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Present and suggested use of the Threshold of Toxicological Concern (TTC) principle in areas of risk assessment relevant for the Norwegian Scientific Committee for Food Safety (VKM).

A document providing background information for discussions within VKM

Opinion of the *Ad hoc* working group for evaluation of the use of the Threshold of Toxicological Concern (TTC) principle in risk assessments performed by the Norwegian Scientific Committee for Food Safety

24 May 2006

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SUMMARY

The threshold of toxicological concern (TTC) is a pragmatic 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 an appreciable risk to human health. It proposes that a minimum value of exposure can be identified for many chemicals, in the absence of a full toxicity database, based on their chemical structure and the known toxicity of chemicals which share similar structural characteristics. The benefits of using the TTC principle for risk assessment of chemicals in food are to focus limited resources of time, cost and scientific expertise on the testing and evaluation of substances with the greatest potential to pose risks to human health and to contribute to a reduction of animal use.

The Panel on food additives, flavourings, processing aids, materials in contact with food and cosmetics (Panel 4) of the Norwegian Scientific Committee for Food Safety (VKM), suggested that it should be evaluated whether the use of the TTC principle could be employed in VKM's risk assessments. An *ad hoc* group consisting of three members from Panel 4, and one member of the Panel on contaminants in the food chain (Panel 5) with expertise in the area drug residues in food of animal origin, was then appointed by the Head Committee, to provide an overview of the available information regarding the use of the TTC principle within the European Union (EU) and other relevant institutions in the areas covered by VKM. This document therefore focuses on the use of the TTC principle in areas relevant for VKM's Panel 4: food contact materials, flavouring substances, food additives, cosmetics and products intended for use in contact with drinking water, and for Panel 5: drug residues in food of animal origin. However, this document is meant to provide background information about the TTC principle to serve as a basis for discussion within VKM's Head Committee and scientific panels across all fields of expertise, on whether and how it could be employed in risk assessment of chemicals for which little toxicological data, but good human exposure data, is available.

A rather wide approach to the subject has been taken, in the sense that the use of this concept in U.S.A. (although under different names), as well as in EU, is reported. Also, the present or suggested use of the TTC principle by industry, in addition to its use by regulatory institutions, is included. The use of TTC outside the food area, such as for risk assessment of industrial chemicals and consumer products, as well as environmentally, is covered briefly. An integrated approach suggested where TTC is only one component in a more efficient risk assessment procedure is also described briefly. Since reliable exposure data on a chemical is a prerequisite for the use of the TTC principle, some information is also given about methods used to obtain exposure data in the various areas.

The TTC principle is already well-established as part of the regulatory risk assessment process for chemically defined flavouring substances, used by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and the EU Flavour Information System (FLAVIS) Working Group under the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC Panel) of the European Food Safety Authority (EFSA). It is also adopted for risk assessment of natural flavour complexes (NFCs) by the Expert Panel of FEMA (the Flavor and Extract Manufacturers Association of the United States) in U.S.A. For food contact materials, defined as indirect food additives in U.S.A., the Threshold of Regulation (ToR) policy is used to exempt such materials from toxicological testing if the migration is below 0.5 ppb (µg/kg), and the degree of migration above this value is used to decide the degree of toxicological testing necessary. For risk assessment of food contact

materials by EFSA, levels of migration are also used to determine how much toxicological data has to be provided for a chemical by the producers, but all substances have to undergo at least some testing. The same is the case for risk assessment of direct food additives in U.S.A. For regulatory risk assessment of cosmetics, the TTC principle is not in use at present. For products intended for use in contact with drinking water in U.S.A., a similar concept, called threshold of evaluation, may be used in certification of products if not enough toxicological data is available for a full risk assessment. TTC is not yet included in the regulatory risk assessment of materials intended for use in contact with drinking water in EU, since a new common system for such approvals is at present under development. For risk assessment of drug residues in food of animal origin, the TTC principle is not adopted, but new risk assessment tools such as TTC, are presently discussed both within the European Medicines Agency (EMEA) and JECFA.

Various organizations, as well as industry, are in the process of discussing and evaluating extensions of the TTC principle to be used in risk assessment of a wider selection of chemicals. The exact uses and levels of TTC exposure values that are already in use or are discussed in the different areas vary a lot, and are described under each subject later in this document.

However, much of the systematic work laying the foundation for broadening the application of the TTC principle has been done in later years by the International Life Sciences Institute (ILSI) Europe. An Expert Group evaluated whether the chemical databases used to establish the TTC values for the three structural classes of chemicals, Cramer class I, II and III, also supported the use of these values for more specific endpoints, such as neurotoxicity, developmental toxicity and immunotoxicity. They suggested a separate TTC value for organophosphates, but concluded that the other endpoints were adequately covered by the structural class III threshold, i.e. for the chemicals with the highest potential for toxicity. They concluded also that the TTC principle should not be used for heavy metals, polyhalogenated dibenzo-*p*-dioxins, dibenzofurans and biphenyls, or other chemicals that accumulate in the body, endocrine disrupting chemicals, including steroids, high molecular weight chemicals, such as polymers, proteins, and other substances inducing allergy, hypersensitivity and intolerance.

Based on all the information obtained about both present regulatory use, suggested new applications and the recommendations made by the ILSI Europe Expert Group, the *ad hoc* group concludes that the TTC principle should be used by VKM in fields where it is already well established as part of the regulatory risk assessment procedure, such as in safety evaluations of flavouring substances and food contact materials. In addition, the TTC principle may be useful in risk assessment of chemicals unintentionally present in low amounts in food as impurities or contaminants, providing exposure can be reliably calculated. It could therefore be relevant for several, if not all, of the panels in VKM.

The *ad hoc* group recommends that this document is used as background information and basis for further discussions in the Head Committee and in the scientific panels of VKM in order to see whether, and how, the TTC principle may be useful in the various fields covered by VKM. The *ad hoc* group also recommends that the further development of the TTC principle, as well as other new methodology in risk assessment, such as *in vitro* tests and quantitative structure-activity relationship (QSARs), should be followed continuously for the benefit of efficient and up-to-date risk assessments by VKM.

NORSK SAMMENDRAG

"The threshold of toxicological concern" (TTC)-prinsippet er et pragmatisk risikovurderingsverktøy som er basert på at det er mulig å etablere en human terskelverdi for eksponering for kjemikalier, som er slik at det under denne verdien er en svært liten sannsynlighet for en vesentlig risiko for menneskers helse. Det antyder at det er mulig å identifisere en minimumsverdi for eksponering for mange kjemikalier, selv uten full kunnskap om deres toksisitet, basert på kunnskap om deres kjemiske struktur og kjent toksisitet av kjemikalier med lignende struktur. Fordelene ved å bruke TTC-prinsippet for risikovurdering av kjemikalier i mat er å fokusere begrensede ressurser som tid, kostnader og vitenskapelig ekspertise på testing og vurdering av stoffer med det største potensialet for å utgjøre en risiko for menneskers helse, og å bidra til reduksjon av bruken av forsøksdyr.

Faggruppen for tilsetningsstoffer, aroma, matemballasje og kosmetikk (Faggruppe 4) i Vitenskapskomiteen for mattrygghet (VKM) foreslo at det skulle vurderes om TTC-prinsippet kunne brukes i VKMs risikovurderinger. En *ad hoc* gruppe bestående av tre medlemmer av Faggruppe 4, og ett medlem av Faggruppen for forurensninger, naturlige toksiner og medisinrester i matkjeden (Faggruppe 5), med ekspertise på medisinrester i mat fra dyr, ble oppnevnt av Hovedkomiteen for å lage en oversikt over tilgjengelig informasjon vedrørende bruken av TTC-prinsippet innen den europeiske union (EU) og andre relevante institusjoner innenfor de områdene som dekkes av VKM. Dette dokumentet fokuserer derfor på bruken av TTC-prinsippet i ansvarsområdene til Faggruppe 4: matemballasje, aromastoffer, tilsetningsstoffer, kosmetikk og produkter for bruk i kontakt med drikkevann, og for Faggruppe 5: medisinrester i mat fra dyr. Men dette dokumentet er ment å gi bakgrunnsinformasjon om TTC-prinsippet som et grunnlag for diskusjon innen VKMs Hovedkomité og faggrupper på alle relevante områder, om og hvordan det kan brukes i risikovurdering av kjemikalier som det finnes lite toksikologiske data for, men hvor gode eksponeringsdata for mennesker er tilgjengelig.

En ganske vid tilnærming er brukt, i den forstand at det er rapportert om bruken av prinsippet (om enn under andre navn) i U.S.A., så vel som i EU. Også nåværende eller foreslått bruk av prinsippet innen industri, i tilegg til bruk av det i regulatorisk sammenheng, er inkludert. Bruk av prinsippet på områder utenom mat, slik som i risikovurdering av industrikjemikalier og forbruksvarer, så vel som i miljøsammenheng, er kort beskrevet. En foreslått integrert tilnærming, hvor TTC er en av komponentene i en mer effektiv risikovurderingsprosedyre, er også kort omtalt. Siden pålitelige data om grad av eksponering for et kjemikalie er en nødvendig forutsetning for å bruke TTC-prinsippet, er det også gitt noe informasjon om metoder for å innhente data om eksponering på de ulike områdene.

TTC-prinsippet er allerede veletablert som en del av risikovurderingen av kjemisk definerte aromastoffer, brukt både av The Joint FAO/WHO Expert Committee on Food Additives (JECFA), og The EU Flavour Information System (FLAVIS)-arbeidsgruppen under faggruppen for tilsetningsstoffer, aromastoffer, prosess-hjelpemidler og matemballasje (AFC-panelet) i EUs vitenskapskomité for mat - The European Food Safety Authority (EFSA). Prinsippet er også tatt i bruk for risikovurdering av naturlige aromapreparater av The Expert Panel of FEMA (the Flavor and Extract Manufacturers Association of the United States) i U.S.A. Når det gjelder stoffer som kan migrere fra matemballasje, definert som indirekte tilsetningsstoffer i U.S.A., brukes "The Threshold of Regulation" (ToR) begrepet om en politikk som brukes til å unnta slike materialer fra toksikologisk testing hvis migrasjonen av et kjemikalie fra slik emballasje er under 0.5 ppb (µg/kg), og graden av migrasjon over denne

verdien brukes til å fastsette hvor mye toksikologisk testing som er nødvendig. I EFSAs risikovurdering av matemballasje brukes også graden av migrasjon til å fastsette hvor mye toksikologiske data om kjemikaliet produsenten må fremskaffe, men alle stoffer må gjennom noen tester. Det samme gjelder for risikovurdering av direkte tilsetningsstoffer i U.S.A. TTC-prinsippet brukes ikke per i dag for risikovurdering av kosmetikk. For sertifisering av produkter til bruk i kontakt med drikkevann i U.S.A. kan et lignende begrep, kalt "threshold of evaluation", brukes hvis det ikke finnes tilstrekkelig toksikologiske data til å gjøre en full risikovurdering. TTC er ikke inkludert i risikovurdering av materialer til bruk i kontakt med drikkevann i EU ennå, siden et nytt felles system for godkjenning av slike materialer er under etablering. Prinsippet er heller ikke tatt i bruk for risikovurdering av medisinrester i mat fra dyr, men nye verktøy for risikovurdering, inkludert TTC-prinsippet, blir for tiden diskutert både innen The European Medicines Agency (EMEA) og JECFA.

Ulike organisasjoner og industrien holder på å diskutere og vurdere en utvidet bruk av TTC-prinsippet i risikovurdering av et større utvalg av kjemikalier. Den eksakte måten TTC-prinsippet er tenkt brukt på, og nivåene på TTC-verdiene, varierer fra område til område, og er beskrevet under omtalen av hvert emne senere i dette dokumentet.

Mye av det systematiske arbeidet som danner grunnlaget for en bredere anvendelse av TTC-prinsippet er gjort i de senere årene av The International Life Sciences Institute (ILSI) Europe. En ekspertgruppe vurderte om de kjemikalie-databasene som ble brukt til å etablere TTC-verdiene for de tre strukturelle klassene av kjemikalier, kalt Cramer klasse I, II og III, også støttet bruken av disse verdiene for mer spesielle toksikologiske effekter, slik som neurotoksisitet, utviklingstoksisitet og immuntoksisitet. De foreslo en egen TTC-verdi for organofosfater, men konkluderte med at de andre effektene ble dekket av TTC-verdien for klasse III-kjemikalier, dvs. for de kjemikaliene med høyest potensial for toksisitet. De konkluderte også med at TTC-prinsippet ikke bør brukes i risikovurdering av tungmetaller, polyhalogenerte dibensodioksiner, dibensofuraner og bifenyl-forbindelser, eller andre kjemikalier som akkumulerer i kroppen, hormonforstyrrende stoffer inkludert steroider, stoffer med høy molekylvekt slik som polymerer, proteiner, og andre stoffer som kan gi allergi, hypersensitivitet eller intoleranse.

Basert på all informasjonen om nåværende regulatorisk bruk, foreslåtte nye anvendelser og anbefalingene fra ekspertgruppen til ILSI Europe, konkluderer *ad hoc* gruppen med at TTC-prinsippet bør fortsatt brukes av VKM på de områdene hvor det allerede er etablert som del av en regulatorisk risikovurderingsprosedyre, slik som i vurdering av aromastoffer og matemballasje. I tillegg kan TTC-prinsippet være nyttig i risikovurdering av kjemikalier som ikke er tilsatt med hensikt, men som oppdages i små mengder i mat som urenheter eller kontaminanter, forutsatt at pålitelig estimering av eksponering er mulig. TTC-prinsippet burde derfor kunne være relevant for bruk i flere, om enn ikke i alle, av faggruppene innen VKM.

Ad hoc gruppen anbefaler at dette dokumentet brukes som bakgrunnsinformasjon og basis for videre diskusjoner både i Hovedkomiteen og i faggruppene i VKM for å se om, og hvordan, TTC-prinsippet kan være nyttig brukt i risikovurdering innenfor de ulike områdene som dekkes av VKM. *Ad hoc* gruppen anbefaler også at den videre utviklingen av bruken av TTC-prinsippet, så vel som av annen ny risikovurderingsmetodologi, slik som innen *in vitro* metoder og kvantitative struktur-aktivitetsrelasjoner (QSARs), følges kontinuerlig, med effektive og oppdaterte risikovurderinger fra VKM som resultat.

TERMS OF REFERENCE

The Panel on food additives, flavourings, processing aids, materials in contact with food and cosmetics (Panel 4) of the Norwegian Scientific Committee for Food Safety (VKM) experienced during their work that for some chemicals, especially used in food contact materials, often very little toxicological data was available on which to base the risk assessments. The panel therefore suggested that it should be evaluated whether the use of the Threshold of Toxicological Concern (TTC) principle could be employed by the various panels of VKM in risk assessments of chemicals without available adequate toxicological data.

On its meeting on 24 May 2005, the Head Committee of VKM supported the suggestion from Panel 4 regarding evaluation of the use of the TTC principle in risk assessments by VKM. An *ad hoc* group consisting of three members from Panel 4, and one member of the Panel on contaminants in the food chain (Panel 5) with expertise in the area of drug residues in food of animal origin, was appointed. In addition to the areas of responsibility that are mentioned in the name of Panel 4, this panel is also responsible for risk assessment of materials and water treatment chemicals intended for use in contact with drinking water.

The *ad hoc* group was asked to give an overview of the available information regarding the use of the TTC principle within the European Union (EU) and any other relevant institutions, in the areas covered by VKM. On the basis of this information, the *ad hoc* group should discuss how the TTC principle could be employed by VKM in the risk assessments of chemicals for which little toxicological data, but good human exposure data, is available.

The present document produced by the *ad hoc* group was to be presented to the Head Committee of VKM in May 2006, and should provide background information and basis for further discussions in the Head Committee as well as in the other scientific panels, in order to reach a decision on whether and how the TTC principle could be used for risk assessments by VKM.

THE THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) PRINCIPLE

Background and definition

The main components of food, such as fats, carbohydrates, proteins, vitamins and minerals, are chemicals, but usually not of health concern, unless they are eaten in excess or in nutritionally inadequate amounts. Processed food may contain chemicals added to preserve, colour, emulsify, sweeten or flavour the food, or to perform a specific functional role in the food. Food may also contain residues of pesticides used on crops or traces of veterinary drugs used in food-producing animals. Chemicals may also be used as processing aids, such as machinery lubricants or antibacterial substances in vegetable washing water, leaving residues on the food. Chemicals present in food packaging materials and kitchen utensils may migrate into food during manufacture, transport, storage and cooking. Food may also contain contaminants of natural origin, such as fungal toxins, metals from natural minerals and soil, or man-made contaminants from the environment such as persistent polychlorinated biphenyls (PCBs) and dioxins. Additionally, chemicals may be generated during cooking of food, such as heterocyclic amines (HCAs) in red meat, or acrylamide in fried potatoes and bread, or

chemicals could be formed during smoking or barbecuing of meat and fish, such as polycyclic aromatic hydrocarbons (PAHs).

For vitamins and minerals in food there is most often knowledge and experience from human consumption about what levels are safe. Also for substances such as food additives, pesticides and veterinary drugs, a lot of knowledge about their toxicological properties is available and they are not given market authorization unless the substances or their potential residues have been evaluated for human health safety. However, the situation is different for chemicals such as food packaging migrants, flavourings, processing aids, or substances formed as reaction products or breakdown products during processing and cooking. For many of these substances, knowledge about their toxicological properties is inadequate for assessing the risks to human health. In addition, the analytical methods are continuously improving, so that trace amounts of increasing numbers of chemicals are now detected in food, and need to be assessed as to their risks for humans by intake of such food. Full toxicological testing of all endpoints of a chemical found to be present in food requires a lot of time, cost, scientific expertise and experimental animals, and is too slow even by concerted international efforts. As a solution to this dilemma, new principles, such as TTC (Box 1), have been suggested and developed to better cope with this situation.

Box 1. The Threshold of Toxicological Concern (TTC) concept (1).

- TTC is a pragmatic 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 an appreciable risk to human health.
- It proposes that a minimum value of exposure can be identified for many chemicals, in the absence of a full toxicity database, based on their chemical structure and the known toxicity of chemicals which share similar structural characteristics.
- The benefits of using the TTC principle for risk assessment of chemicals in food are to focus limited resources of time, cost and scientific expertise on the testing and evaluation of substances with the greatest potential to pose risks to human health and contribute to a reduction of animal use.

The TTC concept should not be confused with the concept of threshold as used in toxicology for a dose or a concentration of a chemical below which a **toxicological effect** is not observed or expected to occur.

