 1: 287-291.

Baron JM, Holler D, Schiffer R, Frankenberg S, Neis M, Merk HF, Jugert FK. Expression of multiple cytochrome p450 enzymes and multidrug resistance-associated transport proteins in human skin keratinocytes. J Invest Dermatol 2001;116: 541-548.

Bergström MA, Luthman K, Nilsson LG, Karlberg A-T (2006a). Conjugated dienes as prohaptens in contact allergy: In vivo and in vitro studies of structure-activity relationships, sensitizing capacity,and metabolic activation. Chemical Research in Toxicology. 19: 760-769.

Bergström MA, Ott H, Carlsson A, Neis M, Zwadlo-Klarwasser G, Jonsson CA, Merk HF, Karlberg AT, Baron JM (2006b). A skin-like cytochrome P450 cocktail activates prohaptens to contact allergenic metabolites. Journal of Investigative Dermatology. 23

Bergström MA (2007). Bioactivation of xenobiotics in the skin. Mechanistic investigations and structure-activity relationship studies of alkene and oxime prohaptens in contact allergy. Monograph, Göteborg University

Bitsch A, Jacobi S, Melber C, Wahnschaffe U, Simetska N and Mangelsdorf I (2006) REPDOSE: a database on repeated dose toxicity studies of commercial chemicals – A multifunctional tool. Re. Toxicol and Pharmacol 46, 202-210.Blackburn K, Stickney JA, Carlson-Lynch SL, McGinnis PM, Chappell L, Felter SP (2005) Application of the threshold of toxic concern approach to ingredients in personal and household care products. Reg Toxicol Pharmacol **43**: 249-259

Boehnlein J, Sakr A, Lichtin JL, Bronaugh RL (1994). Characterization of esterase and alcohol dehydrogenase activity in skin. Metabolism of retinyl palmitate to retinol (Vitamin A) during percutaneous absorption. Pharmaceutical Research. 11: 1155-1159.

Bronaugh RL (2004). Methods for in vitro skin metabolism studies. Dermatotoxicology. 6

Castell JV, Donato MT, Gómez-Lechón MJ (2005). Metabolism and bioactivation of toxicants in the lung. The in vitro cellular approach. Exp Toxicol Pathol. 2005 Jul;57 Suppl 1:189-204

Cheeseman MA, Machuga EJ, Bailey AB (1999). A tiered approach to threshold of regulation. Food Chem Toxicol, **37:** 387-412.

Cheung C, Hotchkiss SA, Pease CK (2003) Cinnamic compound metabolism in human skin and the role metabolism may play in determining relative sensitisation potency. J Dermatol Sci 31:9–19

Collier SW, Storm JE, Bronaugh RL (1993). Reduction of azo dyes during in vitro percutaneous absorption. Toxicology and Applied Pharmacology. 118: 73-79.

Cramer GM, Ford RA, Hall RA (1978). Estimation of toxic hazard – a decision tree approach. Food Cosmet Toxicol, **16:** 255-276.

CREMe (Central Risk & Exposure Modelling e-solution) (2005) European Consumer Exposure to Cosmetic Products - Data Analysis. Final Draft Report, 17th September 2005.

Csanády GA, Filser JG (2001). Toxicokinetics of inhaled and endogenous isoprene in mice, rats, and humans. Chem Biol Interact 1;135-136:679-85.

Delaney EJ (2007). An impact analysis of the application of the threshold of toxicological concern concept to pharmaceuticals, Reg Toxicol Pharmacol **49:** 107-124.

Dobo KL, Greene N, Cyr MO, Caron S, Ku WW (2006). The application of structure-based assessment to support safety and chemistry diligence to manage genotoxic impurities in active pharmaceutical ingredients during drug development, Reg Toxicol Pharmacol **44:** 282-293.

Dressler WE, Appelqvist T (2006). Plasma/blood pharmacokinetics and metabolism after dermal exposure to para-aminophenol or para-phenylenediamine. Food and Chemical Toxicology. 44: 371-379

Drew R and Frangos J (2007). The concentration of no toxicological concern (CoNTC): a risk assessment screening tool for air toxics. J Toxicol Environ Health A. **70**(19):1584-93.

