Toxicology Letters 180 (2008) 151–156

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

The Threshold of Toxicological Concern (TTC) in risk assessment

I.C. Munro[a], A.G. Renwick[b,*], B. Danielewska-Nikiel[a]

[a] CANTOX Health Sciences International, 2233 Argentia Road, Suite 308, Mississauga, Ontario, Canada, L5N 2X7
[b] Emeritus Professor, School of Medicine, Faculty of Medicine, Health and Life Sciences, University of Southampton, Southampton, SO16 7PX, UK

ARTICLE INFO

Article history:
Available online 22 May 2008

Keywords:
Risk assessment
Threshold of Toxicological Concern (TTC)
Flavouring substances
Cosmetics
Household products
Genotoxic impurities

ABSTRACT

The Threshold of Toxicological Concern (TTC) is a level of human intake or exposure that is considered to be of negligible risk, despite the absence of chemical-specific toxicity data. The TTC approach is a form of risk characterisation in which uncertainties arising from the use of data on other compounds are balanced against the low level of exposure. The approach was initially developed by the FDA for packaging migrants, and used a single threshold value of 1.5 μg/day (called the threshold of regulation). Subsequent analyses of chronic toxicity data resulted in the development of TTC values for three structural classes with different potentials for toxicity (1,800, 540 and 90 μg/day). These TTC values have been incorporated into the procedure that is used internationally for the evaluation of flavouring substances. Further developments included additional TTC values for certain structural alerts for genotoxicity (0.15 μg/day), and for the presence of an organophosphate group (18 μg/day). All of these TTC values were incorporated into an extended decision tree for chemicals, such as contaminants, which might be present in human foods. The TTC approach has been shown to have potential applications to risk assessments of cosmetic ingredients, household products and impurities in therapeutic drugs.

1. Introduction

Humans are exposed daily to increasing numbers of chemicals from food, cosmetics, household products, medicines and the environment. Extensive safety data exist for some of these chemicals, but for others only limited data are available currently. Nevertheless, risk assessment for all chemicals is necessary to ensure that the health of the population is not adversely affected. Intentional addition of chemicals to food without adequate safety assessment is not acceptable; however, the generation of substance-specific toxicity data on the thousands of chemicals that may be present at low levels in food, due to migration from packaging or the use of flavouring substances, is not feasible in the near future. Thus, a rigorous, scientifically sound, and practical approach is necessary to allow risk characterisation of the myriad of chemicals to which humans are exposed.

For individual chemicals with known toxicological profiles, there are established procedures for determining levels of exposure without significant health risks to humans. For non-genotoxic chemicals a conventional toxicological safety evaluation relies on the identification of the highest dose level, usually derived from animal toxicity studies, at which the most sensitive adverse effect does *not* occur, and application of an adequate margin of safety to determine a level of exposure that is likely to be safe in humans.

The Threshold of Toxicological Concern (TTC) approach is based on the concept that reasonable assurance of safety can be given, even in the absence of chemical-specific toxicity data, providing that the intake is sufficiently low, i.e. that an exposure level can be defined below which there is no significant risk to human health (JECFA, 2006). The approach is based on the knowledge gained from the general toxicity database that has been developed in the past 50–60 years. The TTC approach is a form of risk characterisation that balances uncertainties inherent in extrapolation of these data to an unstudied substance against the predicted or known low level of exposure.

2. Packaging migrants and the Food and Drug Administration (FDA) threshold of regulation

The concept of a threshold level of intake giving a negligible risk for chemicals without toxicity data was initially proposed by Frawley (1967) for substances intended for use in food-packaging materials. The FDA decided that for substances present in food contact materials, known as indirect additives, it would perform only an abbreviated safety assessment, mainly focused on intake without the need for specific toxicity testing if the concentration in food is below 0.5 ppb (parts per billion). The rationale for this threshold was given in the US Federal Register (Federal Register, 1993,

* Corresponding author. Tel: +44 1229588894.
E-mail address: agr@soton.ac.uk (A.G. Renwick).