For readers who are not already familiar with the TTC principle, a detailed account of the history and development of the principle is given below, since this provides the necessary background for further discussions on whether and how TTC can be used by the scientific panels of VKM. An extensive reference list is provided for those who want even more in depth knowledge about the subjects discussed in this document. For readers familiar with the TTC concept, the first chapter can be skipped, and they can go directly to the chapters on specific applications of TTC relevant for VKM's scientific panels later in this document.

History and development of the TTC principle

Driving forces behind the development of the TTC principle

The TTC concept has evolved during many years as an attempt to develop generic approaches to risk assessment of chemicals in food. The following description of the history and development of the TTC principle is mainly based on recently published summary reports (1,2). The driving forces behind these efforts have been:

- the realization of a partial or complete lack of toxicity data for a large number of chemicals present in food by intention or unintentionally,
- the continuing improvements in analytical methods, which allow more and more chemicals to be identified in food in ever lower concentrations,
- the widely accepted premise that exposure to very low amounts of chemicals is usually without harm,
- the view that the time and attention devoted to a particular chemical should be in proportion to the health risk,
- the limited resources worldwide in capacity for toxicity testing and evaluation,
- the need to minimise the use of experimental animals,
- and the ability to analyse large sets of existing toxicity data to make predictions about the toxicity of other structurally related chemicals.

The Threshold of Regulation (ToR) policy for food packaging materials in U.S.A.

One of the first efforts in the development of the TTC principle was published by Frawley in 1967 (3). Starting from the premise that there must be some uses of food packaging materials that do not involve any hazard to the health of consumers of food, he set about defining a dose which he considered would be without harm. He analysed a large data set of 2-year, chronic toxicity studies on 220 chemicals given via the diet, which at that time represented about 90% of all available chronic toxicity studies. The chemicals were food additives, including colours, industrial chemicals, chemicals found in consumer products, including cosmetics, chemicals used in food packaging materials, pesticides and heavy metals. He divided the chemicals into 5 categories according to the dose at which no toxicological effects were observed, i.e. No Observed Effect Levels (NOELs), being <1, <10, <100, <1000 and <10 000 mg/kg in the diet, respectively, or else >10 000 mg/kg in the diet. The majority of the chemicals (180/220) had NOELs above 100 mg/kg diet. Only 19 had NOELs below 10 mg/kg diet, all of which were pesticides or heavy metals. The 5 chemicals with NOELs below 1 mg/kg diet were all pesticides that were known either to accumulate in the body, or to affect the function of the nervous system at low doses. From this analysis, Frawley suggested that for food packaging chemicals, many of which were untested and of unknown toxicity, the level of 10 mg/kg diet should be selected, since very few chemicals, and only those of a type not likely to be used in food packaging, showed toxicity in animals below this level. An additional 100-fold margin of safety should be applied to this level, giving a figure of 0.1 mg/kg in the total human diet. This was the dietary concentration for any food packaging chemical which he considered could be safely consumed by humans. It would equate to an intake of 150 μg/person/day, assuming an intake of 1.5 kg solid diet daily.

The next major development was the introduction of a ToR policy for indirect food additives, including food contact materials, by the United States Food and Drug Administration (FDA) in 1995 (4). The ToR policy used in U.S.A. is analogue to the TTC concept. This policy was developed over 10 years, as a consequence of a long-established principle of the law, "de minimis non curat lex", which means the law does not concern itself with trifles. For FDA,

this meant that the agency should focus its limited resources on issues of tangible concern rather than trivial ones. Accordingly, the agency developed an approach to set a threshold, intended to protect against all types of toxicity including carcinogenicity, for application in food packaging regulation. If exposure to an individual chemical was below the threshold, consumers would be protected "with reasonable certainty of no harm".

The approach was based on an analysis by Gold *et al.* of nearly 500 chemical carcinogens tested in animals using lifetime exposures, known as the carcinogenic potency database (5). In this database, the potency of each chemical was expressed in terms of the dose that caused cancer in 50% of the animals, the TD50 dose (6). The potencies were plotted as a distribution and then, by sliding the curve to the left, transformed into a distribution of exposures calculated to represent an estimated lifetime risk of one in a million of developing cancer or "a virtually safe dose" (VSD). This distribution of carcinogenic potencies could be used to derive an estimate of the dietary concentration of most carcinogens which would give rise to less than one in a million lifetime cancer risk, using linear extrapolation, and assuming that the risks in animals were representative of those in humans. That concentration was estimated to be 0.5 μg/kg diet, and this figure is used as the basis for the ToR policy. From this, a human daily exposure level of 1.5 μg/person was derived, assuming that a person consumes 1.5 kg of solid food and 1.5 kg of liquid food daily, and that the chemical is evenly distributed throughout the total diet.

Later, the carcinogenic potency database was enlarged to over 700 chemicals (7), but this did not alter the distribution of the calculated risks. Based on this analysis, the consumer should still be protected, even if an untested chemical to which the ToR policy is applied should turn out to be a carcinogen upon later testing. Since toxic effects other than cancer usually occur at much higher exposures, consumers would automatically be protected from these effects too.

This policy contains elements of both scientific and risk management judgements. The ToR policy means that producers can apply for an exemption from regulation of any chemical originating from food contact materials estimated to be present in the diet at levels not exceeding 0.5 μg/kg (0.5 ppb). If the FDA concludes that the conditions for exemption are met, the chemical does not have to undergo toxicological testing nor the normal premarket safety evaluation by the agency. However, basic information, such as chemical name, Chemical Abstract Service (CAS) number, conditions of use and existing toxicological data etc., must be provided. More detailed information about the ToR policy for food contact materials is given later in this document.

Chemical structure determines toxicity and differential TTC values

Munro *et al.* in 1996 (8) went on to develop the concept of generic thresholds by analysing toxic, but non-genotoxic and non-carcinogenic, effects of chemicals, according to their chemical structure. The chemicals are classified into one of three structural classes based on a "decision tree" approach developed earlier by Cramer *et al.* (9). The decision tree is consisting of a total of 33 questions, which each is answered by "yes" or "no". Each answer leads to another question, or to a final classification into one of the three classes, I, II and III, reflecting a presumed low, moderate and serious toxicity (Box 2). The reference database contained 137, 28 and 448 chemicals in class I, II and III, respectively.

Box 2. Cramer's structural classes (9).

- **Class I**: substances with simple chemical structures, for which efficient modes of metabolism exist or other data suggests a low degree of oral toxicity, i.e. substances normally present in the body.
- **Class II**: intermediate substances; they have structures that are less clearly innocuous compared with substances in class I, but do not have structures indicative of toxicity, or of a clear lack of knowledge of their characteristics, as substances in class III. Most of these substances have functional groups that are similar to, but somewhat more reactive than functional groups in class I, or they have more complex structures than substances in Class I, but they are common components of food.
- **Class III**: substances with structures that do not indicate strongly that they are innocuous, or that have indications of significant toxicity, or have reactive functional groups.

A listing of the functional groups that characterize the chemicals in Cramer's class III, i.e. the substances with the highest potential for toxicity, is shown in Box 3.

Box 3. Structures that identify the Cramer class III chemicals, i.e. high potential for toxicity (10)**.**

- aliphatic secondary amino-, cyano-, *N*-nitroso-, diazo-, triazeno-, quaternary *N*-
- unionised substituents containing elements other than C, H, O, N or S (divalent), e.g. halogeno-compounds
- safrole-like compounds
- fused lactone or α,β-unsaturated lactone
- three-membered heterocyclics, e.g. epoxides
- unsubstituted heteroaromatic compounds
- three or more different functional groups (excluding methoxy-, and considering acids and esters as one group)
- unsubstituted aromatic hydrocarbons
- substances without a strong anionic group for every 20, or fewer, carbon atoms (for substances not classified at earlier steps)

A reference database was built using results from oral toxicity tests, included subchronic, chronic, reproductive and developmental toxicity, in rodents and rabbits on 613 organic chemicals with a wide range of structures and uses. From these, the most conservative NOEL for each chemical was selected, based on the most sensitive species, sex and toxic effect, and the cumulative lognormal distributions of the 613 NOELs were plotted in three groups according to the three structural classes. For each of the three distributions of NOELs, a value coinciding with the point on the distribution where 5% of the chemicals had lower NOELs and 95% had higher NOELs, was selected, i.e. the fifth percentile NOEL. The lower fifth percentile NOELs were multiplied by 60, assuming an individual weighs 60 kg, and then divided by a factor of 100 to ensure substantial margins of safety. This gave three parametric estimated values termed "human exposure thresholds" or TTCs, one for each structural class of chemical (Box 4).

Box 4. Derivation of human exposure threshold (of toxicological concern) (TTC) values from toxicity data (8)**.**

Cramer structural class	Fifth percentile NOEL (mg/kg body weight/day)	Human exposure threshold (TTC) (mg/person/day)
I	3.0	1.8
II	0.91	0.54
III	0.15	0.09

Munro *et al.* (8) emphasised that the human exposure thresholds are intended to apply only to structurally defined chemicals for which there is no evidence of genotoxic carcinogenicity, and no structural alerts for genotoxicity, which has a predisposition to damage DNA. Later work increased the number of chemicals in the database from 613 to 900 without altering the cumulative distributions of NOELs, adding further reassurance about the validity of using this database to derive the TTC values.

Comparing these human exposure thresholds, ranging from 90-1800 μg/day, derived from data on non-carcinogenic effects, with the figure of 1.5 μg/day for FDA's ToR based on carcinogenic effects, it can be seen that the thresholds for non-carcinogenic effects are higher by at least an order of magnitude. This is in accordance with knowledge about mechanisms of various toxic effects and the doses that induce them, i.e. it is biologically plausible that some carcinogens induce tumours at lower exposures than the exposures needed to induce other toxic effects.

Validation of the ToR value also for genotoxic carcinogens

Cheeseman *et al.* used the expanded carcinogenic potency database of over 700 chemicals (7), together with short-term toxicity data, results of genotoxicity testing and structural alerts, to identify potent and non-potent subsets of carcinogens (11). This work confirmed the validity of 1.5 μg/person/day as an appropriate threshold for most carcinogens, but also proposed that a tiered ToR could be justified, using thresholds higher than 1.5 μg/person/day for less potent carcinogens. Examination of the expanded database led them to conclude that a dietary threshold of 4-5 μg/kg could be appropriate for substances without structural alerts, and even for substances with structural alerts, if they were negative in genotoxicity tests. The two exceptions to this were *N*-nitroso and benzidine-like compounds, which are more potent carcinogens, and should be excluded from regulation by ToR at all dietary concentrations. If substances had no structural alerts, were negative in tests for genotoxicity, and had LD50 values (i.e. the dose that causes death in 50% of the animals) above 1000 mg/kg body weight, a dietary threshold of regulation in the range of 10-15 μg/kg could be possible. The actual threshold level would depend on the exact LD50 value for that particular substance. The tiered approach has not yet been adopted by FDA.

Cheeseman *et al.* (11) also re-examined the underlying premise of the ToR policy that carcinogenic effects generally occur at lower dietary concentrations than other toxic effects. They 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 repeated dose toxicity tests, in addition to the 709 carcinogens. They searched for the lowest dose at which a toxic effect was seen for each chemical, and divided the lowest effect level for each substance by an uncertainty factor of 1000, to derive a range of "pseudo-acceptable intakes" (PADIs). The most likely (median)

value for the PADI was 8300-fold above the threshold value derived from the carcinogenic potency database. The results therefore supported the contention that a "virtually safe dose" based on carcinogenicity data would also protect against other toxic effects.

Validation of the TTC principle for specific endpoints

In the discussion of TTC, concerns were raised with regard to whether potentially sensitive toxicological effects that might occur at low doses would be covered by the human exposure thresholds of 0.09-1.8 mg/person/day. The effects in question were effects on the nervous system, immune system, endocrine system and development. Although the original database published by Munro *et al.* in 1996 (8) included some studies measuring these endpoints, they were insufficient in number to provide an answer to this question. An Expert Group was therefore set up by the International Life Sciences Institute (ILSI) Europe to examine this question in greater detail (12). The conclusions on which specific endpoints that should be excluded in the TTC approach are summarized in Box 5.

Expanded databases were developed for the toxicological endpoints of neurotoxicity (82 substances, of which 45 had subchronic and chronic neurotoxicity data, and 37 had acute neurotoxicity data), immunotoxicity (37 substances), developmental neurotoxicity (52 substances) and developmental toxicity (81 substances). They were analysed to see if these endpoints were more sensitive than those for structural Class III compounds in the original database (8), and to see whether the TTC of 1.5 μg/person/day derived from the carcinogenic potency database adequately covered such endpoints, plotting the distribution of the NOELs for the substances. There was no difference in the cumulative distribution of NOELs for any of these endpoints other than neurotoxicity, which was lower than for the other selected endpoints, and also for structural Class III compounds. None of the selected endpoints were more sensitive than cancer. Moreover, the TTC of 1.5 μg/person/day, based on cancer as endpoint, covered all these effects, including neurotoxicity, being 2-3 orders of magnitude lower than the neurotoxicity NOELs divided by a safety factor of 100. The ILSI Europe Expert Group concluded that a TTC of 1.5 μg/person/day is conservative, and that chemicals present in the diet that are consumed at levels below this threshold pose no appreciable risk. They further concluded that for chemicals which do not possess structural alerts for genotoxity or carcinogenicity, further analysis may indicate that a higher TTC may be appropriate.

The TTC of 1.5 μg/person/day (0.025 μg/kg body weight/day), used in the ToR policy, is designed to protect against the toxicity of most chemicals, including those of unknown toxicity should they turn out to be carcinogenic. Nevertheless, FDA acknowledges that there may be some chemicals with a very high carcinogenic potency that may be unsuitable for the ToR approach. This question was also addressed by the ILSI Europe Expert Group (10). The carcinogenic potency database used by Cheeseman *et al.* earlier (11), 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. They identified five groups of compounds having a significant fraction of their members that may still be of concern at an intake of 0.15 μg/person/day (0.0025 μg/kg body weight/day), which is 10-fold below the ToR figure. Three of these groups are genotoxic; the aflatoxin-like, azoxy- and *N*-nitroso-compounds, while two groups were non-genotoxic; the 2,3,7,8-dibenzo-*p*-dioxin (TCDD) and its analogues, and the steroids. The ILSI Europe Expert Group concluded that compounds with these structural alerts for high carcinogenic potency require compound-specific toxicity data and should be excluded from any TTC approach. A TTC of 0.15 μg/person/day could be used for all other substances with

structural alerts for genotoxicity which were not part of these five groups of high-potency carcinogens. However, this does not mean that genotoxic substances are allowed to be added deliberately to food, but rather to determine whether there is a risk concern, should they be detected in food, for instance as a contaminant.

The ILSI Europe Expert Group (10) also recommended that polyhalogenated dibenzo-*p*-dioxins, polyhalogenated dibenzofurans and polyhalogenated biphenyls, as well as non-essential heavy metals in elemental, ionic or organic forms, should be excluded because they are known to accumulate in the body, and the employed safety factors may not be high enough to account for species differences in rates of elimination of such chemicals. In addition, such chemicals were not included in the original database of Munro *et al.* (8), on which the TTC approach is based. For heavy metals extensive knowledge of their toxicological effects already exists, making use of the TTC approach unnecessary. The TTC approach should not be used either for other compounds in the diet known to show marked differences between species in their potential for accumulation in the body, for instance the fungal toxin ochratoxin A. Thus, specific considerations of metabolism and accumulation are not necessary in the application of the TTC principle as long as the decision tree is not applied to substances that are likely to show very large species differences in accumulation, such as dioxin-like compounds, or substances that have extremely long half-lives or were not included in the databases used to develop the TTC principle, such as some heavy metals.

Neurotoxicants were also explored further by the ILSI Europe Expert Group (10). Using the expanded database from the earlier ILSI Europe work, and locating the most sensitive indicators of neurotoxic effects that they could find, i.e. cholinesterase-inhibition, they plotted the NOELs for the most potent neurotoxicant, the organophosphates, separately from the other neurotoxicants. They noted that the fifth percentile NOELs for organophosphates were lower, by around an order of magnitude, than the corresponding NOELs for other neurotoxicants. The other neurotoxicants were adequately allowed for by the class III threshold (12). By applying a safety factor of 100 to the fifth percentile NOELs for organophosphates, they derived a human exposure threshold of 18 μg/person/day, and they therefore recommended that this figure should be used for organophosphates rather than the value of 90 μg/person/day used for other compounds in Class III. This step for organophosphates is not intended to replace the normal regulatory assessments and controls for organophosphates used as pesticides, but can be used to determine whether there is any risk should a non-approved or unregulated organophosphate be detected in food, for instance as a contaminant.

The ILSI Europe Expert Group (12) also concluded that whilst thresholds undoubtedly exist for sensitization and elicitation of allergic responses, they have not been established yet even for common allergens, and are known to vary between individuals and within an individual over time. Thus, although the TTC approach does take into account substances causing immunotoxicity other than allergenicity, it can not be used to assess the concern for allergenicity. Allergic risks should be controlled by other means, e.g. labelling. In addition, proteins should be excluded from the TTC approach because of their potential for allergenicity and because some peptides have potent biological activities, and because they were not included in the original database.

The ILSI Europe Expert Group (1) also concluded that because it is not known whether endocrine disrupters, i.e. chemicals that directly or indirectly affect either the structure and/or the function of the hormone producing glands or the parts of the brain that control them, are

active at very low exposures, it would be premature to include low-dose, endocrine-mediated effects in the TTC approach. Moreover, it is likely that for any chemical already identified as a potential endocrine disrupter, toxicological data will be available which can be used for full chemical-specific risk assessment.

Box 5. Summary of specific toxicity endpoints evaluated for exclusion from the TTC principle (1,10,12).