ECHA (2008). Guidance on information requirements and chemical safety assessment; Chapter R.7c: Endpoint specific guidance, European Chemicals Agency, 2008 http://reach.jrc.it/docs/guidance_document/information_requirements_r7c_en.pdf?vers=30_07_08

EFSA (2004). Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to Flavouring Group Evaluation 3 (FGE.03), http://www.efsa.europa.eu/EFSA/Scientific_Opinion/afc_opinion_ej107_fge3_op_en,3.pdf?ssbinary=true

EMEA (2006). European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) Guideline on the Limits of Genotoxic Impurities, CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006, London, UK, 28 June 2006. http://emea.europa.eu/pdfs/human/swp/519902en.pdf

EMEA (2007). Question & Answers on the CHMP Guideline on the Limits of Genotoxic Impurities, EMEA/CHMP/SWP/431994/2007 http://emea.europa.eu/pdfs/human/swp/43199407en.pdf

EMEA (2008a). Committee on Herbal Medicinal Products (HMPC). Guideline on the assessment of genotoxicity of herbal substances/preparations. EMEA/HMPC/107079/2007, London, 21 May 2008.

EMEA (2008b). Committee on Herbal Medicinal Products (HMPC). Overview of comments received on draft Guideline on the assessment of genotoxic constituents in herbal substances / preparations. EMEA/HMPC/107079/2007. London, 21 May 2008

EN ISO 10993-1:2003 Biological evaluation of medical devices – Part 1 Evaluation and testing (ISO 10993-1:2003) (ISO, Geneva, Switzerland)

EN ISO 10993-17:2002 Biological evaluation of medical devices – Part 17 Establishment of allowable limits for leachable substances (ISO 10993-17:2002) (ISO, Geneva, Switzerland)

EN ISO 10993-18:2005 Biological evaluation of medical devices – Part 18 Chemical characterization of materials (ISO 10993-18:2005) (ISO, Geneva, Switzerland)

EN ISO 14971:2007 Medical devices – Application of risk management to medical devices. (ISO 14971:2007) (ISO, Geneva, Switzerland 2007).

Escher S, Bitsch A, Mangelsdorf I (2008). Use of RepDose for evaluation/refinement of the TTC-concept. Report Fraunhofer ITEM 27.06.08

Heise R, Mey J, Neis MM, Marquardt Y, Joussen S, Ott H, Wiederholt T, Kurschat P, Megahed M, Bickers DR, Merk HF, Baron JM. Skin retinoid concentrations are modulated by CYP26AI expression restricted to basal keratinocytes in normal human skin and differentiated 3D skin models. J Invest Dermatol 2006; 126: 2473-2480.

Gold LS, Sawyer CB, Magaw R, Backman GM, de Veciana M, Levinson R, Hooper NK, Havender WR, Bernstein L, Peto R, Pike M, Ames BN (1984). A carcinogenesis potency database of the standardized results of animal bioassays. Environmental Health Perspectives 58: 9-319

ICH (1997). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Topic Q3C. Impurities: Residual Solvents. CPMP/ICH/283/95, approved by CPMP 1997 Sep http://emea.europa.eu/pdfs/human/ich/028395en.pdf

ICH (2002). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Topic Q3A(R). Impurities Testing Guideline: Impurities in New Drug Substances (Revision). CPMP/ICH/2737/99,

approved by CPMP 2002
http://emea.europa.eu/pdfs/human/ich/273799en.pdf

Inchiosa MA (1987). Toxicokinetics, deposition, absorption, distribution and excretion. In: Inhalation Toxicology. Harry Salem (ed), Marcel Dekker Inc., New York, NY, 186.

JECFA (1995). "Evaluation of certain food additives and contaminants. 44th Report of the Joint FAO/WHO Expert Committee on food additives", WHO Technical Report Series, No 859. http://www.who.int/pcs/jecfa/JECFA_publications.htm

JECFA (1996). The safety evaluation of natural flavouring complexes. WHO Food Additives Series, No 52

Kawakubo, Yamazoe, Kato, Nishikawa (1990). High capacity of human skin for N-acetylation of arylamines. Skin Pharmacology. 3: 180-5.

Kawakubo Y, Merk HF, Al Masaoudi T, Sieben S, Blömeke B (2000). N-Acetylation of paraphenylenediamine in human skin and keratinocytes. Journal of Pharmacology and Experimental Therapeutics. 292: 150-155.

