Dossier –
Threshold of Toxicological Concern (TTC)

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1 Introduction

“The number of chemicals is increasing year by year and the analytical chemistry continues to alert us [of] the presence of previously unsuspected substances, but toxicologists cannot keep pace with these developments due to limited resources in time and money.” This sentence was published by Cramer et al. more than 30 years ago and shows one of the prevailing problems in regulatory toxicology [2]. Since many decades, the number of chemicals is steadily increasing (current status: 84 000 chemicals on the TSCA inventory of EPA). At least 4000 of these chemicals are used for the production of food contact materials (FCMs) [3, 4]. They all have to be authorized according to the current national or international legislations. In general, the safety of the FCM has to be guaranteed by the producer. In Europe, this guarantee also includes any unwanted reaction product, impurity and/or breakdown product (according to the Framework Regulation EC 1935/2004, Art. 3). It is a major financial and experimental challenge to fulfill these requirements by supplying the necessary toxicity data for each single substance. Ideally, a full assessment of human safety risks includes migration data, the estimation of exposure and a series of relevant laboratory toxicity tests. In combination, these data allow the calculation of an accepted or tolerated daily intake (ADI or TDI), which is defined as the amount of a chemical that can be consumed daily over a lifetime and does not pose a risk to human health. In Europe, the TDI is used to set legally binding specific migration limits (SML).

An alternative concept of chemical risk assessment was introduced and developed during the last decades: the Threshold of Toxicological Concern (TTC). It defines human exposure threshold values that have a very low probability of causing adverse health effects. The setting of thresholds is an accepted tool in classical toxicology. It is used to determine the TDIs and ADIs via no observed effect levels (NOELs) that are calculated on the basis of toxicological tests. In contrast, the TTC concept allows the determination of exposure threshold values for chemicals in the absence of appropriate toxicological data. Substances are judged by their structural properties and the toxicity data of substances with similar chemical structures. Three requirements that are absolutely essential for the determination of any threshold values are shown in Box 1.

**Box 1. Requirements for the application of threshold approaches.**
- Chemical structure is known.
- Compound is not covered by any exclusion criteria (e.g. genotoxicity and bioaccumulative potential).
- Exposure levels are known.

2 Historical development of threshold concepts

Important scientific results and regulatory developments of risk assessment concepts that are based on the use of threshold values are described in this paragraph. The history of this research, its implementation by regulatory authorities and key figures, which are relevant for the regulation of FCMs, are summarized in Table 1 and Figure 1. A chronological, detailed description of different threshold concepts follows below.

Figure 1. Historical milestones during the development of risk assessment concepts based on threshold values. Red: These events show that the development of the general TTC and ToR concepts are mainly based on carcinogenicity data. Blue: The TTC is based on structural data in combination with toxicological information of related chemicals.
2.1 How it began
In 1967, J.P. Frawley developed a new concept for regulating chemicals used in FCMs [1]. His main aim was the definition of hazard derived from food packaging and comparing it to other chemical hazards such as from air and water pollutants, occupational exposure, drugs and pesticides. In his opinion, the degree of hazard should define the degree of control. He claimed that it is possible to determine safe levels of use for any food-packaging component. To prove this hypothesis, he examined 2-year chronic toxicity studies of 220 different chemicals and classified them according to their no-effect levels. 24 compounds had no-effect levels at 10 ppm or less, and all of them were heavy metals or pesticides. 39 out of 40 substances with a no-effect level between 10 and 100 ppm also belonged to these two groups of chemicals; the remaining substance in this class was acrylamide. According to these results he defined 10 ppm as safe level, applied a further safety factor of 100 and concluded that all non-pesticidal chemicals are safe at concentrations of 0.1 ppm in the diet. Combining this outcome with migration and exposure studies, he suggested that safety can be assured for any component of food packaging below a maximum threshold of 0.2% w/w FCM.