- **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
- **organophosphates** are potent neurotoxins and are evaluated in a separate step in the TTC decision tree, whereas other **neurotoxins** are covered by Cramer structural class III
- **teratotoxins** are covered by Cramer structural class III and do not need separate evaluation in the TTC decision tree
- **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
- **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

The work of the ILSI Europe Expert Group resulted in the construction of a decision tree (Box 7), 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 (10). The decision tree was finalised following a peer review workshop held in March 2003, where the science behind the various steps in the tiered approach was presented and critically discussed. The decision tree comprises a series of steps, each framed as a question, to which the answer, either "yes" or "no", will carry the user through to the next step. 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. A good estimate of intake or exposure is critical to the use of the decision tree, since this determines whether or not the TTC is exceeded. The human exposure threshold (of toxicological concern) (TTC) values suggested used in the TTC decision tree for individual types of

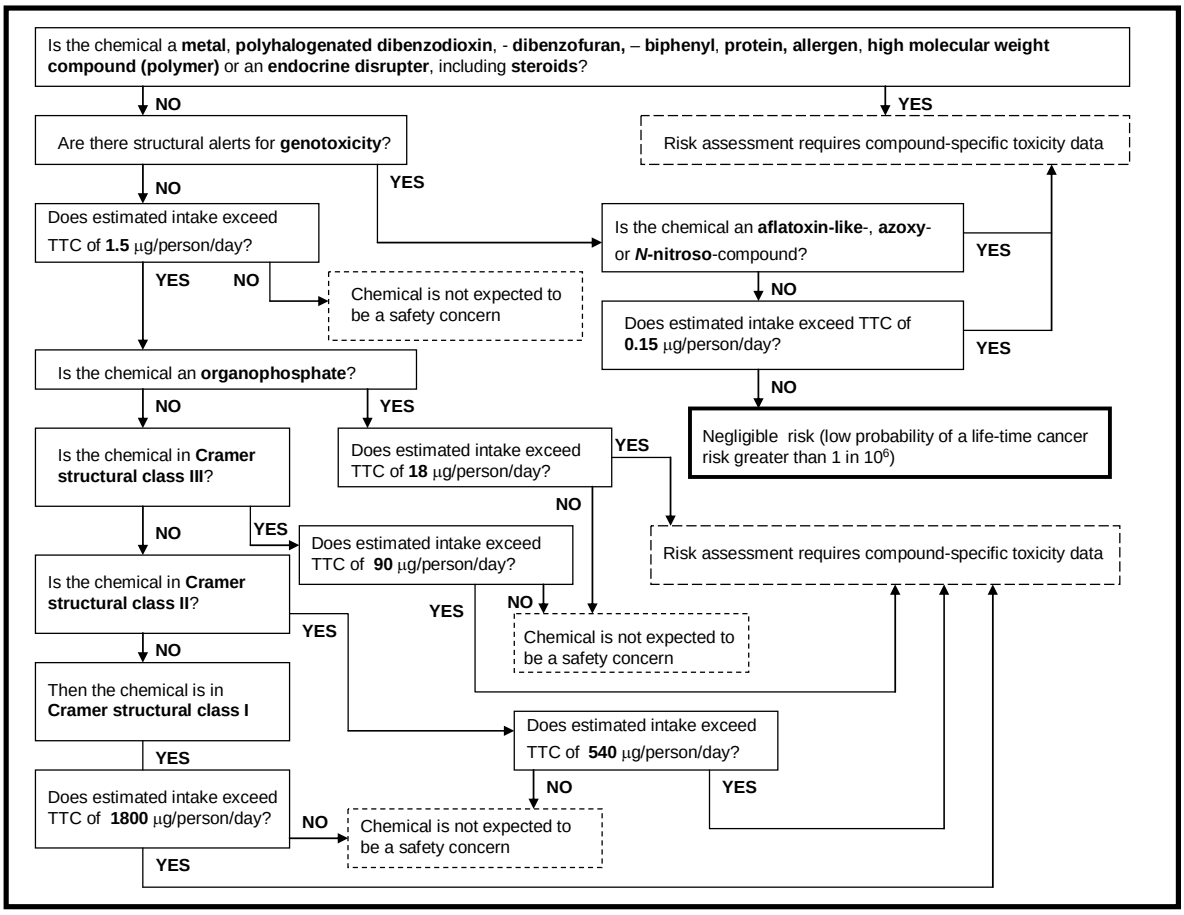
chemicals are summarized in Box 6. However, not all of these TTC values are yet in use, as specified in the footnotes.

Box 6. Human exposure threshold (of toxicological concern) (TTC) values (1)**.**

Type of chemical	μg/person/day	μg/kg body weight/day
Genotoxic compounds	0.15[a]	0.0025
Non-genotoxic compounds	1.5[b]	0.025
Organophosphates	18[c]	0.3
Cramer class III	90[d]	1.5
Cramer class II	540[e]	9
Cramer class I	1800[f]	30

[a]TTC value not used at present, but suggested for genotoxic compounds by the ILSI Europe Expert Group.
[b]TTC value used in regulation of food contact materials in U.S.A. (ToR), and in risk assessment of flavouring substances by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).
[c]TTC value not used at present, but suggested for organophosphates by the ILSI Europe Expert Group.
[d,e,f]TTC values used by the Scientific Committee on Food (SCF)/the European Food Safety Authority (EFSA)/the EU Flavour Information System (FLAVIS) Working Group, and JECFA, for risk assessment of chemically defined flavouring substances, and for natural flavour complexes (NFCs) by the Expert Panel of FEMA (the Flavor and Extract Manufacturers Association of the United States) in U.S.A.
The references to the information in these footnotes, and other values with a use similar to the TTC values here, are described for the specific areas later in this document.

Box 7. The TTC decision tree suggested by the ILSI Europe Expert group. Not all of these TTC values are in use at present (see legend to Box 6). Modified from (1).



The ILSI Europe Expert Group (10) 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 intake estimates. The decision tree provides a structured approach that allows the consistent application of the TTC principle in a risk assessment context. It will then be possible to fix a threshold value for intake for many chemicals even without a full toxicity data set, based on their chemical structure and known toxicity of chemicals with similar structure. An intake below the respective TTC values will be a negligible health risk, i.e. for compounds with structural alerts for genotoxicity a low probability for life time cancer risk over 1 per 10^6.

General view of the European Commission on the TTC principle

In the first report on the harmonisation of risk assessment procedures (13), the Scientific Steering Committee's Working Group on Harmonisation of Risk Assessment procedures in the Scientific Committees advising the European Commission in the area of human and environmental health says in 2000 that "the demand for the demonstration of the safety of an ever widening group of both natural and synthetic chemicals will require, if it is to be addressed successfully, a reliable means of assessing priorities. It is inconceivable for both practical and ethical reasons to achieve this by using a basic data set of *in vivo* and *in vitro* toxicity testing for all agents. Rather, priorities will need to be determined on the basis of reliable assessment of actual exposure levels, and consideration of physico-chemical properties including structural alerts. The underlying premise to support such a strategy is that a common exposure level can be defined that will not cause any significant adverse effect for any chemical regardless of its chemical class, termed threshold of toxicological concern (TTC). On this basis, provided the exposure level to a chemical is below the TTC value, it can be regarded as having no appreciable risk even in the absence of any toxicological data. In practise, it is important to have some additional reassurance by checking that the chemical structure does not indicate the potential for a potent irreversible or serious toxic effects, i.e. there are no structural alerts."

The report says further that "the concept is widely accepted by toxicologists, however, there is an ongoing debate about the actual level at which the TTC value should be set. In view of the great importance of the concept to addressing the risk resulting from exposure to an ever increasing number of chemicals in a transparent manner, the Scientific Committees should address the concept of TTC and identify guidelines as to how it should be applied. It must be noted that the application of TTC depends greatly on the development of agreed methods (including models) for the adequate assessment of total exposure to each chemical. This should therefore be a priority for further research."

In the second report adopted in 2003 (14), the same committee described the attempt to establish a TTC approach that is applicable to the great majority, if not all chemicals, as "a very interesting approach to the use of dose response information". It says further that "the potential practical benefits of the adoption of such a concept in the field of risk assessment are very substantial for those many chemicals where only low level exposure of consumers is likely. In principle, a threshold value could also be set for environmental effects, however, identifying the appropriate value will be more challenging than the selection of the TTC for human protection."

"For chemicals where exposure levels are likely to be consistently low a staged approach to their risk assessment could be adopted:

Stage 1: Examination of the chemical and physical properties to ensure that there are no structural alerts that could indicate a particularly high potency and therefore a need to treat the chemical differently.

Stage 2: Evaluation of the likely worst case, total exposure when the chemical is in use. This should take into account exposure to other closely related chemicals. If the exposure levels are below the TTC, no new toxicological studies would be required.

Stage 3: If the exposure levels are only just below or within an order of magnitude above the TTC value limited toxicological testing would be required concentrating on the potential to cause specific effects, e.g. genotoxicity. At this stage, in principle, *in vitro* tests could have a major role.

Stage 4: Full hazard characterisation. This would only be needed for those chemicals that raised important concerns during stages 1-3.

It should be noted that both the selection of an appropriate TTC value and the reliability of the structural alert scheme are dependent on a very robust and comprehensive database. Adoption of a TTC approach would be in keeping with the aim of the Commission of reducing animal use for testing purposes and avoiding unnecessary costs to industry. It would, however, place much more reliance on the development of reliable means of exposure assessment and provide great assistance in priority setting of chemicals for risk assessment."

In the updated opinion of the Scientific Steering Committee based on the second report from 2003 (15), it is stated that it should be "decided whether or not to adopt thresholds of toxicological and ecotoxicological concerns in a step wise scheme of risk assessment", under the heading: Future work but probable implementation within the short term.

The *ad hoc* group has not been able to locate any documents on further formal decisions regarding the use of the TTC principle within EU, or EFSA in particular, except for what is mentioned under the specific areas later in this document.

Exposure data needed for application of the TTC principle

Conventional compound-specific risk assessment usually relates risk to a certain exposure level of the substance in question. However, since the use of the TTC principle means that consumers could be exposed to substances for which there is little or no toxicity data as long as the exposures are below the relevant TTC value, it is important to ensure that exposure estimates are as complete and accurate as possible, or build in adequate conservatism to account for possible underestimates. The appropriate application of the TTC principle therefore depends on reliable exposure or intake data.

The assessment of (chronic) exposure should be carried out in the most appropriate way in order to provide sound exposure/intake estimates. If such figures are unavailable, science-based methods (16) should be used to estimate potential exposure. A tiered approach based on level of exposure is helpful in securing the appropriate level of testing necessary. If a relatively crude calculation, designed to provide a worst case estimate, does not predict an intake above the relevant TTC value, the use of more sophisticated methods may not be necessary.

It is important that the chronic exposure evaluated is relevant to the exposed population. If the substance in question is used uniquely for a specific purpose, e.g. in a particular food or cosmetic product, the exposure/intake related to that purpose should be assessed. In certain cases combined multiroute/multipathway exposures should be assessed.

To make such an evaluation, it may be necessary not only to consider exposure from a certain food item, if the substance in question is widely distributed across many dietary items instead of being present only in one or a few types of food items. Both food intake data and analytical data on levels in food, i.e. information on both the uses and occurrence in food, need to be sufficiently robust and comprehensive to enable reliable estimates of average and high intakes to be made. Analytical methods used to determine levels in food need to be sufficiently sensitive to detect low concentrations of a substance, relative to the human TTC value, otherwise a large number of non-detectable values may give a misleading picture of the total exposure.

Since particular groups in the population may consume different amounts of specific foods, food intake data may need to be sufficiently detailed to enable these groups to be examined separately, for example by age, gender or ethnicity. See also discussion of potentially vulnerable subpopulations below.

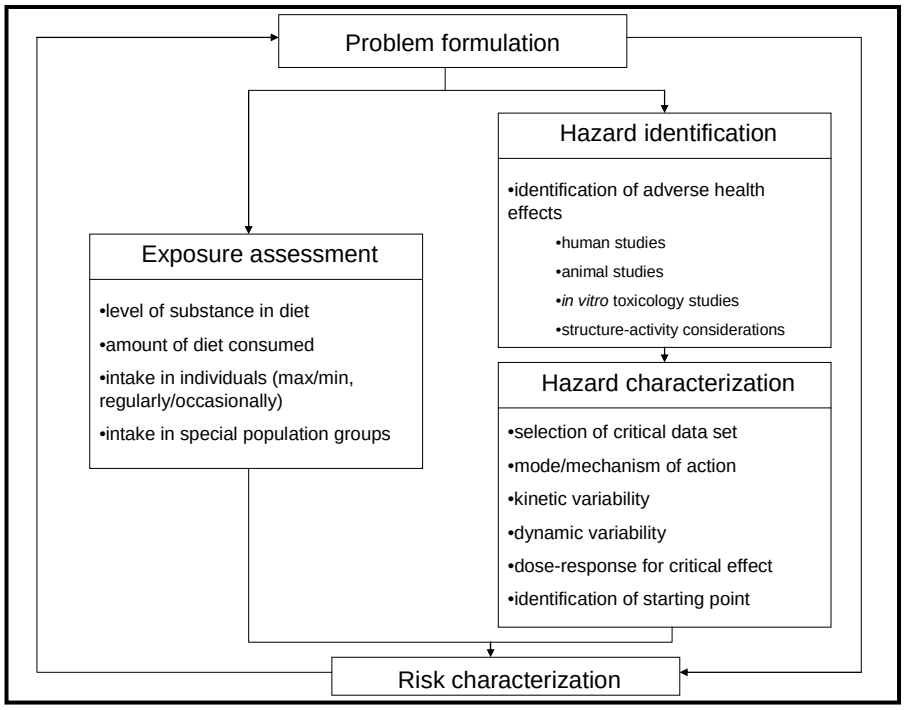
Also, other possible sources of exposure than food must be considered, i.e. air, water, consumer products, workplace etc., otherwise, the total exposure may exceed the threshold value even if exposure through a certain food item does not.

A thorough discussion of the exposure assessment part of the risk assessment process is found in reference 16. A compilation of available models of dietary exposure relevant for VKM has recently been made by the *ad hoc* working group for dietary exposure models (17).

Incorporation of the TTC principle in the risk assessment process

The traditional approach to risk assessment is separated into hazard identification, hazard characterization (including dose-response), exposure assessment and risk characterization (Box 8). Data from toxicity testing of the specific chemical is necessary for hazard identification and hazard characterization, and leads to an assessment of the nature of the adverse effects of the chemical. The risk characterization step brings together hazard identification, hazard characterization and exposure assessment, and gives an estimate of the probability of occurrence and severity of any adverse effects. In the absence of chemical-specific data, data from structurally related substances may be used to assess the nature of potential hazards qualitatively, but seldom quantitatively.

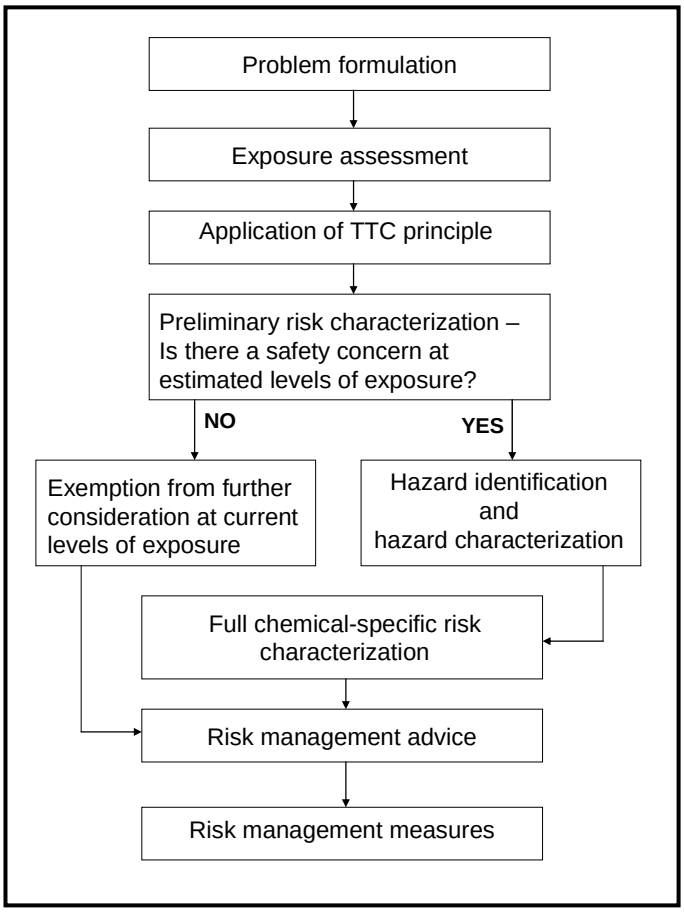
Box 8. The risk assessment process. Modified from (18).



Prior to application of the TTC approach, all available toxicity data on the compound under evaluation should be collected and evaluated. The TTC approach should be used only in cases where the available chemical-specific data is inadequate for regular risk characterization. Any available information on the compound should be considered at the same time as the decision tree is applied, to ensure that any decision is compatible with the available data (Box 9). The application of the TTC principle in food safety evaluation is not meant to replace other regulatory procedures, but rather is a preliminary step in the risk assessment process to aid in the assessment of whether chemical-specific toxicity data is necessary. However, in principle, when the TTC approach is adopted, there is no need for information on hazard identification and hazard characterization, providing that predicted or actual exposures are below the respective TTC values.

The decision tree and the TTC principle are designed as structured aids to expert judgement, and should be applied only by those who have a sufficient understanding of toxicological principles and chemical risk assessment. The output from the decision tree is either that the anticipated exposure would not be predicted to represent a safety concern, or that risk assessment is not appropriate without compound-specific toxicity data. In the latter circumstances, the results of the decision tree could be used to give advice to risk managers about the extent to which exposure would have to be reduced to give a negligible risk. Also, the TTC principle can be applied to set priorities for toxicity testing or to indicate analytical needs.

Box 9. Application of the TTC principle in the risk assessment process. Modified from (2).



Some examples of use of the TTC principle are as follows (1). It is assumed that an adult person may consume 1.5 kg of food and 1.5 kg of beverages per day. For a chemical that is non-genotoxic, non-organophosphate and belonging to structural class III, and therefore has a TTC value of 90 μg/person/day, and occurs uniformly in the whole diet, i.e. 1.5 kg food and 1.5 kg beverages, a maximum intake is reached by concentration in the diet of 30 μg/kg diet. In cases where a given chemical is not present in the whole diet, but only in a specific product, the total exposure to this chemical is determined by its concentration in the product and the amount of the product that is actually ingested daily by consumers of the product. When the chemical is present only in beverages, e.g. 1.5 kg fluids, and does not occur in food, a TTC value of 90 μg/person/day is equivalent to a concentration of 60 μg/kg beverage. When the only route of exposure is via ingestion of a single food product, which is consumed in daily amounts of 100 g, the TTC value of 90 μg/person/day would be reached by concentrations of 900 μg/kg of the chemical in that food.

If the TTC principle is applied to a non-genotoxic and non-organophosphate impurity in an approved food chemical, being an additive with a numerical acceptable daily intake (ADI) of for example 10 mg/kg body weight/day, the TTC of 90 μg/person/day or 1.5 μg/kg body weight/day would give a level of concern for any impurity that was present at more than [(1.5/ADI in μg) x 100]%, and there would be no safety concern for such impurities present at 0.015% or less.