Kroes R, Galli C, Munro I, Schilter B, Tran LA, Walker R, Würtzen G. (2000). Threshold of toxicological concern for chemical substances in the diet: A practical tool for assessing the need for toxicity testing. Food Chem Toxicol, 38: 255-312.

Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG, Würtzen G (2004). Structure-based thresholds of toxicological concern (TTC): Guidance for application to substances present at low levels in the diet. Food Chem Toxicol 42: 65-83.

Kroes R, Renwick AG, Feron V, Galli CL, Gibney M, Greim H, Guy RH, Lhuguenot JC, van de Sandt JJ (2007). Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food and Chemical Toxicol. 45: 2533-2562.

Larsen JC (2006). Risk Assessment of Chemicals in European Traditional Foods. Trends in Food Science & Technology, 17, 471-481.

Lombardi Borgia S, Schlupp P, Mehnert W, Schäfer-Korting M (2008). In vitro skin absorption and drug release - A comparison of six commercial prednicarbate preparations for topical use. European Journal of Pharmaceutics and Biopharmaceutics. 68: 380-389.

Mahmoud A, Haberland A, Dürrfeld M, Heydeck D, Wagner S, Schäfer-Korting M. Cutaneous estradiol permeation, penetration and metabolism in pig and man. Skin Pharmacol Physiol 2005; 18: 27-35.

McGovern T, Jacobson-Kram D (2006). Regulation of genotoxic and carcinogenic impurities in drug substances and products, Trends in Analyt Chem 25: 790-795.

Merk H, Mukhtar H, Kaufmann I, Das M, Bickers DR. Human hair follicle benzo(a)pyrene and benzo(a)pyrene 7,8-diol metabolism: effect of exposure to a coal tar-containing shampoo. J Invest Dermatol 1987; 88: 71-76.

Merk, H.F., Abel, J., Baron, J.M., Krutmann, J., 2004. Molecular pathways in dermatotoxicology. Toxicology and Applied Pharmacology 195, 267–277.

Merk HF, Baron JM, Neis MM, Obrigkeit DH, Karlberg A-T (2007). Skin: Major target organ of allergic reactions to small molecular weight compounds. Toxicology and Applied Pharmacology. 224: 313-317.

Munro IC, Ford RA, Kennepohl E, Sprenger JG (1996). Correlation of structural class with No-Observed-Effect Levels: A proposal for establishing a threshold of concern. Food Chem Toxicol, 34; 829-867.

Münster U, Hammer S, Blume-Peytavi U, Schäfer-Korting M. Testosterone metabolism in human skin cells in vitro and its interaction with estradiol and dutasteride. Skin Pharmacol Appl Skin Physiol 2003; 16: 356-366.

Ng KME, Chu I, Bronaugh RL, Franklin CA, Somers DA (1992). Percutaneous absorption and metabolism of pyrene, benzo[a]pyrene, and di(2-ethylhexyl) phthalate: Comparison of in vitro and in vivo results in the hairless guinea pig. Toxicology and Applied Pharmacology. 115: 216-223.

Ng KME, Chu I, Bronaugh RL, Franklin CA, Somers DA (1991). Percutaneous absorption/metabolism of phenanthrene in the hairless guinea pig: Comparison of in vitro and in vivo results. Fundamental and Applied Toxicology. 16: 517-524.

Nohynek GJ, Skare JA, Meuling WJA, Hein DW, de Bie ATHJ, Toutain H (2004). Urinary acetylated metabolites and N-acetyltransferase-2 genotype in human subjects treated with a para-phenylenediamine-containig oxidative hair dye. Food and Chemical Toxicology. 42: 1885-1891.

Nohynek GJ, Duche D, Garrigues A, Meunier P-A, Toutain H, Leclaire J (2005). Under the skin: Biotransformation of para-aminophenol and para-phenylenediamine in reconstructed human epidermis and human hepatocytes. Toxicology Letters. 158: 196-212.