2.2 The invention of the decision tree
A decade later, Cramer and colleagues further advanced this concept. In their paper, the authors proposed a preliminary assessment of probable risk for chemicals with known structure, but unknown toxicity based on a decision tree. The decision tree compromises 33 questions assigning chemicals into three different classes on the basis of their toxicity (class I – simple structure, low potential toxicity, efficient metabolism, class II – intermediate risk of toxicity, class III – safety cannot be presumed due to structural features). The robustness of the decision tree was tested with 227 known carcinogenic substances of which 226 were assigned to class III. Furthermore, the no-observed-adverse effect levels (NOAELs) of 81 chemicals were plotted against their assignment to the Cramer classes I, II or III. According to these results, presumptive no-effect levels were derived (class I – 50 ppm, class III – 5 ppm) and protection indices were calculated for the three classes based on different exposure scenarios. Cramer et al. highlighted that the knowledge of the chemical structure and estimates of intake are essential for the evaluation of chemicals according to this method. Furthermore, the authors state that the predictive model does not substitute experimental data, which weigh more heavily in further risk assessment.

2.3 The basis for the Threshold of Regulation
In 1986, Rulis reported that the FDA already used a Threshold of Regulation (ToR) concept on a case-by-case basis for low level migrants originating from food packaging, without having formal policy statements justifying this procedure [6]. The aim of this paper was the development of a general policy that allows the exclusion of all chemicals posing a risk to human health already at very low concentrations, while avoiding full petition review at the same time. A probabilistic approach was presented by Rulis that compared toxicological potency data of 343 oral carcinogens derived from the carcinogenic potency database (CPDB) [7] with data on acute toxicity of numerous chemical substances [13]. The TDI<sub>50</sub> of the carcinogens and further risk equivalents were related to dietary exposure and the risk per unit dose or potency for each substance was calculated; these data were plotted as distributions (Figure 2; Box 2). According to this analysis, it seemed obvious that the concentration ranges for acute toxicity and carcinogenic potency all followed log-normal distributions, but they differed in their concentration ranges [6]. The distribution curve representing the 50% lifetime risks for causing tumors (TDI<sub>50</sub>) was moved sideways by linear extrapolation until it showed the curve representing a 10⁻⁴ lifetime risk (Box 3). This distribution of carcinogenic potencies was used to estimate the concentrations in the diet that would give rise to less than a one in a million lifetime risk of cancer.
2.4 Assigning thresholds to the chemical classes

In 1990, Munro summarized the outcome of a workshop on safety assessment procedures for indirect food additives held by the Canadian Centre for Toxicology [15]. The author advanced the ToR concept previously published by Rulis [13]. He critically investigated mathematical operations and also the selection of data sets from different databases. Furthermore, the inclusion of even limited biological data into the probabilistic approach was demanded. To rule out possible genotoxic carcinogens, structure-activity relationships and in vitro short-term genotoxicity tests were assumed to guarantee a high level of safety. Six years later, Munro et al. [8] compiled a reference database of more than 600 chemicals that were tested for a variety of toxicological endpoints and classified them by applying the Cramer decision tree approach. The 5th percentile NOELs were calculated for each structural class and converted into a human exposure threshold by dividing through a safety factor of 100 and assuming a standard person weight of 60 kg (Table 2). The 5th NOEL percentile provides a 95% confidence that the NOEL of any other substance assigned to the same structural class and lacking toxicological data has a NOEL above this value.

Table 2. 5th Percentile NOELs and human exposure thresholds for each Cramer structural class (according to Munro et al. [8]).