The application of the TTC principle is a departure from traditional toxicological evaluation. However, the substances and studies were not randomly included in the databases used to develop the concept, but were compiled in order to set the worst case situation when assessing each specific endpoint. The selection of the parameters, substances and NOELs analysed in the evaluations during the development of the TTC principle was carried out using a number of conservative assumptions (10,11). When establishing the TD50 doses, the most sensitive species and sites where chosen, the databases used contained a very high number of carcinogenic substances, and simple linear extrapolation from the TD50 to a cancer risk of 1 in 10^6 was used. This is conservative because the possible effects of cytoprotective, DNA repair, apoptotic and cell cycle control processes that shape the dose-response were not taken into account. Lastly, for all substances no thresholds in the dose-response were assumed.

Areas of special concern and needs for further development of the TTC principle

Chemical mixtures

The assessment of chemical mixtures is a complex issue, and more work is needed to develop methods to deal with this question, in regular risk assessment as well as when using TTC. In principle, the TTC approach could be used to assess mixtures of substances which have similar toxic mechanisms of action (1). It would be possible to sum their exposures/intakes and compare the combined exposure/intake with the relevant TTC, provided they were of similar potency or were corrected to a similar potency. If the combined intakes were below the TTC, this would indicate that the substances would not be expected to be of concern. If the mechanisms of action of substances in the mixture were known to be dissimilar, then the TTC approach could be used in assessment of each individual substance, one at a time.

As an example, JECFA evaluates structurally related flavouring substances in groups, described in detail later in this document, by conducting individual assessments using the TTC approach on each compound and then considers the safety of the group as a whole. Simple addition of the intakes would not allow for differences in potency or interactions, and would assume that the risk for each substance, based on its structure, is not altered by the presence of the other substances.

When dealing with complex mixtures of diverse chemicals, assessment using the TTC approach should focus on the exposure to a "marker" compound or a major compound which represents a high proportion of the mixture and is of the highest Cramer class of the known constituents in the mixture.

As an added complexity, relevant exposures from sources other than the one under evaluation, e.g. from a certain food, need to be taken into consideration. However, data for exposure from other sources are often not available to consider a complete intake.

Potentially vulnerable subpopulations

Some subpopulations may be at higher risk than others, either because of higher exposure or potentially greater sensitivity to toxicity, such as the elderly due to a reduced capacity for metabolism and excretion of chemicals, infant and children, with immature metabolizing capacity for some chemicals, pregnant women because of the vulnerability of the embryo and fetus, or persons of any age having a genetic polymorphism that impairs or alters their response to a substance.

The database used to identify the NOELs for derivation of the TTC values includes toxicity studies on aged, newborn, very young and pregnant animals, therefore, the TTC should also cover potentially sensitive subpopulations (1). In addition, the use of a factor of 100 to derive a TTC from a NOEL takes into account potential metabolic differences between laboratory animals and humans, and intraindividual differences in humans.

However, subpopulations of individuals with a certain genetic polymorphism that affect the handling and response to a chemical might not be covered. Present knowledge of the nature and prevalence of such polymorphisms in different ethnic groups is not complete, and could erode the 100-fold margin of safety built into the TTC values. Therefore, at present, it is not possible to identify these potentially vulnerable subpopulations. However, this problem applies also to a conventional risk assessment as well as to the TTC approach.

Since the TTC values calculated by the ILSI Europe Expert Group are expressed as μg/person/day and are based on the 60 kg body weight of adults, the intake should be calculated separately for infants and children having a lower body weight and compared to the relevant TTC values, adjusted for body weight (1). For example, for a substance in Cramer class I, the TTC for a 10 kg infant (12-month-old) would be 300 μg/day instead of 1800 μg/day (i.e. 1800 x 10/60), after adjustment for body weight.

In addition, infants and children, because of their smaller size, may also have a higher intake of food or drink than adults expressed on a body weight basis, and therefore an increased risk. They may also consume greater absolute amounts of certain foods, e.g. fruits, than adults, because of dietary preferences, and have a less varied diet, e.g. high intake of infant formula or processed baby food, which affect the intake estimates.

Non-oral exposure and aggregate exposure (multiroute/multipathway)

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 for route-to-route extrapolation. It is also necessary to develop methodology to assess combined multiroute or multipathway exposures. Such methodology is not yet developed. Advances in exposure modelling should also cover the need for assessments of such aggregate exposures, and also cumulative exposures, both in terms of multiple chemicals with the same mode of action and accumulation in the body over time. Several projects are under way developing computer software for better exposure modelling for use in risk assessment (16,17).

RISK ASSESSMENT IN AREAS RELEVANT FOR VKM PANELS 4 AND 5

Food contact materials

EU/Norway
In the EU, food contact materials are regulated by three types of directives: The Framework Regulation (EC) 1935/2004 ("Rammeforordningen"), which sets up general requirements for all food contact materials, specific directives which cover single groups of materials and articles listed in the Framework Directive, and directives on individual substances or groups of substances used in manufacture of materials and articles intended for food contact (19). Of the specific materials, the regulation of plastics (Commission Directive 2002/72/EC) is the most developed. In addition to the plastics directive, the Synoptic Document consists of provisional lists of monomers and additives notified to the European Commission for use in the manufacture of plastics or coatings intended to come into contact with foodstuffs (20). In Norway, food contact materials are regulated in "Forskrift om materialer og gjenstander i kontakt med næringsmidler (Matemballasjeforskriften"), FOR-1993-12-21-1381 (21).

Food contact materials should be safe and should not transfer their components, i.e. the constituents should not migrate, into the foodstuff in unacceptable quantities. Approximately 3000 substances may potentially migrate into food from food contact materials (12). To ensure the protection of the health of the consumer and to avoid any contamination of the foodstuff, two types of migration limits have been established for plastic materials: 1) an Overall Migration Limit (OML) of 60 mg substance/kg foodstuff or food simulant, that applies to all substances that can migrate from food contact materials to foodstuffs, and 2) a Specific Migration Limit (SML), which applies to individual authorised substances and is fixed on the basis of the toxicological evaluation of the substance. The SML can be established in two different ways. For substances with adequate toxicological data, an acceptable daily intake (ADI) or a tolerable daily intake (TDI) is set, and this value is used to calculate the SML. To set this limit, it is assumed that every day throughout the lifetime a person weighing 60 kg eats 1 kg food packed in plastics containing the relevant substance at the maximum permitted quantity. For substances with a reduced toxicological data set, the limits are set according to degree of migration, as shown in Box 10, e.g. the limit is 0.05 mg/kg food when only mutagenicity test data exists for the substances. A material is considered suitable for packaging any type of food if migration into the four simulants (water, 3% acetic acid, 10% ethanol, and olive oil or other fat simulants) are below the SML. If a migration into a given food simulant exceeds the SML, the material is considered unsuitable for the corresponding class of food.

The currently used assumption of intake of 1 kg packed food/60 kg person/day as a standard in exposure calculations is generally assumed to be a conservative estimate. However, it is not realistic in all cases. In some instances, there is an overestimation of the exposure, e.g. to fat-soluble migrants. Therefore, approaches which take better account of the actual level of exposure of consumers to food contact materials in risk assessment are under discussion. As a first step towards introducing consumption-related reduction factors, it was suggested to introduce a fat (consumption) reduction factor (FRF) varying from 1 to 5 in accordance with the quantity of fat present in the fatty foodstuffs, i.e. if the fat content is 20%, the FRF = 1, if the fat content is 100%, the FRF=5. This is now included in the draft of the 4th amendment of the plastics directive (Commission Directive 2002/72/EC). However, this factor should be applied only to lipophilic substances in certain prescribed situations (22).

In other instances, there may be an underestimation of exposure, especially for children, who eat more than adults per kg body weight. In this case, there may also be a need for modification of exposure calculations, as has been suggested by the Norwegian Food Safety Authority (23). The Food Standards Agency in the U.K. has ongoing research projects on packaged food intake and food consumption factors, and whether they can ensure specific protection against chemical migration into food marketed for children (24). The Institute of European Food Studies, Trinity College, Dublin, and their commercial company Creme (Centre for Research on Exposure Modelling Estimates), are working on probabilistic models for food packaging migration that allow probabilistic analysis of human exposure to food packaging migratory compounds (25). There are also ongoing EU research projects on mathematical modelling of migration from food contact materials to foodstuffs that can be used for estimation of consumer exposure (26,27).

Regarding the use of the TTC principle in risk assessment of components migrated from food contact material into food within EU, only preliminary discussions and plans have been found so far. The former Scientific Committee for Food was asked by the EU Commission to give an opinion on the scientific basis of the concept of threshold of regulation in relation to food contact materials, and concluded in their answer expressed on 8 March 1996 that "the concept behind the threshold of regulation policy, that is to say, the proposition that there is a level of exposure to non-carcinogenic chemicals in the diet below which, even in the absence of toxicity data, there is reasonable assurance that no adverse effects would occur in man, is a sound one" (28). They stated further that "before any firm conclusions could be reached on dietary limit value for a threshold of no toxicological concern for non-genotoxic endpoints, it would be necessary to conduct an up-to-date review of existing data covering important endpoints of concern which may give rise to effects at low doses, such as neurotoxic, immunotoxic, endocrinologic and developmentally toxic events." Regarding genotoxic chemicals, they said that "present scientific knowledge does not allow a definite conclusion as to whether or not a true threshold exists for genotoxic carcinogens".

In the document Food Contact Materials – A Practical Guide for Users of European Directives (29), the Threshold of Regulation as used by FDA in U.S.A. is mentioned in a chapter with the heading "Other issues of EU plastic regulation", containing information about "Other problems (that) have been considered at EU level, even though there may not be specific rules on them yet". No more information was given on how EU looks upon the TTC principle in connection with food contact materials. The last update was January 5, 2002.

As far as the *ad hoc* group has been able to find out, EFSA has not yet formally accepted the TTC principle as such, even after the specific non-genotoxic endpoints mentioned above have been evaluated by the ILSI Europe Expert group, and also a separate, lower TTC value has been suggested for genotoxic substances. However, in evaluation of food contact materials migration thresholds are used to decide the amount of toxicity data needed to be supplied by the petitioner to the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC Panel) in EFSA (30). As a general principle, the greater the exposure through migration, the more toxicological information will be required. In case of high migration, i.e. 5 – 60 mg/kg food, an extensive core data set is needed to establish safety (Box 10). In cases of migration between 0.05 – 5 mg/kg food, a reduced core data set may suffice. In case of low migration, i.e. <0.05 mg/kg food, only a limited data set of three *in vitro* mutagenicity tests is needed.

Box 10. A tiered approach for toxicity testing of food contact materials used by EFSA (30)**.**

Degree of migration	Toxicity tests needed
<0.05 mg/kg food	3 *in vitro* mutagenicity tests: • A test for gene mutations in bacteria • A test for gene mutations in mammalian cells (preferably the mouse lymphoma $tk^{+/-}$ assay) • A test for chromosomal aberrations in mammalian cells
0.05 - 5 mg/kg food	• 3 *in vitro* mutagenicity tests as above • A 90-day oral toxicity study • Data to demonstrate the absence of potential to accumulate in man
5 – 60 mg/kg food	• 3 *in vitro* mutagenicity tests as above • 90-day oral toxicity studies, normally in two species • Studies on absorption, distribution, metabolism and excretion • Studies on reproduction in one species, and developmental toxicity, normally in two species • Studies on long-term toxicity/ carcinogenicity, normally in two species • If available, information about occupationally exposed humans

In the draft of the 4th amendment of the Directive 2002/72/EC relating to plastic materials and articles intended to come into contact with foodstuffs, i.e. the plastics directive, the concept of functional barrier is introduced, i.e. a barrier between plastic material or article composed of two or more plastic layers and food, able to prevent the migration in food of substances which may migrate from the plastic layers not in direct contact with food. This functional barrier concept permits the use of non-authorised substances in the layers behind the barrier, provided they do migrate in levels at or below 0.01 mg/kg in food or food simulants, and are not classified by the Directive on dangerous substances, 67/548/EEC, as proven or suspected carcinogenic, mutagenic or toxic to reproduction (CMR) substances. The *ad hoc* group does not know the reasoning behind the suggestion of this particular value, but it is 20 times higher than the ToR value used for food packaging materials in U.S.A. (0.5 ppb or 0.5 μg/kg food).

Biosafepaper - Application of Bioassays for Safety Assessment of Paper and Board for Food Contact is a pre-normative research project with nine European countries, including Norway, as members (31). The project objectives were to establish scientifically sound recommendations for harmonised risk assessment of paper and board in contact with food using a decision tree approach, based on development of a battery of standardized *in vitro* tests for cytotoxicity and genotoxicity, and standardized extraction procedures simulating different foodstuffs. If successful, the same principles may probably also be used for risk assessment of other types of food contact materials. The outcome of the comparison of various *in vitro* cytotoxicity tests is already published (32), and the results of the whole project that was completed in November 2005 were presented at a conference in Brussels on

April 12, 2006. The test battery should be regarded as a screening tool, and the decision tree should help identify the hazards and the way to proceed. It should not be used to reject any products on the basis of test results only, but to find out whether a more thorough risk assessment is needed. Before being used, this new approach needs to be approved by the EU regulatory board for food contact materials, after a positive evaluation of the decision tree and the use of correction factors, needed to relate the extracts to the migration expected into foods, by the AFC Panel of EFSA. The extraction protocols need to be approved by the European Committee for Standardization (CEN), and the *in vitro* tests need to be validated by the European Centre for the Validation of Alternative Methods (ECVAM) and agreed by Organization for Economic Co-operation and Development (OECD) editing the corresponding guidelines.

The Norwegian Food Safety Authority has commented on TTC in the context of comments to a draft of the SuperRegulation (33). They "recommend the use of TTC, which implies a daily intake of no more than 1.5 μg/person/day (60 kg) based on a daily food and drink intake of 3 kg. This corresponds to a Threshold of Regulation (ToR) of 0.5 μg/kg food as used by the FDA. This implies that documentation is not required for not intentionally added substances which migrate in concentration levels less than ToR, provided these substances are non-CMR substances. The Norwegian Food Safety Authority recommends ToR (0.5 μg/kg food) as a general regulatory limit value for not intentionally added substances and not authorized substances from multilayer materials as well as monolayer materials. This limit provides a regulatory limit for the enforcement of Article 2 (Materials and articles shall not transfer their constituents to food in quantities which could endanger human health) in the New Framework Regulation (Directive 89/109/EEC), which applies to such substances."

The Norwegian Food Safety Authority has stated that it will be useful in their future regulatory work with food contact materials towards the EU Commission that VKM has been discussing the use of the TTC principle in risk assessment (personal communication with Adviser Per Fjeldal, December 13, 2005).

U.S.A.

As mentioned above, one of the applications today of the TTC principle is in risk assessment of food contact materials by FDA in U.S.A., where the policy is called Threshold of Regulation (ToR) (4). The FDA includes packaging materials in its definition of food-contact substances. A food-contact substance is specified as any substance that is intended for use as a component of materials used in manufacturing, packaging, transporting or holding food if the use is not intended to have any technical effect in the food. The FDA further identifies any food-contact substance that is reasonably expected to migrate to food under conditions of intended use to be a food additive. It is the extent of migration, in addition to the inherent toxicity of the packaging material components, that comprise the parameters of the risk assessment of packaging materials. Data that must be submitted for risk assessment of such products are the chemical constituents, intended use, information about what type of food (e.g. fatty, aqueous etc.) to be contained in the package, intended technical effects and fates of any components such as stabilizers, catalysts etc., as well as analytical methods for measuring migration of components from the packaging material to solvents simulating aqueous, alcoholic or fatty foods. A comprehensive toxicology profile of the components of the packaging material, including decomposition products and any substances used in their manufacture, is evaluated.

A key component of the safety evaluation is the extent of anticipated human exposure (Box 11). The amount of toxicity testing is tied to perceived risk. The FDA permits the application of the TTC principle, called ToR in the United States, to packaging materials when the overall dietary concentration of a packaging material migrant is below 0.5 ppb (0.5 μg/kg), which equals an intake of 1.5 μg/person/day, assuming a total daily intake of food and drink of 3 kg (1.5 kg of solid food and 1.5 kg of liquid food), and no toxicity testing is then required. Above this threshold, the degree of testing increases as exposure increases. Components of food-contact articles entering the diet in concentrations above the threshold of 1 ppm and that meet the food additive definition in the Federal Food, Drug, and Cosmetic Act (FFDCA) must be regulated after an extensive safety review via the food additive petition process (see section below on direct food additives).

Box 11. A tiered approach for toxicity testing of indirect food additives used by FDA (34)**.**

Dietary concentration (DC) of migrant	**Toxicity tests needed**
<0.5 ppb <0.5 μg/kg <1.5 μg/person/day	No testing required, although basic information about the chemical and a toxicity profile based on available data is expected
>0.5 ppb - <50 ppb >0.5 μg/kg - <50 μg/kg >1.5 μg/person/day - <150 μg/person/day	Only genotoxicity tests (e.g. *in vitro* bacterial mutagenicity and *in vitro* mouse lymphoma $tk^{+/-}$ assays) are needed
>50 ppb - <1 ppm >50 μg/kg - <1 mg/kg >150 μg/person/day – <3 mg/person/day	Additional genotoxicity tests (e.g. *in vivo* rodent assay for chromosomal damage) and two subchronic oral toxicity test are needed, one in rodent and one in non-rodent species
>1 ppm >1 mg/kg >3 mg/person/day	Complete toxicology testing may be required, as specified for direct food additives

The ToR is defined as a specific level of dietary exposure that is well below the dietary exposures that typically induce toxic effects, and therefore, pose only negligible safety concerns. Although the ToR is designated to protect against all types of toxicity, including carcinogenicity, and should therefore be sufficiently low to ensure the protection of public health even if the substance in question is later shown to be carcinogenic, a substance exempted from full testing using ToR should not contain structural alerts indicative of potential carcinogenicity, and there can not be any evidence that the substance is a known carcinogen in animals or humans. The FDA is prohibited by law (Section 409(c)(3)(A) of the FFDCA from regulating known carcinogens as food additives. In U.S.A., food contact materials are regulated as indirect food additives (see section on Food additives later in this document). Lists of such structural alerts indicating carcinogenicity are given in references 35-37. Complete details of the criteria for ToR exemption are given in Title 21 of the U.S. Code of Federal Regulations, section 170.39 (21 CFR 170.39).

In the food contact notification (FCN) programme newly implemented in U.S.A., by which FDA reviews food contact substances for safe use (38), structure-activity relationship (SAR) analysis is used in qualitative and quantitative risk assessments. Also, decision tree procedures, such as the one by Cramer *et al.* (9), may be used in this process (34).

Experience with use of the ToR principle in U.S.A. indicates that it is highly practical and cost-saving, since approximately two-thirds of the reviews conducted by FDA were favourable. It is estimated that the use of ToR has reduced the workload of the FDA by around 15% (1). Further development of the principle may justify higher thresholds of regulation, leading to an even better use of limited resources and more timely risk assessments.