OECD Guideline n° 427 on skin absorption, *in vivo* Method (2004). http://titania.sourceoecd.org/vl=6576764/cl=17/nw=1/rpsv/ij/oecdjournals/1607310x/v1n4/s28/p1

OECD Guideline n° 428 on skin absorption, *in vitro* Method (2004). http://titania.sourceoecd.org/vl=6576764/cl=17/nw=1/rpsv/ij/oecdjournals/1607310x/v1n4/s29/p1

Omdahl JL, Morris HA, May BK. 2002. Hydroxylase enzymes of the vitamin D pathway: Expression, function, and regulation. Annu Rev Nutr 22:139–166.

Reilly TP, Lash LH, Doll MA, Hein DW, Woster PM, Svensson CK (2000). A role for bioactivation and covalent binding within epidermal keratinocytes in sulfonamide-induced cutaneous drug reactions. Journal of Investigative Dermatology. 114: 1164-1173.

Safford, RJ (2008). The dermal sensitisation threshold—A TTC approach for allergic contact dermatitis. Regul Toxicol Pharmacol. **51**(2):195-200.

SCF (1992). Guidelines for Presentation of Data for Toxicological Evaluation of a Substance to be Used in Materials and Articles Intended to Come into Contact with Foodstuffs (Opinion expressed on 18 May 1990). SCF 26th Series Report. Report EUR 13913en. European Commission Directorate General - Internal Market and Industrial Affairs, Luxembourg. http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_26.pdf

SCF (1998). "Opinions of the Scientific Committee for Food on: The scientific basis of the concept of threshold of regulation in relation to food contact materials (expressed on 8 March 1996)", Reports of the Scientific Committee for Food (Thirty-ninth Series) pp 1-16.

SCF (1999). Opinion on a Programme for the Evaluation of Flavouring Substances (Expressed on 2 December 1999) Scf/Cs/Flav/Taskf/11 Final 6/12/1999

SCF (2001), Guidelines of the Scientific Committee on Food for the presentation of an application for a safety assessment of a substance to be used in food contact materials prior to its authorisation (updated on 13 December 2001). http://ec.europa.eu/food/fs/sc/scf/out82_en.pdf

SCCNFP/0167/99, Opinion of the SCCNFP concerning basic criteria for the in vitro assessment of percutaneous absorption of cosmetic ingredients, adopted by the SCCNFP during the 8th plenary session of 23 June 1999

SCCNFP/0750/03, Opinion of the SCCNFP concerning basic criteria for the in vitro assessment of percutaneous absorption of cosmetic ingredients, updated October 2003, adopted by the SCCNFP during the 25th plenary session of 20 October 2003

SCCP/0970/06, Opinion of the SCCP concerning basic criteria for the in vitro assessment of percutaneous absorption of cosmetic ingredients, updated March 2006, adopted by the SCCP during the 7th plenary session of 28 March 2006

Seko N, Bando H, Lim CW, Yamashita F, Hashida M. Theoretical analysis of the effect of cutaneous metabolism on skin permeation of parabens based on a two-layer diffusion/metabolism model. Biol Pharm Bull 1999; 22: 281-287.

Smith CK, Moore CA, Elahi EN, Smart ATS, Hotchkiss SAM (2000). Human skin absorption and metabolism of the contact allergens cinnamic aldehyde, and cinnamic alcohol. Toxicology and Applied Pharmacology. 168: 189-199.

US FD&C Act (1958) "Federal food, drug and cosmetic Act, as amended Title 21 U.S. Code", U.S. Governmental Printing Office, Washington (cited in Rulis, 1986; 1989).

US FDA (1995) "Food Additives: Threshold of regulation of substances used in food contact articles: Final rule", Federal Register. 60: 36582-36596. www.cfsan.fda.gov/~lrd/t36582.html

US FDA (2005). Guidance for Industry: Submitting Requests under 21 CFR 170.39 Threshold of Regulation for Substances used in Food-Contact Articles. CFSAN/Office of Food Additive Safety, April 2005

Yourick JJ, Bronaugh RL (2000). Percutaneous penetration and metabolism of 2-Nitro-p-phenylenediamine in human and fuzzy rat skin. Toxicology and Applied Pharmacology. 166: 13-23.

Velasquez DJ (1990). Toxicologic responses to inhaled aerosols and their ingredients. In: Respiratory Drug Delivery. Byron PR (ed), CRC Press, Boca Raton, FL, 45.