<table>
<thead>
<tr>
<th>Cramer class</th>
<th>Number of chemicals</th>
<th>5th percentile NOEL (mg/kg/day)</th>
<th>Human exposure threshold (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>137</td>
<td>3.0</td>
<td>1.8</td>
</tr>
<tr>
<td>II</td>
<td>28</td>
<td>0.91</td>
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<tr>
<td>III</td>
<td>448</td>
<td>0.15</td>
<td>0.09</td>
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</tbody>
</table>

2.5 FDA adopts the ToR

In 1995, the FDA passed a rule on the 'Threshold of regulation for substances used in food-contact articles’ (21 C.F.R. §170.39) [5]. In general, the rule is based on the assumption that certain dietary concentrations of substances derived from FCMs do not present health or safety concerns. For non-carcinogenic compounds, this threshold follows the de minimis principle and is set at 0.5 ppb, corresponding to dietary exposure levels at or below 1.5 μg per person and day. These numbers were derived from the distribution of TD_{50} for 343 chemical carcinogens and its linear extrapolation to 10^{-6} lifetime cancer risk as reported by Rulis [6]. However, carcinogenic compounds or suspected carcinogens cannot be authorized using the ToR rule at all, because they are prohibited by the Delaney Clause (Section 409 of the 1958 Food Additives Amendment to the 1954 Federal Food, Drug and Cosmetic Act). Substances previously regulated as food additives that are also present in FCMs can be regulated according to the ToR rule if the exposure derived from the FCMs does not contribute to more than 1% of the acceptable daily intake (ADI). This rule does not classify the chemicals into different classes according to their toxicity (e.g. Cramer classes I-III), but only defines one general threshold. The complete rule is attached in the appendix. The FDA provides a guidance document for industry how to submit a request for regulation under the ToR rule [16]. This request should include information about application, exposure and toxicity of the substance to be regulated.

2.6 Tiered ToR as basis for increased threshold levels?

In 1999, Cheeseman et al. developed a tiered approach that aimed to extend the single threshold of regulation (0.5 ppb, [5]). The comprehensive study analyzed a cohort composed of 709 carcinogens from the CPDB and compared them with reproductive
Toxicity tests for 3306 compounds and multi-dose toxicity tests for 2542 compounds. The authors correlated the outcome of the Ames assay with the potency of carcinogens and concluded that mutagenic carcinogens are three times more likely to be very potent than non-mutagenic carcinogens. The potency of carcinogens was calculated based on the TD50 of the respective substance. Cheeseman and colleagues could imagine the regulation of less potent carcinogens according to the ToR rule in case of sufficient biological evidence. Furthermore, results of acute toxicity tests were included into the previous correlation between carcinogenic potency and mutagenicity, but no clear associations were shown. At the time of the study, eight structural classes of potential carcinogens had enough evidence to be excluded from the consideration under the ToR process by the FDA (nitroso compounds, endocrine disruptors, strained heterocyclic rings, heavy metal compounds, α-nitro-furyl compounds, pyrazines/triazines/azides and azoxy compounds, and polycyclic amines). Cheeseman et al. showed that all these classes had likelihoods between 80 and 97% that they will cause a more than 10⁶ lifetime risk to develop cancer when present at 5 ppb in the diet. At dietary levels up to 0.5 ppb, this likelihood was reduced to 48-84%. N-Nitroso compounds were shown to be the most potent carcinogens amongst the investigated chemicals. The authors clearly state that mutagenic chemical structures such as N-nitroso and benzidine-like compounds have to be completely excluded from the ToR rule, but they could imagine a threshold of 4 to 5 ppb for non-mutagenic carcinogens. Concluding, the authors recommend that a range of dietary concentrations between 0.5 and 15 ppb (corresponding to 1.5 to 45 μg per person and day) should be applied as tiered threshold levels depending on the structure-activity relationship, genotoxicity and short-term toxicity to increase the effectiveness of the existing ToR process.

2.7 Is carcinogenicity the most sensitive endpoint?
In 2000, Kroes et al. investigated a variety of toxicological endpoints to secure the safety of the general threshold of 1.5 μg/person/day. The authors showed that carcinogenicity was the most sensitive endpoint. Special emphasis was placed on endocrine disruptors and allergens present in food. It was concluded that the above-mentioned general threshold protects the consumer from adverse effects by carcinogens and endocrine disruptors, but allergens should not be regulated by threshold approaches due to missing NOELs.