0378-4274/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.toxlet.2008.05.006

1995) and was based on dose-response data from animal studies for both cancer and non-cancer effects. The Federal Register (1993) stated "*most carcinogens pose less than one in a million lifetime risk if present in the daily diet at 0.5 ppb. Therefore FDA tentatively finds that establishing a 0.5 ppb dietary concentration level as the "threshold of regulation" for food contact articles would result in a negligible risk, even in the event that a substance that is exempted from regulation as a food additive were later shown to be a carcinogen*". This analysis was based on the distribution of carcinogenicity potency data in animal cancer bioasssays with linear extrapolation to a 10^{-6} lifetime risk estimate. The Federal Register (1993) also stated that "*A 0.5 ppb threshold is 2000 times lower than the dietary concentration at which the vast majority of studied compounds are likely to cause non-carcinogenic toxic effects and 200 times lower than the chronic exposure level at which potent pesticides induce toxic effects*".

In 1995, the U.S. FDA established a "threshold of regulation" of 0.5 ppb (equivalent to 1.5 μg/person/day) for indirect food additives that are not known to be carcinogens and do not contain structural alerts indicative of carcinogenicity (Federal Register, 1995). At 0.5 ppb about 40% of studied animal carcinogens gave a lifetime risk greater than 10^{-6},but this percentage would only hold for unstudied substances if 100% of chemicals were subsequently shown to be carcinogens. Munro (1990) further evaluated this threshold for food-packaging materials and determined that a dietary level of 1 ppb would not pose an appreciable risk. Based on a probabilistic analysis, only 4% and 5% of unstudied compounds would give a lifetime risk greater than 10^{-6} at dietary concentrations of 0.5 ppb and 1 ppb, respectively, if 10% of compounds were carcinogens (Munro, 1990). No toxicity testing is required by the FDA for substances without structural alerts for genotoxicity, or that are not known carcinogens or potent toxins based on existing data, if the estimated daily exposures were less than 1.5 μg/person (Munro et al., 2002).

3. Flavouring substances and the development of TTC values for different structural groups

The TTC concept was extended by Munro et al. (1996) who developed human exposure thresholds for each of three structural classes of chemicals (Class I, II and III) identified using the Cramer et al. (1978) decision tree. This decision tree divides chemicals into the three classes based on structural properties suggestive of varying inherent risks of toxicity.

(i) Class I substances have simple structures, are efficiently metabolised and are of low potential toxicity.
(ii) Class II substances are less clearly innocuous than those of Class I, but do not have a positive indication of toxicity or of the lack of knowledge, which are characteristic of Class III substances.
(iii) Class III substances contain structural features that permit no strong initial presumptions of safety, or that may even suggest significant toxicity.

Munro et al. (1996) derived TTCs for Cramer et al. (1978) structural classes based on an analysis of data from toxicity studies on 137, 28 and 448 compounds in Classes I, II and III, respectively. The analysis used NOAELs (no observed adverse effect levels) from studies in rodents or rabbits (data from studies on dogs or other species were not included because of the low group sizes). A limited number of the NOAELs were from sub-chronic studies, and these were divided by a three-fold uncertainty factor (WHO, 1994) to convert them into equivalent chronic NOAELs. The distributions of the NOAELs (in mg/kg body weight/day) for each structural class were plotted and the 5th percentile of each distribution used as the basis for deriving a TTC: this approach meant that there was a 95% probability that the NOAEL for any unstudied compound in that class would be higher than the value used. The 5th percentile NOAELs of 3.0, 0.91 and 0.15 mg/kg body wt/day for Classes I, II and III, respectively, were divided by the usual 100-fold uncertainty factor (WHO, 1987) and multiplied by 60 kg to derive TTC values of 1800, 540 and 90 μg/person/day, respectively.

Thereafter, a procedure was developed to evaluate flavouring substances on the basis of these TTC values (Munro et al., 1999), which was subsequently used by the Joint FAO/WHO Expert Committee on Food Additives in 1996 for the first time (JECFA, 1997). The TTC approach is particularly suitable for the safety assessment of flavouring substances because they are added to foods at very