Wilkinson SC, Williams FM (2007). Cutaneous metabolism. Dermal Absorption and Toxicity Assessment. 177: 89-115. In: Dermal Absorption and Toxicity Assessment (Roberts M, Walters K. eds.) 2nd edition, Informa Healthcare, New York (2007).

**References Table 3**

1. SCCNFP/0822/04. Opinion on Furfural, Adopted by the SCCNFP during the 28th plenary meeting of 25 May 2004
2. SCCP/0935/05 Opinion on Coumarin (sensitisation only), Adopted by the SCCP during the 8th plenary meeting of 20 June 2006
3. SCCP/1068/06 Opinion on Methyl-N-methylanthranilate (photo-toxicity only), Adopted by the SCCP during the 10th plenary of 19 december 2006
4. SCCNFP/0787/04. Opinion on Acid blue 9. COLIPA n° C40, Adopted by the SCCNFP on 23 April 2004 by means of the written procedure
5. SCCP/1035/06. Opinion on HC Blue N°2 COLIPA N° B37, Adopted by the SCCP during the 10th plenary of 19 December 2006
6. SCCNFP/0792/04. Opinion on Acid Red 18 COLIPA N° C175, Adopted by the SCCNFP on 23 April 2004 by means of the written procedure
7. SCCP/0867/05. Opinion on para-Aminophenol COLIPA n° A16, Adopted by the SCCP during the 3rd plenary meeting of 15 March 2005
8. SCCP/0891/05. Opinion on Benzoic Acid and Sodium Benzoate, Adopted by the SCCP during the 4th plenary of 21 June 2005
9. SCCNFP/587/02. Opinion on concerning A clarification on the formaldehyde and para-formaldehyde entry in directive 76/768/EEC on cosmetic products, Adopted by the SCCNFP during the 22nd plenary meeting of 17 December 2002
10. SCCP/1044/06. Opinion on Diethylene Glycol Monoethyl Ether (DEGEE), Adopted by the SCCP during the 10th plenary of 19 December 2006
11. SCCNFP/0663/03. Opinion concerning Ethoxyethanol, Ethoxyethanol acetate, 2-Methoxyethanol and 2-Methoxyethanol acetate (glycol ethers and their acetates) Adopted by the SCCNFP during the 23rd plenary meeting of 18 March 2003
12. SCCNFP/0411/01. Opinion concerning Diethyl phthalate, Adopted by the SCCNFP during the 20th plenary meeting of 4 June 2002
13. SCCNFP/0833/04. Opinion concerning Dibutylphthalate, Adopted by the SCCNFP on 1 July 2004 by means of the written procedure
14. SCCP/1016/06. Opinion on Phthalates in cosmetic products. Adopted by the SCCP at its 11th plenary meeting of 21 March 2007
15. SCCP/ /1029/06. Opinion on Toluene (its use as a solvent in nail cosmetics), Adopted by the SCCP during the 9th plenary meeting of 10 October 2006
16. SCCNFP/0077/98. Opinion concerning Hydroquinone as a skin depigmenting agent (COLIPA n° A21) Adopted by the SCCNFP during the 5th plenary meeting of 25 November 1998
17. Report by the SCC on the use of hydroquinone as a skin-b!eaching product (Opinion expressed 24 - 2 - 1983).
18. SCCNFP/1991/97. Opinion concerning Acetonitrile. Adopted by the SCCNFP during the 2nd plenary meeting of 21 January 1998
19. SCCNFP/0011/98. Opinion concerning Acrylamide residues in cosmetics. Adopted by the SCCNFP during the 9th plenary meeting of 30 September 1999

## Annex I - Dermal exposure

### Dermal absorption

The term dermal/percutaneous absorption describes the passage of compounds across the skin.

When consumer products, including cosmetic products, come in contact with the skin or are topically applied, dermal absorption of different ingredients may occur and determines the systemic exposure to these compounds. This is the case both for intentionally added substances and for inadvertent contaminants and impurities.

Dermal absorption of individual ingredients can be determined experimentally *in vivo* (OECD 427) or *in vitro* (OECD 428). In case of cosmetic ingredients, *in vivo* testing will not longer be possible from 11 March 2009 onwards due to the provisions of the 7$^{th}$ Amendment to Dir 76/768/EEC (2003/15/EC). The "Draft Guidance Document for the conduct of skin absorption studies" (OECD 2004) provides general guidance for both types of experimental studies but for cosmetic ingredients additional criteria compiled by the SCC(NF)P need to be taken into consideration (SCCNFP/0167/99 and its updates SCCNFP/0750/03 and SCCP/0970/06).