2.8 ILSI expert workshop
In March 2003, the ILSI Europe Expert Group held a workshop on the TTC concept with participants from academic science, regulatory authorities and industry. One year later, Kroes et al. published a paper presenting the outcome of this workshop [10]. Several specific topics related to the TTC were investigated and recommendations were given:

- Structural alerts for high potency carcinogens: The authors picked up the 709 carcinogenic compounds already investigated by Cheeseman et al. and added more recent compounds from the CPDB, resulting in a total of 730 compounds. These substances were separated into 18 structural groups and all of them should be of concern in the safety review. Nevertheless, five groups were treated separately due to their high risks to cause cancer even at low intake levels. These five groups were named the cohort of concern (COC) and should not be regulated under the TTC approach at all. The estimated intake of any compound belonging to these five groups shall not exceed 0.15 μg/person/day. They can be sub-grouped into genotoxic carcinogens ( aflatoxin-like compounds, N-nitroso-compounds and azoxy-compounds) and non-genotoxic carcinogens (steroids and polyhalogenated dibenzo-p-dioxins and dibenzofurans). The application of a TTC was proposed for other carcinogens based on linear extrapolation of the animal dose-response data down to a theoretical life-time risk of 10⁻⁶ (see Box 3).
- The toxicity of different neurotoxicants was investigated and the authors showed that organophosphates are the most potent compounds in this database. Thus, they suggested a TTC of 18 μg per person and day for organophosphates and recommended the application of a cumulative TTC for all organophosphate esters in the diet, because they act via the same mechanism. All other neurotoxicants should be assigned to Cramer class III.
- The regulation of teratogens under the TTC was also questioned. Kroes et al. anticipated teratogenicity and embryotoxicity to be threshold phenomena. Furthermore, they showed that compounds with high teratogenicity were also high-potency carcinogens, thus being excluded from the TTC approach very early in the decision tree. All other teratogens should be classified according to the Cramer classification system.
- Endocrine disrupting chemicals were discussed mainly with a focus on their possible low-dose effects, but the inclusion of these phenomena into the TTC was judged to be too premature based on the scientific uncertainties.
- Food-derived allergens were recognized as group of chemicals that act via threshold mechanisms, but a general lack of dose-response data was claimed. Proteins were completely excluded from the TTC due to their general allergic potential.
- Possible risks caused by metabolic activation, toxicokinetics and bioaccumulation were evaluated to be covered by the Cramer decision tree and by applying high safety factors. Nevertheless, substances that show large species differences in accumulation have to be excluded from the TTC concept according to the authors.
- Exposure data were identified as absolutely necessary for the proper application of the TTC approach. The ToR, which is used by the US FDA, assumes that a compound is present in the whole diet at constant concentrations. In contrast, the suggested TTC concept demands the knowledge of human exposure data. As a result of these studies and conclusions, the authors developed a decision tree that leads to three possible answers: (a) substance would not be expected to be a safety concern, (b) negligible risk or (c) risk assessment requires compound-specific toxicity data. The application of the TTC approach was suggested for compounds that are present in food at low concentrations and for which sound intake and exposure data are known.

2.9 Proof of principle
In 2011, Pinalli et al. conducted a “proof of principle” of the TTC approach [14]. The authors used a database of 232 chemicals that were used in FCMs and classified them by applying the Cramer decision tree. The results were compared with the dataset obtained by Munro et al. [8] and further support the Cramer classification system. NOELs of both datasets were used to calculate ratios of the TDI over the TTC value for each single compound. 96% of these ratios were higher than 1 indicating that the TTC approach is more conservative for these chemicals than the TDI approach. The remaining 4% of substances can be divided into a group of compounds that should not be evaluated by the TTC approach at all due to structural alerts or certain functional groups (3%) and chemicals for which the TTC approach is less conservative than the TDI approach (1%). The authors could not explain why these chemicals were judged to be less hazardous according to the TTC approach when compared to the experimental results.
2.10 EFSA evaluates the TTC concept for FCMs