Flavouring substances

Flavourings are substances used to give flavour and/or odour to food. Various types of flavourings are defined by EU legislation; natural, natural-identical or artificial flavouring substances, flavouring preparations of plant or animal origin, and process flavourings which evolve flavour after heating and smoke flavourings (39). In Norway, flavouring substances are regulated in "Forskrift om aromaer mv til næringsmidler (Aromaforskriften"), FOR-1993-12-21-1379 (40), which is based on Council Directive 88/388/EEC with amendments (39).

The two main types of flavouring ingredients are chemically identified flavourings and naturally-occurring flavour mixtures isolated primarily from plants (41). The vast majority of chemically identified flavourings (ca. 1700) exists naturally in foods or is formed during preparation of foods via heating and mixing. The remaining ca. 350 substances that are produced by synthesis and are not found in nature, are structurally related to naturally-occurring flavourings. Regardless of their origin, essentially all chemically identified flavourings belong to approximately 40 well-defined structural chemical groups. Each flavour ingredient can therefore be evaluated individually and within the context of its chemical group. There are about 400 natural flavour complexes (NFCs) in current use as flavours. Also these contain constituents formed by well-recognized biochemical pathways in plants and exhibit similar skeletal structures and possess a limited number of functional groups, and therefore the vast majority of the constituents fall into a few well-defined chemical groups. If the structure of a substance under evaluation can be assigned to a well-defined chemical group for which safety data exists, the substance in question can be evaluated even if little or no toxicological data exists on that particular substance.

More than 2800 different chemically defined flavouring substances are claimed by industry to be currently added to foods and beverages in Europe or U.S.A. They are volatile organic chemicals, and the majority has simple, well-characterized structures with a single functional group and low molecular weight (<300 g/mol) (42). The use of flavouring substances is generally self-limiting and governed by the flavour intensity required to provide the necessary organoleptic appeal. Thus, they are used in low concentrations resulting in very low human intakes. Most flavourings are consumed by humans in amounts of less than 1 mg/person/day (41,42).

JECFA and EU

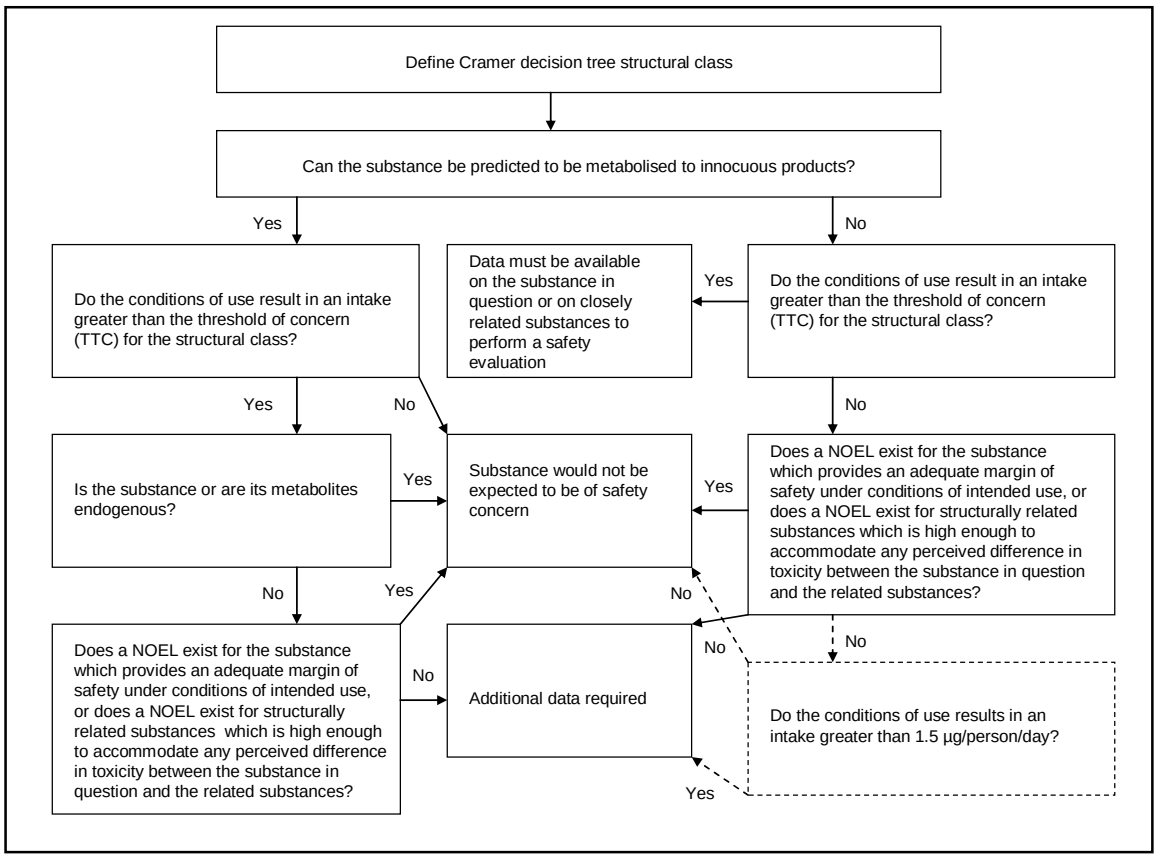
Individual flavouring agents have been evaluated by JECFA since 1967 (41). Approximately one substance was evaluated annually, and an ADI was assigned. In 1995, a novel safety evaluation programme was adopted, using a group assessment approach. More than 1300 substances are assessed as safe for use as flavourings under current conditions of intake. JECFA has used the TTC approach for both evaluation of individual flavouring substances and of NFCs.

In Europe, the Committee of Experts on Flavouring Substances (CEFS) of the Council of Europe (CoE) published a "Blue Book" in 1973, which provided a list of evaluated flavour substances, the majority of which apparently had been adopted from the Flavor and Extract Manufacturers Association of the United States (FEMA) Generally Recognized as Safe (GRAS) lists in U.S.A. From 1993 to 1995, the EU SCF convened a Flavour Working Group to evaluate the safety of these substances. After a hiatus, the Flavour Working Group was reconvened in 2000 to continue the evaluation process. By the foundation of EFSA from the European Parliament and Council regulation (EC) No 178/2002 of 28 January 2002, the SCF and its Working Group were succeeded by the EFSA AFC Panel.

The TTC principle is now used by EFSA to evaluate flavouring substances, basically according to the procedure adopted by JECFA in 1997 (43). The method was evaluated by SCF in 1999, and adopted for use in the EU with some modification (44). The draft opinions are prepared by the FLAVIS Working Group, being led by the Institute of Food Safety and Nutrition at the Danish Veterinary and Food Administration. They are thereafter evaluated by the Flavourings Working Group under the AFC Panel in EFSA, and then passed on to the AFC panel for final adoption. The end goal is to achieve a EU positive list of chemically defined flavouring substances. Information about the EU legislation regarding flavourings and an updated status report on the evaluation programme on flavouring substances in Europe are available (39). The database of flavouring substances now contains 2748 substances (May 4, 2006). The positive list of flavourings is estimated to be finished in 2007.

The safety evaluation of flavouring substances both by JECFA and FLAVIS/EFSA takes into account available information on structure-activity relationships, metabolism, intake and toxicity data (Box 12). First, the substances are determined to belong to one of three Cramer classes according to their chemical structure (9). Structural class I covers substances with presumptive low level of toxicity, structural class II contains substances which presumptive medium toxicity, while structural class III contains substances with significant toxicity. A TTC value is established for each structural class, derived from NOELs from a large database on subchronic and chronic animal studies on organic compounds (8), being 1800, 540 and 90 µg/person/day, for class I, II and III, respectively. Thereafter, it is considered whether the substances can be metabolized to innocuous products or not. If the answer to this question is "yes", the next step is to examine whether estimated intake of the substance is greater than the TTC value for its structural class, calculated by the Maximised Survey-derived Daily Intake (MSDI) method (see below). If the estimated intake is below the respective TTC value, the flavouring would not be expected to be of safety concern. If the intake is above the TTC value, but the flavouring or its metabolites are endogenous, the same conclusion is reached. If they are not endogenous, toxicity data has to be taken into account. For flavourings not predicted to be metabolized to innocuous products and with an intake above the respective TTC value, more data must be available on the flavouring or closely related substances to perform a safety evaluation. For flavourings not predicted to be metabolized to innocuous products and with an intake below the respective TTC value, toxicity data is taken into account. From the NOEL value it is determined whether there is an adequate margin of safety under the condition of intended use. If the margin is high enough the substance will not be considered to be of a safety concern. If the margin is low, additional data on the substance is required.

Box 12. The decision tree procedure for risk assessment of chemically defined flavouring substances. The EU does not accept flavourings based solely on an estimated intake lower than the TTC value of 1.5 μg/person/day (stippled), as is used by JECFA (modified from 41-43)**.**



The method used by SCF/EFSA/FLAVIS mainly follows the decision tree procedure established by JECFA with a few exceptions (Box 12). The potential genotoxicity of the substances is not explicitly addressed in the JECFA procedure. Flavourings should, according to the SCF opinion from 1999, also be examined for structural alerts for genotoxicity (44). If evaluation of metabolism, structural alerts or test results indicate that the substances are likely to be genotoxic, they are not put through the decision tree procedure. Also, as SCF previously, EFSA/FLAVIS do not accept the use of flavourings on the sole basis that the estimated intake of this substance is lower than the TTC of 1.5 μg/person/day, as is used by JECFA. It is argued that the TTC of 1.5 μg/person/day of a flavouring substance will present, at most, an insignificant risk (42). The arguments given for this view are the following: the value is set based on carcinogenicity data, being a sensitive endpoint in susceptible animal species with relevance to humans, and the data base used represents a worst case situation since the chemicals were tested over a lifetime by daily administration at the maximum tolerated dose (MTD). The procedures used to establish the TD50s involved numerous conservative assumptions, linear extrapolations from the lowest TD50 were used for each substance in the database, and the use of structural alerts makes it unlikely that any untested flavouring should turn out to be a genotoxic carcinogen. Lastly, many of the flavourings are actually consumed in even lower levels than 1.5 μg/person/day, and specific endpoints, such as developmental toxicity, neurotoxicity and immunotoxicity, demonstrated even higher human exposure thresholds than 1.5 μg/person/day.

The TTC value of 1.5 μg/person/day does not represent the absolute certainty that an untested chemical present in food below this value will represent less than 10^{-6} risk, but rather that there is a 95% probability that the cancer risk from such a chemical is less than 10^{-6}. The *ad hoc* group has not been able to establish whether this residual uncertainty for the possibility that a highly potent genotoxic carcinogen might inadvertently be considered acceptable using this concept, or a general, fundamental difference in risk assessment policy, possibly regarding the discussion of thresholds even for effects of genotoxic substances, or some other arguments, are the reasons behind why SCF/EFSA have not accepted the TTC value of 1.5 μg/person/day.

Intake estimation is an important step in safety evaluation of flavouring substances by the TTC approach. Two methods are at present used to estimate intake of flavourings, the Maximised Survey-derived Daily Intake (MSDI) method and a modified Theoretical Added Maximum Daily Intake (mTAMDI) method. Although both are used in the opinions adopted by EFSA, the final evaluations are based on the MSDI method. However, if the calculated mTAMDI for a flavouring substance exceeds the relevant threshold for its structural class, more reliable exposure data is requested by which the substance will be re-evaluated (45).

The MSDI method is derived from the annual European production volume of flavourings as reported by the industry. In deriving the MSDI, it is assumed that the production figure only represents 60% of the use in food due to underreporting from industry in Europe. In addition, it is assumed that only 10% of the population are consumers of the particular substance (eaters only). The resulting figure gives an estimate of the average intake of the flavouring among consumers (46).

Using the MSDI method for intake estimations has several limitations. The MSDI data is derived from surveys on annual production volumes in Europe which were conducted in 1995 by the International Organization of the Flavor Industry (IOFI). This information is old, and the production of flavours has probably changed considerably since 1995. The MSDI method does not take into account the consumption pattern of subgroups in the population. It does neither consider geographic variations in the use of the flavourings, nor the fact that a specific flavouring substance can be used only in one or very few food categories. Data from U.S.A. shows that there may be a great variation in the periodically reported production volumes, with several orders of magnitude for a specific flavouring (47). However, new data for estimation of intake with the MSDI method is announced to be available in 2006.

The TAMDI method uses figures for an assumed amount of flavoured foods and beverages consumed, and for the content of the particular flavouring in these foods and beverages. The method concentrates on those foods and beverages to which flavourings may be added. Due to lack of sufficient data for food and beverage consumption SCF made use of a modified estimate of consumption figures for artificial sweeteners worked out by the Codex Alimentarius Commission (Codex) (46). The food and beverage consumption is multiplied by corresponding upper use level of the particular flavouring supplied by the industry.

One of the main limitations of the TAMDI method is that it often overestimates the level of intake, sometimes by orders of magnitude (44,46). The main reasons for this are that it is assumed that all flavoured food and beverages contain the specific flavour and that all flavoured products contain the upper use levels. However, in 2004, the AFC Panel in EFSA decided that flavouring evaluations should be supplemented with a modified TAMDI method,

described above, in addition to the MSDI method, using normal use levels rather than upper use levels (45).

U.S.A.

The first GRAS list of flavouring substances was published by the FDA in 1958. Since 1960, the risk assessments of flavouring substances in U.S.A. have been performed by the Expert Panel of FEMA (41). More than 2000 chemically identified substances used as flavour ingredients in food have been evaluated during the last four decades. Although the panel supports the TTC approach, the evaluation of the safety of a GRAS candidate flavouring substance is based on a comprehensive evaluation of all available scientific data on the substance and structurally related substances. As for the evaluations performed by JECFA and EFSA, the GRAS evaluations also take advantage of the fact that most flavourings belong to relatively few well-defined structural groups, within which there exists a reasonable homology in terms of toxicity and metabolic fate.

The criteria used by the Expert Panel for determination of GRAS for flavour ingredients are intake of the flavour ingredients intentionally added to food based on recommended levels of use in specific food categories, such as baked goods or chewing gum, and the total annual amount of flavour ingredient sold into the market-place by the flavour manufacturers of U.S.A.; natural occurrence, purity and specifications; chemical structure and interaction with biologically important macromolecules; metabolic and pharmacokinetic characteristics; toxicity testing including that for general toxicity, carcinogenicity, genotoxicity, and developmental and reproductive toxicity, immunotoxicity and neurotoxicity.

Intake is predicted using data from the industry-wide annual poundage surveys, and assuming that only 10% of the population consumes the total annual reported volume of use of a flavour ingredient. Under some circumstances where there may be a specialized eaters group, the Expert Panel will estimate intake for a subset of specialized eaters, i.e. cool-mint gum chewers. To correct for possible incompleteness in the poundage surveys, this data is corrected with a factor corresponding to the reporting efficiency in the individual survey, which was 60% of total annual volume of the flavouring agents reported by the industry in 1977, and 80% since 1999. The per capita daily intakes (PCI) are calculated from the annual volume, in kg, for the population in U.S.A. The calculated PCI is then multiplied by ten to obtain a reasonable conservative estimate for intake by the eaters of the ingredient. The PCIx10 method used in U.S.A. is similar to the MSDI method used in Europe, and the intake can be calculated by the following equation:

$$\text{Intake } (\mu g/\text{person/day}) = \frac{\text{annual volume of production (kg)} \times 10^9\ (\mu g/kg)}{\text{population of consumers} \times 0.6 \text{ (or } 0.8) \times 365 \text{ days,}}$$

assuming the population of consumers to be 32×10^6 in Europe and 26×10^6 in U.S.A. The intake is corrected for possible incompletely reported annual volume of flavouring substances with a correction factor of 0.6 in Europe and 0.8 in U.S.A. (48).

Since development of the TTC approach in 1995, the Expert Panel of FEMA has adopted the TTC principle according to the chemical classes and thresholds described above for EFSA in their safety evaluation of NFCs, such as essential oils (41). They state that the TTC approach provides an efficient method to organize and prioritize the significant amount of data on the relatively large number of chemical constituents and chemical groups in a NFC, and can be used to evaluate the small amounts of unidentified substances in such a complex mixture.

Food additives

EU/Norway
Food additives are substances added intentionally to foodstuffs to perform certain technological functions, for example to colour, to sweeten or to preserve. In the EU, food additives are regulated by a framework directive (Council Directive 89/107/EEC) and three specific directives; on colours, sweeteners and the remaining food additives (49). Only those additives that are explicitly authorised may be used. Most food additives may only be used in limited quantities in certain foodstuffs. If no quantitative limits are set, it may be used according to good manufacturing practice (GMP), i.e. only as much as necessary to achieve the desired technological effect. Food additives may only be authorised if there is a technological need for their use, they do not mislead the consumers, and they present no health hazard to the consumers. Prior to their authorisation, food additives have been evaluated for their safety by SCF or EFSA. Furthermore, all authorised food additives have to fulfil purity criteria which are set out in detail in three separate directives (49). In Norway, food additives are regulated in "Forskrift om tilsetningsstoffer til næringsmidler (Tilsetningsstofforskriften"), FOR-1993-12-21-1378 (50), which is a compilation of the various EU Directives. In the Nordic countries, a positive list of food additives with ADI values has been compiled based on the EU Directives.

No fixed programme for testing of food additives is laid down, but a general framework covering core studies and other additional tests is given in the document Guidance on submissions for food additive evaluations by the Scientific Committee on Food (51). The studies required will depend on the chemical nature of the additive, its proposed uses and levels of use in the food, and whether it is a new additive or a re-examination of an existing additive. Since only food additives that have been through a full toxicological evaluation are allowed to be used according to the regulations, the TTC principle is not relevant in the risk assessment of food additives. However, the TTC approach may possibly be used should an unsuspected chemical or impurity be detected in a food additive, as described below for other groups of chemicals in food.

U.S.A.
Legally, in U.S.A. the term food additive refers to "any substance the intended use which results or may reasonably be expected to result - directly or indirectly - in its becoming a component or otherwise affecting the characteristics of any food" (52). This definition includes any substance used in the production, processing, treatment, packaging, transportation or storage of food. If a substance is added to a food for a specific purpose in that food, it is referred to as a direct additive, for example, the sweetener aspartame. Many direct additives are identified on the ingredient label of foods. Indirect food additives are those that become part of the food in trace amounts due to its packaging, storage or other handling. For instance, minute amounts of lipophilic chemicals may migrate from plastic packaging into fatty foods during storage (see above).