The determined amount of substance that may cross the stratum corneum and enter into the deeper skin layers is considered as relevant for safety evaluation on the condition that the experimental setup mimics the real life conditions. The dermal absorption is expressed in mg/cm$^2$ or as a percentage of the applied dose and is used to calculate the systemic exposure dosage SED (mg/kg bw/day) of the compound under consideration.

For safety evaluation of cosmetic ingredients, the SCCP applies a default value for dermal absorption of 100% for the calculation of the Margin of Safety (MoS) if no adequate dermal absorption data is available.

### Skin metabolism

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 structure with barrier function, there is growing evidence that metabolizing enzymes and transport proteins are involved in the regulation of transport processes through the skin, functioning as a quasi biochemical barrier of the skin (Baron and Merk, 2001, Merk et *al*., 2004, Merk et *al*., 2007).

Enzymes in the skin catalyze a wide variety of metabolic reactions. The major enzymes present in the liver also have been identified in skin but at much lower activity levels. Important chemical groups such as esters, amines, alcohols, acids, etc. are metabolized in the skin. This was demonstrated with human skin *in vivo* and *in vitro*, with keratinocytes, and with reconstructed epidermal skin models (Bronaugh 2004). Esterase activity was demonstrated using substrates such as parabens (Bando et *al*., 1997, Seko et *al*., 1999), glucocorticoid diesters (Lombardi Borgia et *al*., 2008), methyl salicylate, and retinyl palmitate (Boehnlein et *al*., 1994). Also azoreductase activity was identified in the skin (Collier et *al*., 1993) resulting in the formation of aromatic amines from azo dyes, a mechanism that might play a role in allergic reactions to certain azo dyes.

Many reactions catalysed by Cytochrome P450 family enzymes have also been demonstrated in the skin. Retinoids (Heise et *al*., 2006), Vitamin D (Omdahl et al., 2002), estradiol (Mahmoud et *al*., 2005), and testosterone (Münster et *al*., 2003) metabolism was demonstrated in the context of dermal drug delivery systems. Aromatic hydrocarbon activation was studied with substrates such as phenanthrene and benzo(a)pyrene (Merk et *al*., 1987, Ng et *al*., 1991, 1992). The presence of multiple CYP enzymes in the skin was not only shown at activity level but also at mRNA and protein levels (Baron et *al*., 2001). N-

Hydroxylation of sulfonamides in human keratinocytes was correlated to protein binding and cytotoxicity (Reilly et al., 2000).

Oxidative bioactivation of prohaptens to haptens in the skin is of interest. Cinnamic alcohol is metabolised to cinnamic aldehyde during skin penetration by alcohol dehydrogenase (Smith et al., 2000, Cheung et al., 2003). In studies with model alkenes it could be shown that for allylic conjugated dienes the metabolically formed epoxides are the haptens. This includes $\alpha$-terpinene, a major constituent of Tea Tree Oil (Bergström et al., 2006a, 2006b). A review on prohaptens requiring metabolic activation in the skin is available (Bergström, 2007).

Detoxification capacity (phase II enzymes) may be even more pronounced in the skin. Activity of glutathione-S-transferases, glucuronyl transferases, sulfotransferases, and N-acetyltransferases as well as glycine conjugation were reported in cutaneous tissues or cells. A review on cutaneous metabolism was recently published (Wilkinson and Williams, 2007). N-Acetyltransferases (NATs) are important enzymes in amine metabolism. It was shown using two arylamines (p-aminobenzoic acid and 2-aminofluorene) that human skin possesses a high capacity for N-acetylation (Kawakubo et al., 1990). Both acetyltransferase classes (NAT1 and NAT2) exhibit polymorphisms. The sulfonamide drugs sulfamethoxazole and dapsone were N-acetylated in human keratinocytes (Reilly et al., 2000); the hair dye substance 2-nitro-p-phenylenediamine was nearly completely metabolized, mainly to an acetylated derivative, in rat and human skin *in vitro*, (Yourick and Bronaugh, 2000).