Recently, the Scientific Committee of EFSA thoroughly analyzed and evaluated published data on the TTC. In 2012, they published a Scientific Opinion on exploring options for providing advice about possible human health risks based on the concept of TTC [12]. In general, the committee recommends the TTC as useful screening tool for substances with known chemical structure and missing toxicological data. The advantages and also the open questions of the TTC concept were highlighted in a detailed discussion. For the application of this approach, EFSA demands a comprehensive exposure assessment and an adjustment for the body weight. The current thresholds (Table 1) were calculated on the basis of 60 kg body weight, but they do not protect infants and children with (much) lower body weights. Thus, EFSA proposes that the TTC values should be converted to μg/kg body weight/day making the approach more conservative (Table 1). In 2012, EFSA published a Guidance Paper that recommends the application of default body weights of 70 kg for adults, 12 kg for toddlers and 5 kg for infants for risk assessments [17]. The Cramer classification system was acknowledged as essential and conservative component of the current TTC approach, but its limitations were pointed out and improvements were suggested (e.g. the treatment of class II components as if they were class III substances, because class II is less well defined and sparsely populated). The TTC values for Cramer class I and class III substances and for organophosphates and carbamate substances were considered to be sufficiently protective. The impact of recent EU-wide work on endocrine disrupting chemicals (EDCs) on the TTC approach was recommended to be taken into account after finalization, but in the meantime EDCs other than steroids should be evaluated under the TTC approach. Known impurities, breakdown-down and reaction products were proposed to be assessed using the TTC concept. The threshold level for substances with structural alerts for genotoxicity was confirmed to be 0.15 μg/person/day. The following categories of substances were suggested to be excluded from the approach: COC, inorganic substances, metals, organometallics, proteins, steroids, chemicals that (might) bioaccumulate, nanomaterials, radioactive substances and mixtures of unknown chemical structures. Finally, the authors emphasized again that the TTC is a probability-based tool and cannot guarantee complete certainty. According to personal information from the EFSA CEF panel, the TTC is currently not being used for food contact substance risk assessment due to public controversy of the concept.

3 Current and possible future applications of the TTC

- As mentioned above, the FDA introduced the ToR approach in 1995. Chemicals having a cumulative estimated daily intake below 1.5 μg/person/day and no indications for carcinogenicity can be authorized in the absence of any toxicological data [5].
- Besides the ToR approach, the TTC concept was adopted for the regulation of flavoring substances by the European Commission (EC) [18] and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) [19-22]. Both institutions established a decision tree approach based on the classification system published by Munro et al. [8], but JECFA further included the general ToR of 1.5 μg/person/day.
- In 2011, Koster et al. proposed a TTC approach for the regulation of unknown substances found in food samples [23]. The examples given in this paper include the evaluation of non-intentionally added substances (NIAS) in a food contact material that was produced by a new procedure. According to the authors’ opinion, chemicals that belong to the “TTC excluded classes” can be identified and excepted by a combination of expert judgment and targeted analysis. On the other hand, the genotoxic potential of unknown substances cannot be evaluated without at least some structural information. In this case, the authors propose the application of a worst-case scenario setting a threshold of 0.15 μg/person/day for these compounds. Furthermore, they suggest the development of more sophisticated analytical methods and better bioassays to exclude the presence of genotoxic substances.
- The European Medicines Agency (EMA; before Dec. 2009 EMEA) published a guideline regulating genotoxic impurities in pharmaceutical products based on the TTC concept [24, 25]. Also the FDA discussed the application of the TTC for the regulation of genotoxic and carcinogenic impurities in drugs [26]. The TTC approach could additionally be used for the environmental risk assessment of pharmaceuticals as proposed by EMA [27].
- Further possible applications of the TTC concept were suggested for cosmetics and consumer products [28, 29]. In 2012, the EFSAs Panel on Plant Protection Products (PPR) adopted a Scientific Opinion recommending the TTC approach for metabolites and degradation products of pesticides [30].
- Proposals for exposure-based waiving of toxicity tests under REACH also included the TTC concept [31].