Food and colour additives are regulated by the FFDCA of 1938, which gives the FDA authority over food and food ingredients and defines requirements for truthful labelling of ingredients. The Food Additives Amendment to the FFDCA, passed in 1958, requires FDA approval for the use of an additive prior to its inclusion in food. It also requires the manufacturer to prove an additive's safety for the ways it will be used. The Food Additives Amendment exempted two groups of substances from the food additive regulation process. All substances that the FDA or the U.S. Department of Agriculture (USDA) had determined

were safe for use in specific food prior to the 1958 amendment were designated as prior-sanctioned substances. Examples of prior-sanctioned substances are sodium nitrite and potassium nitrite. A second category of substances excluded from the food additive regulation process are generally recognized as safe (GRAS) substances. GRAS substances are those whose use is generally recognized by experts as safe, based on their extensive history of use in food before 1958 or based on published scientific evidence. Salt, sugar, spices, vitamins and monosodium glutamate are classified as GRAS substances, along with several hundred others. Manufacturers may also request FDA to review the use of a substance to determine if it is GRAS. Since 1958, the FDA and the USDA have continued to monitor all prior sanctioned and GRAS substances in light of new scientific information. If new evidence suggests that a GRAS or prior sanctioned substance may be unsafe, federal authorities can prohibit its use or require further studies to determine its safety.

In 1960, Congress passed similar legislation governing colour additives. The Color Additives Amendments to the FFDCA require dyes used in foods, as well as in drugs, cosmetics and certain medical devices, to be approved by the FDA prior to their marketing. In contrast to food additives, colour additives in use before the legislation were allowed to be used continuously only if they underwent further testing to confirm their safety. Of the original 200 provisionally listed colour additives, 90 have been listed as safe, and the remainder has either been removed from use by the FDA or withdrawn by industry.

Both the Food Additives and Color Additives Amendments include a provision which prohibits the approval of an additive if it is found to cause cancer in humans or animals. This clause is often referred to as the Delaney Clause, named for its Congressional sponsor, James Delaney. The GMP regulation limits the amount of food and colour additives used in foods. Manufacturers may use only the amount of an additive necessary to achieve the desired effect.

To market a new food or colour additive, a manufacturer must first petition the FDA for its approval. Approximately 100 new such petitions are submitted to the FDA annually, most of which are for indirect additives such as packaging materials. A food or colour additive petition must provide convincing evidence that the proposed additive performs as it is intended. Animal studies using large doses of the additive for long periods are often necessary to show that the substance would not cause harmful effects at expected levels of human consumption. Studies of the additive in humans also may be submitted to the FDA. In deciding whether an additive should be approved, the agency considers the composition and properties of the substance, the amount likely to be consumed, its probable long-term effects and various safety factors. Since absolute safety of any substance can never be proven, the FDA determines if the additive is safe under the proposed conditions of use, based on the best scientific knowledge available. If an additive is approved, the FDA issues regulations that may include the types of foods in which it can be used, the maximum amounts to be used, and how it should be identified on food labels. Additives proposed for use in meat and poultry products also must receive specific authorization by the USDA. Federal officials then carefully monitor the extent of Americans' consumption of the new additive and results of any new research on its safety to assure its use continues to be within safe limits.

In addition, the FDA operates an Adverse Reaction Monitoring System (ARMS) to help serve as an ongoing safety check of all additives. The system monitors and investigates all complaints by individuals or their physicians that are believed to be related to specific foods; food and colour additives; or vitamin and mineral supplements. The ARMS computerized

database helps officials decide whether reported adverse reactions represent a real public health hazard associated with food, so that appropriate action can be taken.

The FDA applies a tiered system in safety evaluation of direct food additives or colour additives used in food, which involves assigning the additive to a concern level based on information on the additive's structural configuration and an estimation of exposure (53).The additive is first assigned to one of the structural classes; A, B or C, with C having the highest potential for toxicity. Human exposure to the additive is then estimated, and within each structural category, estimated human exposure will determine the initial concern level to which the additive is assigned. The initial concern levels; I, II and III, with III having highest concern, are then used to decide which toxicological tests are necessary (53). However, available toxicology information can change the concern level and alter the recommended set of toxicity tests. Final concern levels may therefore be different from the initial concern levels, and will be based on estimated human exposure, and actual information about metabolism and toxicity of the compounds. The toxicological principles for the safety assessment of direct food additives are under revision (54), and it is unclear exactly which exposure levels are used to categorize the concern levels at the moment. The tiered system applied for direct additives is separate from the tiered system used for indirect additives (described above for food contact materials). However, the guidelines developed for the toxicity tests are valid both for direct and indirect additives.

Cosmetics

EU/Norway

In Norway, cosmetics and personal care products are regulated in "Generell forskrift for produksjon, import og frambud mv av kosmetikk og kroppspleieprodukter (Kosmetikkforskriften"), FOR-1995-10-26-871 (55), which is based on the EU Council Directive 76/768/EEC (56) with amendments.

The safety of a cosmetic product in EU is the full responsibility of the manufacturer, the first importer into the EU market, or the person responsible for placing the product on the market. The Scientific Committee on Consumer Products (SCCP) is the scientific committee in EU responsible for risk assessments of consumer products, i.e. non-food products intended for the consumer, which include cosmetics. The former Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) made detailed guidelines for risk assessments of cosmetics (57), which are still used by SCCP. The safety of a cosmetic product is based on the safety of its ingredients, which are evaluated by toxicological testing. The guidelines are extensive, and include a full evaluation of the effects of a chemical on all toxicological endpoints, without the use of a TTC approach. The calculation of exposure to a cosmetic ingredient is based on the specific use of the product(s) containing the ingredient, since cosmetic products vary a lot in application method, concentrations of an ingredient in the products, amount used per application, frequency of application, total body area of application, contact time etc. The specific exposure scenario is translated into a systemic exposure dose (SED) expressed in mg/kg body weight/day. Calculations of SED should preferably be based on the absolute amount bioavailable after a certain time period, based on the highest anticipated concentration. All relevant ways of exposure are taken into account, being dermal, oral and/or by inhalation, depending on the particular product/ingredient. The last step in the risk characterization is to divide the lowest NO(A)EL value obtain in an animal experiment with SED to obtain the margin of safety (MOS). MOS should be at least 100 to declare a substance safe for use.

With the aim to update this guideline, a study was performed by the European Cosmetic, Toiletry and Perfumery Association (COLIPA), which produced European exposure distributions reflecting the daily amounts of cosmetic products used by consumers (58). This was achieved by combining data from two large European databases on cosmetic usage with data from a large habits and practices study, and analysing the combined data using the CREMe (Central Risk & Exposure Modelling *e*-solution) exposure modelling computer programme (Monte Carlo analysis), to produce a population distribution curve of exposure. Other models for calculation of exposure to cosmetics are also available (17).

U.S.A.
In U.S.A., the safety and labelling of cosmetics are regulated by the Federal Food, Drug, and Cosmetic Act (FFDCA), and the Fair Packaging and Labelling Act (FPLA) (59), under FDA's Center for Food Safety and Applied Nutrition (CFSAN). The legal authority of the FDA over cosmetics is different from other products regulated by the agency, such as drugs. Cosmetic products and ingredients are not subject to FDA premarket approval, with the exception of colour additives. The cosmetic producers are responsible for substantiating the safety of their products and ingredients before marketing. In general, except for colour additives and those ingredients which are prohibited or restricted from use in cosmetics by regulation, a manufacturer may use any ingredient in the formulation of a cosmetic provided that the ingredient and the finished product are safe, the product is properly labelled, and the use of the ingredient does not otherwise cause the cosmetic to be adulterated or misbranded under the laws that the FDA enforces. The *ad hoc* group has not found any information about the use of the TTC principle in connection with cosmetics in U.S.A.

Industry
The TTC principle has apparently not been included in regulation of cosmetics neither in Europe nor in U.S.A. However, initiatives have been taken by the cosmetic industry to evaluate such a use.

COLIPA has sponsored an Expert Group on the Application of the Threshold of Toxicological Concern (TTC) to the Safety Evaluation of Cosmetic Ingredients and End Products (60). So far, no documents from this expert group have been found to be publicly available.

A recent paper evaluated the applicability of the database used to develop the TTC principle to ingredients used in consumer products such as personal and household care products, based on a comparison of the diversity of chemical structures in these products with those in the original TTC database, and by confirming that the range of NOELs for these ingredients is consistent with the range of NOELs in the original database (61). The results showed good coverage of the product ingredient structures, and confirmed that the NOELs for the ingredient chemicals were similar in range to the original dataset, supporting the use of the TTC principle also for risk assessment of ingredients in such consumer products.

The TTC principle has already been used in risk assessment of ingredients in consumer products, such as personal and household products, by industry. An example is the risk assessment of isoeugenol, an ingredient in fragrances found in a variety of consumer products including various cosmetics and household cleaning products, by HERA, an industry programme to carry out Human and Environmental Risk Assessments on ingredients of household cleaning products (62).

There are some 8000 cosmetic ingredients listed in the reference book Blue List (2001) and even more in the International Nomenclature of Cosmetic Ingredients (INCI) list, of which only about 5% have been evaluated for their effects on human health (63). It is anticipated that the level of work on cosmetics and personal care products will increase in response to a further tightening of regulatory requirements, making more efficient methods for risk assessment necessary.

The databases used to develop the TTC principle comprise experiments using 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 for route-to-route extrapolation. To be able to use the TTC approach for personal and household care products, including cosmetics, where dermal exposures are more important than oral exposures, the TTC principle needs further development. However, it is suggested that in the absence of data on route-specific bioavailability, an equal oral and dermal bioavailability can be assumed, and that this assumption, in the context of the TTC approach, should provide a conservative way forward (61). This may be a valid assumption for most chemicals, but not necessary for all, and needs to be validated.

For some cosmetic products, dermal, inhalation and oral exposures may all apply simultaneously. The TTC approach is not yet developed to deal with such multiroute exposures, and also in this context, more developed methodology is needed.

However, the TTC approach may probably be helpful in a preliminary risk assessment of an unsuspected chemical or impurity detected in a consumer product, as described below for other groups of non-intentionally added chemicals.

Products intended for use in contact with drinking water

EU/Norway
At present, very different national systems exist around Europe for risk assessment and approval of materials intended for use in contact with drinking water. In Norway, this work is performed by the Norwegian Institute of Public Health (NIPH), Division of Environmental Medicine (see www.fhi.no, only information in Norwegian). In this work, the regulations used in Germany are followed, since detailed regulations in this area are not established nationally in Norway, and Germany has one of the most developed such systems. The TTC principle is not used in this German system of approval employed in Norway. The same regulations are used by the NIPH in risk assessments as well as approvals of materials to be used in contact with drinking water offshore.

It is the manufacturers and/or the importers of such products who are responsible for producing the products according to good manufacturing practice and for the quality of the products. The content of impurities and the migration of components directly or indirectly from such products to drinking water should be as low as technically possible. Furthermore, the migrating substances should not pose any risk to human health.

However, development of a common system for approval of materials intended for use in contact with drinking water within EU, called the European Acceptance Scheme (EAS), has been going on since 1999. Because these materials are defined as construction products, this work is based upon both the Construction Products Directive - Council Directive 89/106/EEC

(64), as well as the Drinking Water Directive - Council Directive 98/83/EC (65). The corresponding Norwegian regulations are "Forskrift om krav til byggverk og produkter til byggverk (TEK) (Byggeforskriften"), FOR-1997-01-22-23 (66), and "Forskrift om vannforsyning og drikkevann (Drikkevannsforskriften"), FOR-2001-12-04-1372 (67). At the moment, it is not clear when EAS will be adopted and most likely replace the various existing national systems of approval in Europe.

Within EAS, the list for plastic food contact materials developed by SCF, and later by 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. As described above, in evaluation of these food contact materials migration threshold values are used to decide the amount of toxicity data needed to be supplied by the petitioner to the AFC Panel in EFSA (30). As a general principle, the greater the potential exposure through migration, the more toxicological information will be required. It is quite possible that this approach will be employed to be able to assess and approve all the numerous products that are used in contact with drinking water, when the EAS process is more mature. In addition to the use of reduced packages of toxicity data according to preset migration limits, a TTC threshold limit below which no toxicity data is required has also been discussed within EAS. A threshold of 0.1 µg/l, based on limits for the genotoxic substances acrylamide and epichlorohydrin in the Drinking Water Directive, has been considered. However, it will probably be for the proposed European Body responsible for EAS, which is not yet established, to decide upon this.

According to "Drikkevannsforskriften" (67), approvals of water treatment chemicals for use in contact with drinking water onshore are required in Norway. Such chemicals are regulated by the Food Act, which is administered by the Norwegian Food Safety Authority. The NIPH, Division of Environmental Medicine, performs toxicological evaluations of such chemicals for the Norwegian Food Safety Authority, who has the authority to actually approve such products for use in contact with drinking water onshore. Water treatment chemicals for use in contact with drinking water offshore are evaluated as well as approved by NIPH. The TTC principle is at present not used in these toxicological evaluations of water treatment chemicals either for use onshore or offshore.

An ILSI Europe workshop held in 1998 suggested that the TTC principle should be developed to facilitate progress in risk assessment for drinking water contaminants (68). A scientific judgement should be made as to what level of contamination in drinking water represents a threshold of toxicological concern, and any contaminants found below such a threshold level would be considered to have low priority for risk assessment or monitoring. Such an approach would leave a manageable number of chemicals for further consideration. As an example, they stated that the large number of pesticides found in raw waters would be unlikely to remain as priority chemicals under such a scheme since they are generally present at such low levels.

U.S.A.

The Safe Drinking Water Act (SDWA) is the main federal law that ensures the quality of drinking water in U.S.A. (69). Under the SDWA, the United States Environmental Protection Agency (EPA) sets national health-based standards for drinking water to protect against both naturally-occurring and man-made contaminants that may be found in drinking water. While the EPA and the state governments set and enforce standards, local governments and private water suppliers have direct responsibility for the quality of the water at the tap. For non-federally regulated drinking water systems, i.e. private wells serving fewer than 25 persons,

which are not covered by the SDWA, the Centers for Disease Control and Prevention (CDC), under the Department of Health and Human Services (HHS), provides technical assistance regarding potential adverse health effects from drinking water contaminants (70).

It is the NSF International (previously called The National Sanitation Foundation), an independent, private, non-profit, third-party organization, which does certification, testing and writes standards for product, material and system assessments in connection with drinking water in U.S.A. (71). NSF International is recognized by the World Health Organization (WHO) as a Collaborating Center in areas of water and food safety. Instead of issuing letters of approval to manufacturers of products intended to be used in contact with drinking water, the EPA gave in 1988 a contract to a consortium led by the NSF International to certify direct water additives (drinking water treatment chemicals) and indirect additives (drinking water system components). The organization makes standards that establish criteria for evaluation of potential health effects from chemicals and materials to be used in the whole drinking water system, from the source to the consumers tap, and also contain maximum levels for contaminants. The ANSI/NSF Standard 60 establishes criteria for evaluation of potential and/or known health effects of chemicals used to treat drinking water. The ANSI/NSF Standard 61 addresses contaminants that may leach or migrate from drinking water system components, requiring these contaminants to be at safe levels that will not cause adverse human health effects.

Manufacturers of drinking water products submit applications for product certification to the NSF International. During the certification procedures, toxicologists first review the product formulation to determine which analytical tests are necessary to evaluate the product for conformance with the standard. In this process, consideration is given to degree of toxicological concern during the selection of the testing protocol for potential contaminants. The certification process of a product also includes initial audits of the manufacturing facility, product testing according to the standard, and later unannounced audits and sample monitoring.

The method of risk assessment used by NSF International shall be determined by the quality and quantity of toxicity data available for the product component under evaluation according to the ANSI/NSF Standard 61. When available toxicological data is insufficient to perform either a qualitative or a quantitative risk assessment, or when toxicological data is available, but the normalized contaminant concentration does not exceed the applicable "threshold of evaluation" value, a qualitative review of the available data shall be performed to determine whether adverse health effects can result at the threshold of evaluation concentration. This threshold of evaluation concept is based on the TTC/ToR principle. At present, two levels are used for chronic exposure; toxicity testing is not required for a substance having a normalized concentration of ≤ 3 µg/l during static normalization conditions, or ≤ 0.3 µg/l during flowing normalization conditions. For short-term exposure, if a short-term toxic effect is not identified by the available data, the initial (day 1) laboratory concentration shall not exceed 10 µg/l. These threshold of evaluation values shall not be applied to any substance for which available toxicity data or sound scientific judgement, such as structure-activity relationships, indicate that an adverse health effect results at these exposure concentrations. If normalized contaminant concentrations for chemicals that do not meet the minimum data requirements for full risk assessments exceed the threshold of evaluation concentrations, it is possible to determine chemical class-based evaluation criteria for the substances on the basis of the known toxicities of other chemicals of similar structure and functionality. Such class-based evaluation criteria shall not be used for any substance for

which adequate data exists to perform a chemical-specific risk assessment. The current use of the threshold of evaluation concept is intended to be expanded to include multiple levels, and at present six levels are proposed.

The WateReuse Association in U.S.A., a non-profit organization whose mission is to advance the beneficial and efficient use of water resources, has recently announced that they are sponsoring a research project that shall identify hormonally active compounds, pharmaceutical ingredients and personal care product ingredients of most health concern from their potential presence in water intended for indirect potable reuse (72). In the request for proposals, they suggest to use the TTC principle for an initial assessment of personal care products identified in municipal wastewater. If the levels exceeded the TTC values, compound-specific toxicological data would be required.

Drug residues in food of animal origin

EU/Norway

The definition of drug residues applied in EU is given in Article 1 in Regulation (EEC) No 2377/90 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (73): "Residues of veterinary medicinal products: means all pharmacologically active substances, whether active principles, excipients or degradation products, and their metabolites which remain in foodstuffs obtained from animals to which the veterinary medicinal product in question has been administered".

As a member of the European Economic Area (EEA) agreement, Norway has implemented Council Regulation (EEC) No 2377/90 (73). Furthermore, the drug residue surveillance programme implemented in Norway has to be in accordance with Council Directive 96/23/EC on measures to monitor certain substances and residues thereof in live animals and animal products (74). The corresponding Norwegian regulations are "Forskrift om kontrolltiltak for restmengder av visse stoffer i animalske næringsmidler, produksjonsdyr og fisk for å sikre helsemessig trygge næringsmidler (Restkontrollforskriften"), FOR-2000-01-27-65 (75), and "Forskrift om grenseverdier for rester av veterinærpreparater i næringsmidler av animalsk opprinnelse (Veterinærpreparatrestforskriften"), FOR-1996-10-10-997 (76).

While regulatory approaches for the assessment of human health risk of drug residues following use of a veterinary medicinal product vary among national authorities and international agencies, the common objectives include three critical evaluations and decisions: 1) determination of an ADI for consumption of residues for the life span of an individual; 2) maximum residue limits (MRLs) allowable in all edible foodstuffs derived from treated animals to be consumed by humans such that the ADI is not exceeded, and 3) withdrawal times needed after the last administration of the drug for residues to fall below the MRLs.