Several recent publications focused on skin metabolism of p-phenylene diamine (PPD) and related compounds which are important constituents of oxidative hair dyes. PPD was acetylated by human skin tissue and keratinocytes *in vitro* and evidence was provided that the reaction is predominantly attributable to NAT1 (Kawakubo et al., 2000). In reconstructed human epidermis, PPD and p-aminophenol were transformed to their respective acetylated derivatives (Nohynek et al., 2005). Following application of an oxidative hair dye containing PPD to human scalp the major urinary metabolites were mono- and diacetylated PPD (Nohynek et al., 2004). It was concluded that topically applied PPD (and p-aminophenol) is metabolized in the skin resulting in systemic exposure to acetylated metabolites (Dressler and Appelqvist, 2006).

Conclusion

The major enzymes found in the liver may also be present in the skin, but at lower activity levels compared to other tissues. This activity is inducible by xenobiotics. Numerous enzyme activities have already been identified in the skin. There are examples that only small percentages of absorbed substances are metabolized. On the other hand, in some cases complete biotransformation during dermal absorption was observed. Detoxification capacity (phase II enzymes) may be even more pronounced in the skin. Oxidative bioactivation of prohaptens to haptens in the skin is considered a hazard of xenobiotics applied topically. To date, the fate of chemicals in the skin with regard to type and degree of metabolism remains a matter of uncertainty.

## Annex II - Inhalation exposure

Cited from TGD[1]:
Substances that can be inhaled include gases, vapours, liquid aerosols (both liquid substances and solid substances in solution) and finely divided powders/dusts. Such substances may be absorbed from the respiratory tract or, through the action of clearance mechanisms, may be transported out of the respiratory tract and swallowed. This means that absorption from the gastrointestinal tract will contribute to the total body burden of substances that are inhaled.

### Gases and vapours

In general, gases and vapours are readily absorbed across the lungs. Absorption of gases and vapours occurs predominantly in the alveoli by passive diffusion along a concentration gradient. The major determinant of absorption of gases and vapours in the respiratory tract is solubility in blood. However, the gas or vapour must also be sufficiently lipophilic to cross the alveolar and capillary membranes therefore a moderate Log P value (between 0 - 4) would be favourable for absorption. The rate of systemic uptake of very hydrophilic gases or vapours may be limited by the rate at which they partition out of the aqueous fluids (mucus) lining the respiratory tract and into the blood. Such substances may be transported out of the lungs with the mucus and swallowed or may pass across the respiratory epithelium via aqueous membrane pores. Highly reactive gases or vapours can react at the site of contact thereby reducing the amount available for absorption. Beside the physico-chemical properties of the compound physical activity has a great impact on absorption rate and must also be addressed (Csanady and Filser, 2001).

### Liquid aerosols and finely divided powders/dusts

The potential for liquid aerosols or finely divided powders to be inhaled will be determined by their particle size. Precise deposition patterns for dusts will depend not only on the particle size of the dust but also the hygroscopicity, electrostatic properties and shape of the particles and the respiratory dynamics of the individual. Thus it is only possible to make very general statements about sites of deposition for inhaled dusts. Note that these generalizations apply only to particles which are compact and symmetrical in shape. As a rough guide, particles with aerodynamic diameters below 100 µm have the potential to be inhaled. Particles with aerodynamic diameters of above 1- 5 µm have the greatest probability of settling in the nasopharyngeal region whereas particles with aerodynamic diameters below 1- 5 µm are most likely to settle in the tracheobronchial or pulmonary regions (Velasquez, 1990). Therefore any powder that contains particles with aerodynamic diameters below 100 µm is potentially of concern. Once a liquid droplet or dust particle has deposited in the airways, it can be absorbed across the respiratory tract epithelium, cleared from the lungs via the mucociliary mechanism or lymphatic system or retained within the lungs (Inchiosa, 1987). Highly reactive substances may react at the site of contact thereby reducing the amount available for absorption.