4 Tools for the application of the TTC

4.1 Software

During the last decades, tools were developed helping to classify chemicals according to their toxicity. As mentioned earlier, the Cramer decision tree divides chemicals into three structural classes. The software TTxTree is based on the Cramer classification system [2] implementing some extended rules [32]. The Kroes TTC decision tree [10] and further prediction tools and databases. It can be downloaded free of charge from the Joint Research Centre (JRC) homepage [33]. The software is based on the distribution of potencies for chemicals that share similar structural characteristics with the compound of interest. Nevertheless, expert judgment is generally demanded during the classification process and cannot be replaced by exclusive use of the software [34]. An investigation by Lapenna and Worth also points out the current limitations of the Cramer classification system in TTxTree [35]. The OECD QSAR toolbox [36] is one further, more comprehensive software that can be used to classify chemicals according to their toxicity, but it has not been used for the TTC or ToR approaches so far.

4.2 Databases

All threshold approaches were developed on the basis of databases representing different toxicological endpoints. Table 3 summarizes the total numbers of chemicals that were included in the studies, the investigated toxicological endpoints and the database and/or literature that was used as reference source.

5 Discussion

The TTC approach is already used by different regulatory agencies, but its application for FCMs is still under discussion, as can be seen by the recent Scientific Opinion published by EFSA [12]. The TTC concept is based on several assumptions and probabilities, thus it cannot guarantee complete certainty. Critical issues were pointed out by authors who worked on the development of the TTC concept and these different perspectives help to get an overview about the advantages and disadvantages of the approach. General advantages seem to be the reduction of animal testing and an easier prioritization

5
of risk assessment resources. Most researchers agree that toxicity data regarding not fully characterized chemicals have to be included during the classification, but no clear advice exists so far on how to realize this. Further critical questions come up during discussions on the TTC concept, but they apply also for the traditional risk assessment: How are mixtures assessed? Does the approach guarantee protection during sensitive periods of development? Are substances that follow non-monotonic dose response curves (e.g. some endocrine disruptors) covered by the TTC concept?

5.1 Correlation between animal models and human health risks

Rulis concluded that his model of linear extrapolation of TD<sub>50</sub> to a virtually safe dose (VSD; as it was later named by Cheeseman et al. [9]) is only valid providing the following requirements: (i) Results of the animal carcinogenic assay may be related directly to the potential human health risk. (ii) The linear proportional extrapolation model on the published TD<sub>50</sub> values to an upper-bound risk of 10<sup>-6</sup> or less is valid. (iii) The carcinogens used for the model comprise a representative set of chemicals used as FCMs [6]. There still might be no clear answers to these questions, but also the traditional toxicological approaches relate the results of animal carcinogenicity assays with the effects on human health. The linear extrapolation model was questioned by Munro et al. [8], but nevertheless it was judged to be conservative. A higher number of carcinogens was tested later on without significant changes in the distribution of the TD<sub>50</sub>s, indicating that the chosen chemicals cover the available chemical space of carcinogens [9]. The linear extrapolation models do not take into account relevant data on inter- and intraspecies variability [37], although it might be possible to include a safety factor to reduce these risks.

5.2 Exposure

The quality of the TTC concept strongly depends on the available exposure data. Ideally, not only oral exposure has to be taken into account for each chemical, but also dermal or air-borne exposure routes contribute to the total exposure. The correct and careful application of exposure data has to protect consumer groups with especially high exposure levels and groups that are more sensitive towards certain exposures. In the U.S. both the classical risk assessment and the ToR are based on exposure data calculated from the dietary interview files of NHANES [38] and the consumption factors of the FDA [39]. In Europe, a 7th framework funded project, named “Flavourings, Additives and food Contact materials Exposure Task (FACET)” aimed to create a food chemical exposure surveillance system that covers representative regions of the EU. This project might be a first step towards a comprehensive database that also considers national and regional eating habits and could be used as basis for a future application of the TTC approach.