In order to use a medicinal product in a food animal in any country within the EEA the pharmacologically active substances included in the medicinal product have to be listed in either annex I, II or III of Regulation (EEC) No 2377/90 (73). Annex I contains pharmacologically active substances for which a MRL has been approved, and Annex III contains pharmacologically active substances for which a provisional MRL has been set. Substances, for which it appears through the evaluation process that it is not necessary for the protection of public health to establish a maximum residue limit, are included in Annex II.

Annex IV contains prohibited substances. Lists of evaluated substances and MRLs can be found on the European Medicines Agency (EMEA) web site (77).

The *ad hoc* group could not identify any risk assessments of veterinary drug residues in which TTC had been used as a reference limit. However, both EU and Codex are currently evaluating if alternative exposure limits, such as TTC, could be recommended to be used complementary to and/or as an alternative to the ADI.

Within EU, EMEA is responsible for the risk assessment of both human and veterinary drugs. Within EMEA, the Committee for Medicinal Products for Veterinary Use (CVMP) is responsible for the evaluation of veterinary drugs, including the risk assessment of residues in foods following the use of veterinary drugs in food animals. Currently, the CVMP applies only the ADI as the reference limit in the risk assessment of residues and for the derivation of MRLs. However, according to the CVMP Safety Working Party (SWP) work programme for 2006, the SWP is going to consider alternative reference limits during the spring session (78).

Currently, EMEA evaluates drugs based on documentation provided by the holder of the pharmaceutical preparation. The pharmaceutical industry will generally not apply for market authorisation for drug preparations with limited sales potential, often referred to as "orphan drugs". This implies that drugs for the treatment of rare diseases and intoxications are not evaluated by EMEA. However, to avoid causing unacceptable suffering of animals the veterinarians may sometimes use orphan drugs, i.e. preparations containing substances that are not evaluated by EMEA, and consequently not included in any of the annexes of Regulation (EEC) No 2377/90.

VKM could possibly perform risk assessments of orphan drug residues in food animals in Norway. If sufficient toxicological data is not available to support the derivation of an ADI, TTC might be an alternative exposure limit in such assessments.

JECFA/Codex

Based on scientific expert advice provided by JECFA, the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) is adopting international MRL values, so-called Codex MRLs. So far, Codex has adopted MRLs for residues of approximately 50 veterinary drugs. However, it is estimated that JECFA has evaluated only less than one third of the pharmacological substances used in food animals worldwide (79). The consequences are that many substances with the potential to leave residues in foods, and to create problems in international trade, have no ADI and no international MRLs. But the magnitude of the problem varies substantially. Whilst developed countries have a fully developed regulatory system, many developing countries lack effective legislation on the registration of veterinary medicines and/or the means of implementing their legislation as a result of insufficient resources, knowledge and technical expertise. The 15th CCRVDF meeting agreed to establish a working group to develop recommendations on how to deal with compounds without an ADI or a MRL. The working paper prepared by this group (80), and to be discussed at the 16th CCRVDF meeting in May 2006, recommends that for those substances for which it is not possible or practical to establish an ADI or a MRL, Codex should work in conjunction with JECFA to consider alternative risk assessment tools such as margin of exposure, threshold of toxicological concern and statistical approaches. Using tools such as these, JECFA should develop an estimate of the risks associated with the anticipated exposure of consumers to residues of veterinary drugs in food.

To estimate the intake of residues of veterinary drugs in food, JECFA uses a very conservative approach, called theoretical maximum daily intake (TMDI). It is assumed that all animals are treated at the maximum label dose and duration, that all residues are at the MRL values, and that the residues are consumed daily for a lifetime (81). Because this scenario is highly unlikely, it results in unrealistically high intake estimates, and is therefore suggested changed. The consequences, however, would be significant, because it would require reconsidering the MRLs for a large number of drugs that have been recommended by JECFA on the basis of the TMDIs. An Update Project (82) will investigate the procedures for intake assessment used by JECFA and JMPR (The Joint FAO/WHO Meetings on Pesticide Residues) for all classes of chemicals in food, including residues of veterinary drugs, and will consider ways to harmonize such methods for long and short term exposure scenarios. The pattern of use of veterinary drugs varies considerably from country to country, and such information is generally not available to JECFA. Therefore, it is very difficult to estimate the percentage of national herds that is likely to be treated with a substance at any one time and the consumer consumption patterns from national surveys to a level sufficient for estimating intake. The issue of estimation of drug residue levels in animal-derived foods ingested by consumers will also be considered by the Update Project.

U.S.A.
In U.S.A., The Center for Veterinary Medicine (CVM) at the FDA regulates the manufacture and distribution of food additives and drugs that will be given to animals, including animals from which human foods are derived. The *ad hoc* group was not able to locate any information that indicates that the FDA apply TTC as a reference limit for the risk assessment of residues following use of veterinary drugs.

Other suggested uses of TTC in connection with pharmaceuticals
Although outside VKMs area of responsibility, it is interesting that the TTC approach has also been suggested used for risk assessments of genotoxic impurities in pharmaceutical preparations and in pharmaceutical manufacturing operations.

EMEA has evaluated use of the TTC principle in risk assessment of genotoxic impurities in human pharmaceutical preparations (83). EMEA considers the need for a pragmatic approach for toxicological assessment of genotoxic substances without sufficient evidence for a threshold-related mechanism, realizing that a complete elimination of such impurities from the drug substances is often unachievable. In such cases, the TTC principle can be used to estimate an acceptable risk level. The principle should not be used for risk assessment of high-potency genotoxic carcinogens, and shall not be used for evaluation of carcinogens for which adequate toxicity data (chronic exposure) is available; for these substances a chemical-specific risk assessment is performed. The evaluation is based on a threshold exposure value of 0.15 μg/person/day for genotoxic substances. However, a threshold exposure value of 1.5 μg/person/day is fixed for genotoxic impurities in pharmaceuticals, related to a life-time cancer risk of 10^{-5}, justified since pharmaceuticals have a benefit.

A recent paper further proposed a staged TTC approach for the control of intake of genotoxic impurities in human pharmaceuticals over various periods of exposure, including during clinical development (84). The delineated acceptable daily intake values suggested were 1.5, 10, 20, 40 and 120 μg/person/day, for exposure periods of >12 months, i.e. lifetime exposure, >6-12 months, >3-6 months, >1-3 months and ≤1 month, respectively.

The concept that exposure thresholds can be identified for individual chemicals is already embodied in the practice of setting ADIs for chemicals whose toxicological profiles are known. However, the TTC concept extends the ADI methodology to address substances that have very limited or no toxicity data, but for which reasonable exposure estimates can be made, and taking the chemical structure into consideration. In a recent paper, ADIs were recommended, based on the TTC principle, to support pharmaceutical manufacturing quality operations, with specific application to cleaning validation and the resolution of atypical extraneous matter investigations of relatively unstudied compounds in active pharmaceutical ingredients and finished pharmaceutical products when limited or no toxicity data is available (85). Recommendations were provided on ADI values that correspond to three categories of compounds; those that are likely to be carcinogenic; potent or highly toxic; or not likely to be potent, highly toxic or carcinogenic, being 1, 10 and 100 µg/person/day, respectively.

Oral inhaled and nasal drug products (OINDPs) could leach chemical components from the container or its components, such as valves or gaskets, or from its labels, adhesives, inks etc., to the sensitive nasal and lung mucosa. The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group has since 2001 developed a Safety Concern Threshold (SCT) and a Qualification Threshold (QT) for use in risk assessments of such leachables from OINDPs (86). The SCT is a threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects. The SCT will not be applied to certain classes of compounds with special safety concerns, e.g. nitrosamines, polynuclear aromatics, mercaptobenzothiazole etc. The SCT is set to 0.15 µg/day. The QT is a threshold below which a given leachable is not considered for safety qualification, i.e. toxicological assessments, unless the leachable presents structure-activity relationship concerns, and was based on non-carcinogenic endpoints. The QT is set to 5 µg/day.

APPLICATIONS OF TTC IN AREAS OUTSIDE OF VKM

Industrial chemicals

The TTC principle could also be applied to other sectors of risk assessments, such as occupational and environmental settings. Also, in these sectors humans are exposed to a diverse array of chemicals, and there is an urgent need for the evaluation of a large number of chemicals, while at the same time reducing the reliance on animal experiments.

The ToR concept has been proposed extended from a risk assessment method for carcinogens to be also a method for risk assessment of mutagens (87). A threshold limit value could be determined that could be set for either daily exposure, an analytical detection level or a cleaning limit for manufacturing equipment, and which could be used in an occupational setting, for instance in pharmaceutical industry.

It has been estimated that there are over five million man-made chemicals known, of which only approximately 70 000 are in commercial use today (12). Furthermore, there are more than 100 000 naturally occurring substances of known structure, but probably many more exist, for which the structure has not yet been elucidated. There are more than 2 000 high production volume chemicals (HPVCs; chemicals that are imported/produced in quantities of >1000 tonnes/year), of which approximately 10 substances have been assessed in EU per year (88). In addition, there are 30 000 lower production volume chemicals (LPVCs). As a

consequence of these high numbers, very little is known about the properties and risks of >95% of the chemicals.

The TTC principle has been proposed as a tool in performing risk assessment of industrial chemicals by ECETOC (the European Centre for Ecotoxicology and Toxicology of Chemicals) within REACH (Registration, Evaluation, Authorisation of Chemicals), the proposed European chemical legislation (89). They suggested a tiered approach consisting of three phases, Tier 0, Tier 1 and Tier 2, where the level of refinement and detail of information required for risk assessment were proportional to the potential risks of a chemical, based on consideration of both hazards and exposures together, rather than in isolation. The suggestion comprised the use of generic threshold values based on hazard categories. For risk assessment of exposure to these chemicals by consumers, the Generic Lowest Effect Values (GLEVs) were based on the EU classification limit for repeated dose toxicity, while for occupational exposure, Generic Exposure Values (GEVs) were derived from occupational exposure limits (OELs). Both GLEVs and GEVs were adjusted with assessment factors.

A Nordic project has evaluated how different TTC-like concepts have been used, and assessed their potential usability in risk assessment of industrial chemicals within REACH (90). The expert group concluded that it was premature to use the TTC concept within REACH due to limitations and uncertainties in the derivation of TTCs, as well as the fact that the TTC principle has not yet been evaluated for the diverse group of industrial chemicals. In addition, they were doubtful about whether it is possible to obtain a sufficient level of protection in risk assessment of industrial chemicals by the use of the TTC principle.

In order to reduce animal testing under REACH, and also because of the ban on tests on animals and the ban on the marketing of products/ingredients tested on animals stipulated in the 7th Amendment to the Cosmetics Directive (56), a broader strategy for risk assessment has been suggested, called Intelligent Testing Strategies (ITS) (88). In this approach, multiple elements are integrated, including *in vitro* tests, chemical categories, a.o. read-across, *in silico* approaches, i.e. computational models including quantitative structure-activity relationships (QSARs), and exposure considerations, including the TTC principle and exposure-based waiving. In ITS, the methods for hazard assessment are considered in a holistic manner, rather than examining each method separately.

Environmental risk assessment

The TTC principle could be further developed also for environmental risk assessment. Since the TTC principle is based on safety evaluations relating to daily intake throughout life, the approach could be used as a science-based alternative to define concentrations of chemicals in nature as part of the application of the precautionary principle.

The TTC principle has been endorsed by the former EU Scientific Committee on Toxicology, Ecotoxicology and the Environment (CSTEE) (91).

There is presently no use of the TTC concept as regards regulatory environmental assessments. However, two different approaches that can be seen as environmental TTC, the "action limit" and the Exposure Threshold of No Concern (ETNC) for the pelagic freshwater compartment, i.e. "$ETNC_{aquatic}$", have been found in the literature.

EMEA has proposed a guideline for the use of a step-wise, tiered procedure for the environmental risk assessment of human pharmaceuticals, without actually mentioning TTC (92). In phase I, a Predicted Environmental Concentration (PEC) of the pharmaceutical is calculated for surface water. If the PEC is above a certain action limit, then the assessment is continued into phase II, which is divided in tier A and tier B, being increasingly refined. However, the suggested action limit of 0.01 µg/l was questioned by the CSTEE since drugs with lower effect concentrations were found. In addition, the focus on acute toxicity was questioned, as chronic toxicity was considered more relevant for pharmaceuticals.

A different approach was applied deriving an environmental $ETNC_{aquatic}$ value (93). The concept is so far limited to the pelagic freshwater compartment because of a general lack of data regarding effects of industrial chemicals on sediment, marine or soil species. This approach was based on existing toxicological databases of acute and chronic endpoints and substance hazard assessments for organisms in the freshwater environment, and a categorisation of organic chemicals into four different modes of action. The stratified data were fitted to a lognormal distribution from which a fifth percentile, with a 50% confidence interval, was determined. This value was then divided by an assessment factor, ranging from 1 to 1000 depending on the data, to obtain the $ETNC_{aquatic}$.

As the environmental TTC approaches were developed only for direct effects on the pelagic freshwater ecosystem, no effects due to bioaccumulation, or accumulation in other compartments, were taken into consideration. Additionally, the concept does not cover metals or other inorganic compounds, or ionisable organic compounds. The use of non-testing information, as compared to experimental data, may imply a higher risk of not considering the toxicity of degradation products and metabolites, which may prove important if they are more toxic than the parent compounds.

POSSIBLE APPLICATIONS OF TTC IN VKM'S RISK ASSESSMENTS

General applications

The *ad hoc* group has identified the following general potential applications of the TTC principle in VKM's risk assessments:

- As a preliminary step in risk assessment of chemicals discovered to be present at low concentrations in food, and for which toxicity data is lacking, but for which exposure assessments can provide reliable intake estimates. Such substances may at first be flavourings, substances migrating from food contact materials, some contaminants in the environment, and substances used at low concentrations in a very limited number of food items which are consumed in very low quantities, but may in the future, when the principle is further developed, be used in other areas such as for cosmetics and personal care products.

- In the setting of priorities, depending on the level of concern, for more in depth substance-specific risk assessments. The TTC approach can be used to identify those substances for which exposure estimates exceed the relevant TTC value and which therefore may require further information for risk assessment. Such information may be more toxicological testing, depending on their structure and the degree to which they exceeded the TTC value. As such, the outcome of the use of the TTC approach may be applied as reasoning

behind suggestions put forward by the Norwegian Food Safety Authority to the EU Commission regarding joint efforts to obtain a more complete toxicity database for a particular substance in food.

- In the setting of priorities for development of better analytical methods. Substances for which present analytical methods do not allow for accurate measurements at concentrations relevant to their particular structural class TTC value, may point to the need for more sensitive analytical methods.

- In the setting of priorities for more refined intake data. Substances for which intake estimates are close to the relevant TTC values, but contain some uncertainties, may require more refined estimates of intake. As such, the outcome of using the TTC approach may be a help in setting national priorities in the development of food intake studies and more specifically, be helpful in improving existing food questionnaires. It may also point to certain food types in national surveys, and to specific food contact materials in the Norwegian Food Safety Authority's surveillance programmes, which should be given priority.

Obvious benefits of using the TTC principle in VKM's work are to avoid unnecessary risk assessments when human intakes are below the relevant TTC values, and then allow limited resources of time, cost and expertise within VKM to be used for evaluation of those substances with greater potential to pose risks to human health. In addition, the outcome of using the TTC approach may be useful for the Norwegian Food Safety Authority in setting priorities, as suggested above.

To be able to use the TTC principle in their risk assessments, the panels in VKM would require reliable estimates of intake of the particular chemical under evaluation, which may not be available today. However, estimates of exposure are also necessary in ordinary risk assessments, and not particular for the TTC approach.

Also needed is thorough knowledge about the chemical's structure and inherent properties. This will demand specialist competence in organic chemistry, biochemistry, SARs, QSARs etc. Knowledge of a chemical's metabolism, as well as knowledge of whether the substance is endogenous, in the human body, is important. Persons with adequate such competence may not be included in the panels at present. The panels may therefore need to be complemented with persons having a higher competence in these areas, or the persons attending the panels at present may need further education in these fields, or an option may be to seek scientific advice outside the panels to obtain this competence on a case-by-case basis. However, there are computer software programmes on the market that can be of help. An example is toxTree 1.00, which is able to estimate toxic hazard by applying the Cramer decision tree approach, and which is available as a free download upon registration from the European Chemicals Bureau (ECB) website (94). Other examples are the software programmes Derek for Windows - for predicting the toxicity of chemicals, Vitic - a database of toxicological information, and Meteor - for predicting metabolic fate, all from Lhasa Limited (95). These and other software programmes are already in regulatory use (96,97).

Applications specific for each scientific panel

Based on the information gathered, described and discussed in this document, the *ad hoc* group has identified the following potential areas where the TTC principle may be relevant for each of VKM's scientific panels. Since the *ad hoc* group consisted only of members from two of the eight scientic panels in VKM, panels 4 and 5, and therefore had limited knowledge about the other groups' areas of responsibility, the list is intended only as a basis for further discussions within each of the other scientific panels on whether TTC shall be used, and how.

Panel on biological hazards (Panel 1)
Although not directly related to the TTC principle as such, it is interesting that the FDA's Center for Veterinary Medicine (CVM) in U.S.A. has considered the establishment of two types of regulatory thresholds intended to arrest the further emergence of resistant foodborne pathogens (98). One is a "human health threshold", which is the unacceptable prevalence of infections in humans that are treated with an antimicrobial drug, and are associated with bacteria resistant to that drug, and for which the resistance is attributable to the use of an antimicrobial drug in animals. The "resistance threshold" is the maximum allowable prevalence of resistant bacteria isolated from animal-derived food, that is the level of such resistant bacteria at which there would still be reasonable certainty that the human health threshold would not be crossed. Similar use of thresholds may possibly be relevant for Panel 1.

Panel on plant health, plant protection products and their residues (Panel 2)
The TTC principle is not designed to replace conventional approaches to risk characterization for established and well-studied chemicals, such as pesticides. Also, the separate step for organophosphate pesticides in the TTC decision tree is not intended to replace the normal regulatory assessments and controls for organophosphates used as pesticides, but can be used to determine whether there is any risk concern should a non-approved or unregulated organophosphate be detected in food as a contaminant.

However, in U.S.A. it is possible to request that a pesticide may be regulated by the ToR policy, either in the course of a pesticide registration action, a reregistration or during a tolerance reassessment (99). A use of a pesticide may be below the ToR if no residues of the pesticide are detected in a commodity under the expected conditions of use, after analysis with a sensitive analytical method, or if the estimated potential risk of any theoretically possible residues in food is not of concern.