### Lung metabolism

The lung tissue expresses several enzymes involved in the metabolising of xenobiotics.P450 enzymes (e.g. CYP1A1, CYP1B1, CYP2A6, CYP2B6, CYP2E1 and CYP3A5) are expressed in bronchial and bronchiolar epithelium, Clara cells, type II pneumocytes, and alveolar macrophages. The individual Cytochrome P450 isoforms have different patterns of localisation within pulmonary tissue. Lung cells also express Phase II enzymes such as epoxide hydrolase, UGT1A (glucuronyl transferase) and GST-P1 (glutathione S-transferase) (Castell JV *et al.*, 2005)

[1] http://ecb.jrc.ec.europa.eu/TGD/

## Annex III - Legislation relevant for Products

### The General Product Safety Directive (GPSD)

A revised GPSD (2001/95/EC) entered into force 15 January 2004. The objectives of the Directive are both to protect consumer health and safety and to ensure the proper functioning of the internal market. The GPSD is intended to ensure a high level of product safety throughout the EU for consumer products that are not covered by specific sector legislation (e.g. toys, chemicals, cosmetics, machinery). The Directive also complements the provisions of sector legislation which do not cover certain matters, for instance in relation to producers' obligations and the authorities' powers and tasks. The Directive provides a generic definition of a safe product. Products must comply with this definition. If there are no specific national rules, the safety of a product is assessed in accordance with European standards, Community technical specifications, codes of good practice, the state of the art and the expectations of consumers.

### Sector-specific legislation

In general, the GPSD applies in a complementary way to products and/or risks covered by sector-specific product safety legislation. The most important pieces of legislation from a consumer point of view are Chemicals, Toys, Personal protective equipment, Cosmetics, Pharmaceuticals.

### The "Limitations Directive" for Dangerous Substances and Preparations

Some substances and preparations are not considered dangerous and circulate freely on the European market without any particular rules. Others are classified as dangerous and can circulate freely only when packaged and labelled in accordance with Directive 67/548/EEC (for dangerous substances) or Directive 1999/45/EC (for dangerous preparations). In a relatively small number of cases the rules for classification, packaging and labelling are insufficient to reduce risks and must be supplemented by rules to restrict marketing and use under the Limitations Directive, i.e. Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations.

Substances falling under the Limitations Directive are listed in the Annex I to that Directive which also specifies the restrictions on marketing and use applying in each particular case. Where a substance is not already listed in Annex I, the name of the substance and the desired limitations on marketing and use are added using proposals to the Council and the Parliament to amend the Directive. Where a substance is listed and the requirement is to change the limitations already in place, this is done by a Commission Directive adapting the existing limitations to technical progress.

### Adopted AMENDMENTS to Directive 76/769/EEC

| | |
|---|---|
| Mercury in measuring devices | 2007/51/EC of 25 September 2007 |
| Perfluorooctane sulfonates (PFOS) | 2006/122/EC of 12 December 2006 |
| Phthalates in toys and childcare articles | 2005/84/EC of 14 December 2005 |
| Polycyclic aromatic hydrocarbons – PAH | 2005/69/EC of 16 November 2005 |
| Toluene and trichlorobenzene | 2005/59/EC of 26 October 2005 |
| Nonylphenol, Nonylphenol ethoxylate and cement | 2003/53/EC of 18 June 2003 |
| Substances classified as carcinogens, mutagens or substances toxic to reproduction (CMR) | 2001/41/EC of 19 June 2001<br>2003/36/EC of 26 May 2003 |

| | |
|---|---|
| | 2003/34/EC of 26 May 2003<br>2005/90/EC of 18 January 2006 |
| Penta/octabromodiphenyl ether | 2003/11/EC of 6 February 2003 |
| Directive Azo-colorants | 2002/61/EC of 19 July 2002 |
| Short Chain Chlorinated Paraffins (SCCP) | 2002/45/EC of 25 June 2002 |

**Adaptations of Annex I of Directive 76/769/EEC to technical progress**

| | |
|---|---|
| Arsenic | 2006/139/EC of 20 December 2006 |
| PentaBDE (Pentapromodiphenyl ether) | 2004/98/EC of 1 October 2004 |
| Nickel | 2004/96/EC of 27 September 2004 |
| Azo colorants | 2004/21/EC of 24 February 2004 |
| Blue colorant/Azo-dye | 2003/3/EC of 6 January 2003 |
| Organostannic compounds | 2002/62/EC (+ corrigendum) of 9 July 2002 |
| Hexachloroethane | 2001/91/EC of 29 October 2001 |
| Creosote | 2001/90/EC of 26 October 2001 |