5.3 TTC and NIAS

Knowing the chemical structure of compounds is one major requirement for the application of the TTC concept as risk assessment tool (Box 1). However, Koster et al. advanced the TTC concept and proposed its application also for the risk assessment of NIAS, where chemical structures are not always available [23]. The main advantage of this development is the relatively simple and inexpensive possibility to perform a risk assessment for chemicals that otherwise would not be assessed at all. On the other hand, the uncertainties drastically increase: Although many genotoxic compounds can be excluded by targeted analyses in combination with expert judgment, it is still impossible to prove their absence without knowing the chemical structure and without toxicological tests. The authors proposed a decision tree that should guarantee high

<table>
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<tr>
<th>Toxicological data obtained from</th>
<th>Toxicological endpoint(s)</th>
<th># of chemicals</th>
<th>Reference</th>
</tr>
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<tbody>
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<td>• Carcinogenicity</td>
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<td>• Teratogenicity</td>
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<td>• Several endpoints</td>
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<td>• Munro database [8]</td>
<td>• Several endpoints</td>
<td>613</td>
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levels of safety, but they also clearly state the current limitations. They suggested further improved bioassays and better analytical techniques to overcome these restrictions. The problem on how to quantify unknown compounds detected by certain chromatographic techniques was not highly ranked in this paper, although it causes higher uncertainties. The responses of unknown compounds were compared with the responses of several standards and the levels of concern were defined accordingly. Although the exact response of unknown chemicals still cannot be predicted, no safety factor was used to correct for this uncertainty. The responses of some analytical detectors, which are proven for ‘uniform’ responses, differ by a factor of approximately 6 according to Koster et al. [38]. Based on this information, a safety factor of 10 could be conceivable to include the risk of low-responding analytes.

5.4 Data management and updates
According to Dewhurst and Renwick [40], a publicly available, centralized toxicological database and optimized software tools should be established. This proposed database should be set up, expanded and continuously maintained. The inclusion of new data should be possible at any time. As a consequence, the Cramer decision tree and the set thresholds should be re-evaluated according to any changes in the database. The authors further suggested a standardized, transparent and reliable bioinformatics approach that aims at identifying structural alerts for DNA reactivity. A standardized chemical domain analysis and the possibility of predicting metabolites were additionally proposed improvements. Any update or change of these tools should be subject to global peer-review. These plans sound very reasonable and attractive, but the implementation of any modification might be difficult: Can authorities act quickly enough to adjust their regulations according to any novel development? Do strategies exist that can combine incomplete toxicity data and results obtained from the TTC approach? Compared to the traditional risk assessment that includes complete toxicological data sets for each single compound, any changes in the decision tree or any other underlying tools or threshold value might affect the classification of many chemicals regulated under the TTC approach.

**Abbreviations**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>ADI</td>
<td>Acceptable Daily Intake</td>
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<tr>
<td>COC</td>
<td>Cohort of Concern</td>
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<td>CPDB</td>
<td>Carcinogenic Potency Database</td>
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<td>EFSA</td>
<td>European Food Safety Agency</td>
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<td>European Medicines Agency (before 2009: EMEA)</td>
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<td>Food Contact Material</td>
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<td>No Observed Effect Level</td>
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</tr>
<tr>
<td>TDI</td>
<td>Tolerable Daily Intake</td>
</tr>
<tr>
<td>ToR</td>
<td>Threshold of Regulation</td>
</tr>
<tr>
<td>TTC</td>
<td>Threshold of Toxicological Concern</td>
</tr>
<tr>
<td>SML</td>
<td>Specific Migration Limit</td>
</tr>
<tr>
<td>VSD</td>
<td>Virtually Safe Dose</td>
</tr>
</tbody>
</table>

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