Panel on genetically modified organisms (Panel 3)
The use of the TTC principle is most likely not relevant.

Panel on food additives, flavourings, processing aids, materials in contact with food and cosmetics (Panel 4)
The TTC approach can be used as a practical and valuable tool to assist in the risk assessment of a large number of low exposure substances found in food, such as flavouring substances, migrating food packaging materials and other food contact materials e.g. kitchen utensils and processing aids, as well as for materials intended for use in contact with drinking water. However, the TTC principle is not designed to replace conventional approaches to risk characterization for established and well-studied chemicals, such as food additives.

The TTC principle should be developed further to other categories of chemical use such as in cosmetics and personal care products. In that case, appropriate methodologies should be developed to allow for other ways of exposure than oral intake, and to assess multi-route exposures.

Panel on contaminants in the food chain (Panel 5)
The TTC approach might be used in risk assessments of orphan drug residues in food animals. The TTC approach could also possibly be used to evaluate the risk from natural plant constituents, some fungal toxins or other low level contaminants in food, but it should not be used in risk assessments of heavy metals, dioxin-like compounds, ochratoxin or other compounds known to accumulate in the body, according to the evaluations of the TTC principle provided by ILSI Europe, as described above.

Panel on animal feed (Panel 6)
The TTC principle can possibly be used in risk assessment of low level contaminants found in animal feed, its raw materials or additives.

Panel on nutrition, dietetic products, novel food and allergy (Panel 7)
The use of the TTC principle is most likely not relevant, and in particular, can not be used in risk assessment of allergy, according to the evaluations of the TTC principle provided by ILSI Europe, as described above.

Panel on animal health and welfare (Panel 8)
The use of the TTC principle is most likely not relevant.

CONCLUSIONS AND RECOMMENDATIONS BY THE *AD HOC* GROUP

It is the opinion of the *ad hoc* group that the TTC principle should continue to be used in fields where it is already well established as part of the regulatory risk assessment procedure, such as in safety evaluations of flavouring substances and food contact materials. It could also be relevant for several, if not all, of the panels in VKM responsible for other areas. The TTC principle has been discussed and evaluated extensively in later years especially by ILSI Europe, and will most certainly be developed further by this or other European and international organizations to allow a wider application to the vast array of low-molecular-weight substances that are present in human environments in trace amounts, either naturally or as a result of human activity. In general, the TTC principle may be useful in risk assessment of unintentionally present chemicals, as impurities or contaminants, detected in low amounts in most food areas, providing exposure can be reliably calculated.

The *ad hoc* group recommends that this document is used as background information and basis for discussions in the Head Committee and in the scientific panels of VKM in order to see whether, and how, the TTC principle may be useful in the various fields covered by VKM. In particular, the scientific panels should decide whether enough developmental work has been done by ILSI Europe and others for the TTC principle to be valid used in risk assessments in their areas of responsibility.

The further development of the TTC principle, as well as other new methodology in risk assessment, such as *in vitro* tests and QSARs, should be followed continuously for the benefit of efficient and up-to-date risk assessments by VKM.

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TERMINOLOGY

Acceptable daily intake (ADI): an estimate of the amount of a substance in food or drinking water, expressed on a body mass basis, usually mg/kg body weight, which can be ingested daily over a lifetime by humans without appreciable health risks

The Adverse Reaction Monitoring System (ARMS): a system operated by FDA in U.S.A. which monitors and investigates all complaints about food additives, and thereby help to serve as an ongoing safety check of all food additives

The Center for Food Safety and Applied Nutrition (CFSAN): is one of six product-oriented centres, in addition to a nationwide field force, that carry out the mission of the FDA

The Center for Veterinary Medicine (CVM): the centre at FDA that regulates the manufacture and distribution of food additives and drugs that will be given to animals, including animals from which human foods are derived

The Centers for Disease Control and Prevention (CDC): among other tasks gives advice concerning safety of non-federally regulated private drinking water sources, under the HHS in U.S.A.

Centre for Research on Exposure Modelling Estimates (Creme): a company developing software for the analysis of human exposure to a wide range of food-borne chemical hazards, a.o. the Central Risk & Exposure Modelling *e*-solution (Creme), a Monte Carlo probabilistic risk assessment software

CMR substances: substances that are Carcinogenic, Mutagenic or toxic to Reproduction

The Code of Federal Regulations (CFR): is the codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government in U.S.A.

The Codex Alimentarius Commission (Codex): created in 1963 by FAO and WHO to develop food standards, guidelines and related texts such as codes of practice under the Joint FAO/WHO Food Standards Programme. The main purposes of this Programme are protecting the health of the consumers and ensuring fair trade practices in the food trade, and promoting coordination of all food standards work undertaken by international governmental and non-governmental organizations

The Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF): the main work of this committee is to elaborate MRLs for veterinary drugs in meat and milk

The Committee for Medicinal Products for Veterinary Use (CVMP): the committee within EMEA responsible for veterinary drugs

The Committee of Experts on Flavouring Substances of the Council of Europe (CEFS): a committee within the Council of Europe responsible for safety evaluation of flavouring substances

The Council of Europe (CoE): the oldest political organisation in Europe founded in 1949, with 46 countries as members, distinct from EU

Cramer's structural classes: a system of dividing chemicals into three different classes according to their structure, predicting increasing potential for toxicity from class I to III

Decision tree: a structured approach for making step-by-step decisions about individual chemicals

2,3,7,8-dibenzo-*p*-dioxin (TCDD): one of the polyhalogenated dibenzo-*p*-dioxins

Dietary concentrations (DC): analogues to TTC values, used in the food contact notification programme by FDA in U.S.A.

The EU Flavour Information System (FLAVIS): a database containing information on almost 2800 chemically defined flavouring substances, and a Working Group preparing draft opinions on flavouring substances, which thereafter are evaluated by the AFC Panel in EFSA

The European Acceptance Scheme (EAS): a new common system for approval of construction products in contact with water intended for human consumption under development within EU

The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC): a scientific, non-profit association established in 1978 to provide a forum for the European chemical industry, financed by 50 of the leading chemical companies

The European Centre for the Validation of Alternative Methods (ECVAM): was established by the European Commission in 1991 to promote the scientific and regulatory acceptance of alternative methods which are of importance to the biosciences, through research, new test development and validation, and the establishment of specialised databases, with the aim of contributing to the replacement, reduction and refinement of laboratory animal use

The European Chemicals Bureau (ECB): provides scientific and technical support to the conception, development, implementation and monitoring of EU policies on dangerous chemicals, and ensures the development of methodologies and software tools to support a systematic and harmonised assessment of chemicals addressed in a number of European directives and regulations

The European Committee for Standardization (CEN): was founded in 1961 by the national standardization bodies in the European Economic Community and EFTA countries for producing voluntary technical standards

The European Cosmetic, Toiletry and Perfumery Association (COLIPA): an organization set up in 1962 to promote the interest of the cosmetic, toiletry and perfumery industry throughout Europe

The European Economic Area (EEA): it came into being on January 1, 1994, and was designed to allow EFTA countries to participate in the European single market without having to join the EU. Current members are three of the four EFTA states - Iceland, Liechtenstein and Norway, the EU and the 25 EU Member States

The European Food Safety Authority (EFSA): the institution responsible for risk assessment regarding food and feed safety in EU

The European Free Trade Association (EFTA): is an intergovernmental organisation promoting free trade and strengthening economic relations, with Iceland, Liechtenstein, Norway and Switzerland as members

The European Medicines Agency (EMEA): a European agency responsible for the evaluation of medicinal products

The European Union (EU): a union of twenty-five independent states based on the European Communities and founded to enhance political, economic and social co-operation, founded in 1993

Exposure Threshold of No Concern (ETNC): an environmental risk assessment term analogous to TTC

The Fair Packaging and Labelling Act (FPLA): a law that applies to labelling on many consumer products in U.S.A.

Fat (consumption) reduction factor (FRF): a factor suggested to be introduced for fatty foods with more than 20% fat, because it has been demonstrated that consumption of fat is much less than 1 kg/day, which is the currently used assumption of intake used in risk assessment of food contact materials, leading to overestimates of the exposure to fat-soluble migrants

The Federal Food, Drug, and Cosmetic Act (FFDCA): is a law in U.S.A. that authorizes EPA to oversee the safety of foods, drugs, and cosmetics

The Flavor and Extract Manufacturers Association of the United States (FEMA): is the oldest and largest national association of the flavour industry and is engaged principally in activities which ensure a substantial supply of safe flavour materials, founded in 1909

The Food and Agriculture Organization of the United Nations (FAO): an organization founded in 1945, leading international efforts to defeat hunger, help to modernize and improve agriculture, forestry and fisheries practices and ensure good nutrition, serving both developed and developing countries

Food contact notification (FCN): a process for authorizing new uses of food additives that are food contact substances, used by the FDA in U.S.A.

Generally recognized as safe (GRAS): is a designation used by the FDA in U.S.A. saying that a chemical or substance added to food is considered safe by experts, and so is exempted from the usual FFDCA food additive tolerance requirements

Generic Exposure Values (GEVs): exposure values used for occupational exposure, derived from OELs, suggested used analogous to TTC values in risk assessment of industrial chemicals

Generic Lowest Effect Values (GLEVs): exposure values used for consumers, based on the EU classification limit for repeated dose toxicity, suggested used analogous to TTC values in risk assessment of industrial chemicals

Good Manufacturing Practice (GMP): a.o. limits the amount of food and colour additives used in foods to only the amount necessary to achieve the desired effect

Heterocyclic amines (HCAs): so-called food mutagens, substances formed during cooking of meat and fish from reaction between amino acids and creatine at high cooking temperatures
High production volume chemicals (HPVCs): chemicals that are imported/produced in quantities of >1000 tonnes/year

Human and Environmental Risk Assessments on ingredients of household cleaning products (HERA): an industry programme for risk assessment of such products

Human exposure threshold (of toxicological concern) value (TTC value): a generic value for human exposure to a chemical falling within a particular structural class, below which there would be no appreciable risk to health

Intelligent Testing Strategy (ITS): a strategy which considers the methods used for hazard assessment in a holistic or integrated/intelligent manner, rather than examining each method separately

The International Life Sciences Institute (ILSI): is a non-profit, worldwide foundation established in 1978 to advance the understanding of scientific issues relating to nutrition, food safety, toxicology, risk assessment, and the environment. Approximately sixty percent of the institute's funding originates from its member companies, with the remainder split between foundations, government agencies and sales. ILSI Europe was established in 1986 primarily by its industry members

The International Nomenclature of Cosmetic Ingredients (INCI): an inventory of ingredients employed in cosmetic products, compiled on the basis of information supplied by the industry, on the basis of Council Directive 93/35/EEC of 14 June 1993, the sixth amendment to the Cosmetics Directive. The inventory is purely indicative and shall not constitute a list of substances authorized for use in cosmetic products

The International Organization of the Flavor Industry (IOFI): is the representative of the global flavour industry, acting to promote the benefits and safe use of flavours

The Joint FAO/WHO Expert Committee on Food Additives (JECFA): is an international scientific expert committee that is administered jointly by FAO and WHO. Founded in 1956, it initially evaluated the safety of food additives, now also of contaminants, naturally occurring toxicants and residues of veterinary drugs in food

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR): is an expert committee responsible for reviewing and evaluating toxicological residue and analytical aspects of pesticide residues in food

Lethal dose 50 (LD50): the dose that causes death in 50% of the animals in one administration (acute toxicity)

Lower production volume chemicals (LPVCs): chemicals that are imported/produced in quantities of between 10 and <1000 tonnes/year

Lowest observed (adverse) effect level (LO(A)EL): the lowest dose of a substance for which an (adverse) effect can be observed in a long-term toxicity animal study

Margin of safety (MOS): the ratio between NOAEL identified for a toxic effect and the estimated or predicted exposure dose or concentration, for example the ratio of NOAEL divided by SED, used in risk characterization of cosmetic ingredients with a threshold effect

Maximised Survey-derived Daily Intake (MSDI): a method used to estimate intake of flavouring substances

Maximum residue level (MRL): the highest amount of a pharmaceutical residue allowed in edible foodstuffs derived from treated animals to be consumed by humans

Maximum tolerated dose (MTD): a high dose used in chronic toxicity testing that is expected on the basis of an adequate subchronic study to produce limited toxicity when administered for the duration of the test period

Modified Theoretical Added Maximum Daily Intake (mTAMDI): a method used to estimate intake of flavouring substances, using 35 food groups based on Codex food categories instead of a small number of broad food groups applied in the original TAMDI method

Natural flavour complexes (NFC): essential oils, extracts or oleoresins, the volatile or non-volatile flavouring constituents of plant sources such as leaves, fruits, buds, bark etc.

No observed (adverse) effect level (NO(A)EL): the highest dose of a substance for which no (adverse) effects can be observed in a long-term toxicity animal study

The Norwegian Food Safety Authority (Mattilsynet): is a governmental body with the main responsibility for the implementation of legislation in the fields of food and feed control, additives, pesticides, contaminants, packaging materials, dietetic foods, new foods, nutrition, fortification, radiation and label, i.e. has the responsibility for the control of the whole food chain, and also performs duties related to cosmetics and medicines, as well as does inspections

The Norwegian Institute of Public Health (NIPH): is a national centre for expert knowledge of epidemiology, infectious disease control, environmental medicine, forensic toxicology and research on drug abuse

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet - VKM): a national independent scientific committee established in 2004 to assist the Norwegian Food Safety Authority with risk assessments

Occupational exposure limits (OELs): values set by competent national authorities or other relevant national institutions as limits for concentrations of hazardous compounds in workplace air

Oral inhaled and nasal drug products (OINDPs): medications to be administered by inhalation through the mouth or nose

The Organization for Economic Co-operation and Development (OECD): an organization producing internationally agreed decisions and recommendations in many fields, including guidelines for toxicological tests

Overall Migration Limit (OML): the overall limit for a chemical that is allowed to migrate from any plastic food contact material to 1 kg food; i.e. 60 mg/kg food

The Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC): one of the scientific panels of EFSA

Per capita daily intake x 10 (PCIx10): the method used to calculate exposure to flavouring substances in U.S.A., is similar to the MSDI method used in Europe
Polychlorinated biphenyl (PCB): an organic compound with 1 to 10 chlorine atoms attached to a biphenyl and with a general structure of $C_{12}H_{10-x}Cl_x$

Polycyclic aromatic hydrocarbons (PAHs): organic molecules that consist of three or more rings containing carbon and hydrogen and that are commonly produced by fossil fuel combustion

Predicted Environmental Concentration (PEC): is an indication of the expected concentration of a material in the environment, taking into account the amount initially present, or added to, the environment, its distribution, and the probable methods and rates of environmental degradation and removal, either forced or natural

The Product Quality Research Institute (PQRI): is a collaborative process involving FDA's Center for Drug Evaluation and Research (CDER), industry and academia in research related to pharmaceutical products, established in 1996

Pseudo-acceptable daily intake (PADI): an intake for a substance derived by applying a 1000-fold uncertainty factor to the lowest LOEL for non-carcinogenic endpoints

Quantitative structure-activity relationship (QSAR): a mathematical model that relates a quantitative measure of chemical structure, e.g. a physicochemical property, to a physical property or to a biological effect, e.g. a toxicological endpoint

Registration, Evaluation and Authorisation of Chemicals (REACH): the proposed European legislation for industrial chemicals

The Registry of Toxic Effects of Chemical Substances (RTECS): electronical toxicology database, from U.S. Government Public Health Service

The Safe Drinking Water Act (SDWA): the federal law that regulates drinking water quality in U.S.A.

Safety Working Party (SWP): working group within EMEA

The Scientific Committee on Consumer Products (SCCP): the present scientific committee in EU responsible for questions concerning the safety of consumer products, i.e. non-food products intended for the consumer, in particular, questions in relation 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

The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP): the former scientific committee in EU responsible for scientific and technical questions concerning consumer health relating to cosmetic products and non-food products intended for the consumer, especially substances used in the preparation of these products, their composition, use as well as their types of packaging

The Scientific Committee on Food (SCF): the former scientific committee in EU responsible for scientific and technical questions concerning consumer health and food safety associated with the consumption of food products and in particular questions relating to toxicology and hygiene in the entire food production chain, nutrition, and applications of agrifood technologies, as well as those relating to materials coming into contact with foodstuffs, such as packaging, active until the foundation of EFSA in 2002

The Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE): the former scientific committee in EU responsible for scientific and technical questions relating to examination of the toxicity and ecotoxicity of chemical, biochemical and biological compounds whose use may have harmful consequences for human health and the environment

Specific Migration Limit (SML): a limit for how much of a specific chemical (in mg) is allowed to migrate from any plastic food contact material into 1 kg of food, under its conditions of use

Structural alert: a particular chemical grouping within a chemical structure which is known to be associated with a particular type of toxic effect, e.g. genotoxicity

Structure-activity relationship (SAR): a qualitative association between a chemical substructure and the potential of a chemical containing the substructure to exhibit a certain biological effect

Systemic exposure dose (SED): the amount of a cosmetic ingredient expected to enter the blood stream and therefore be systemically available, expressed in mg/kg body weight/day

Theoretical maximum daily intake (TMDI): a method for estimation of intake of veterinary drug residues in food of animal origin

Threshold: in toxicology often meaning the dose or exposure concentration of a chemical below which a stated effect is not observed or expected to occur

Threshold of Regulation (ToR): a policy of the U.S. Government allowing regulation of food contact materials and certain other chemicals present only at very low levels in the diet by an abbreviated procedure, instead of the full food additive petition process

Threshold of Toxicological Concern (TTC): a concept that proposes human exposure threshold values for groups of chemicals determined by their inherent toxicological properties, below which there would be no appreciable risk to health

Tolerable daily intake (TDI): an estimate of the amount of a contaminant in food or drinking water, expressed on a body mass basis, usually mg/kg body weight, which can be ingested daily over a lifetime by humans without appreciable health risks
Tumour dose 50 (TD50): the dose that causes cancer in 50% of the animals

The United States Department of Agriculture (USDA): is working with food safety as one of its many tasks

The United States Department of Health and Human Services (HHS): is working with food, drug and drinking water safety among many other tasks

The United States Environmental Protection Agency (EPA): protects human health and the environment by a.o. setting national health-based standards for drinking water to protect against both naturally-occurring and man-made contaminants that may be found in drinking water
The United States Food and Drug Administration (FDA): regulates a.o. food, human drugs, animal feed and drugs, and cosmetics, under the HHS

Virtually safe dose (VSD): a human exposure over a lifetime to a carcinogen which has been estimated by mathematical modelling to result in a very low incidence of cancer, i.e. 1 case of cancer in a million people

The World Health Organization (WHO): is the United Nations specialized agency for health

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