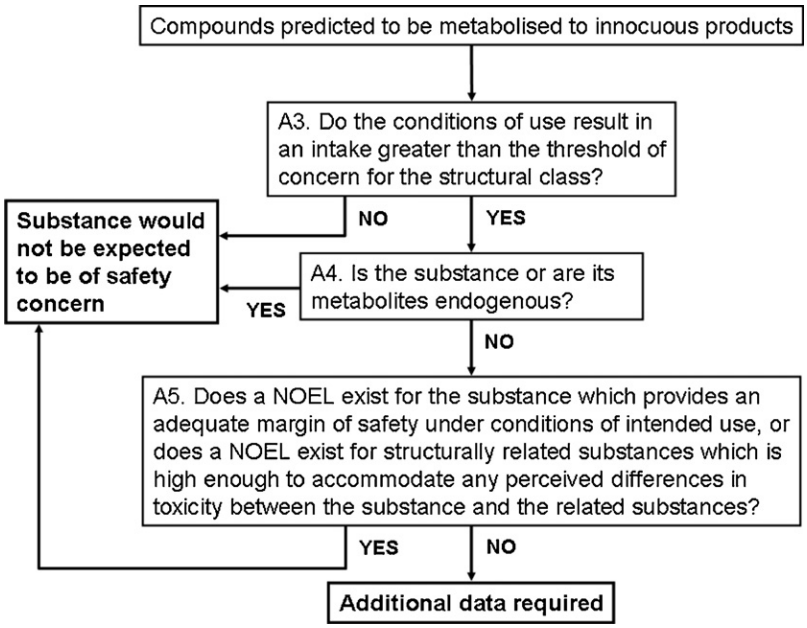

Fig. 1. The JECFA procedure for the evaluation of flavouring substances considered to be metabolised to innocuous products (from Renwick, 2004).

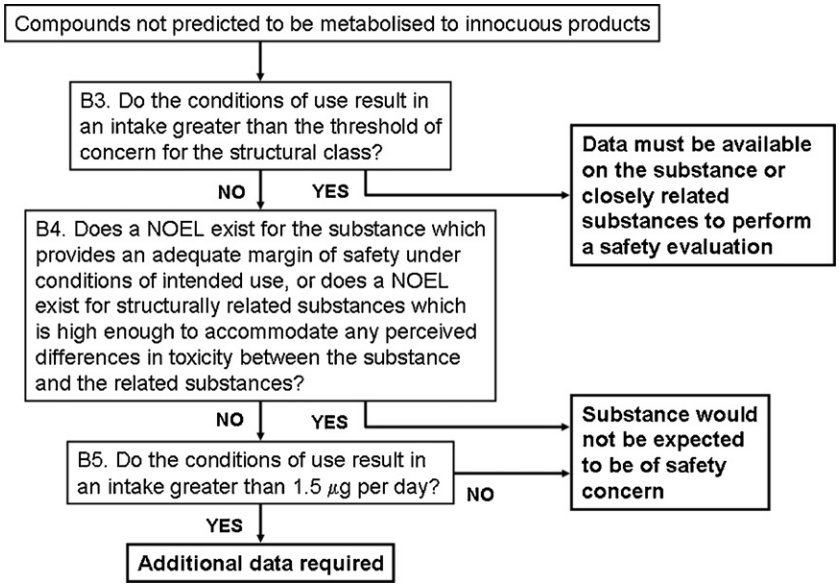

Fig. 2. The JECFA procedure for the evaluation of flavouring substances not considered to be metabolised to innocuous products (from Renwick, 2004).

low levels and the fact that their characteristic organoleptic properties result in self-limited exposures. The procedure combines data on intake, metabolism, and structure-activity relationships with toxicity data and is based on a series of questions, with each "yes" or "no" answer leading to the next question. The decision tree separates flavours into those that are known or predicted to be metabolised to innocuous products (Side A; Fig. 1), and those considered not to form innocuous metabolites (Side B; Fig. 2).

Over the past decade, the safety of over 1600 flavouring substances has been evaluated by JECFA using this procedure. Since it was first implemented, two studies have been conducted to validate the procedure used by JECFA by calculating margins of safety for all of the flavouring agents that have been evaluated thus far (Munro and Kennepohl, 2001; Munro and Danielewska-Nikiel, 2006). Both studies demonstrated that the calculated margins of safety, between chemical-specific or relevant NOAELs and the estimated intake, were greater than 100 for more than 99% of the flavouring agents evaluated, thereby confirming the validity and utility of the TTC values.

Because the TTC approach is a form of risk characterisation, the evaluation is dependent on sound estimates of intake/exposure. JECFA has relied on per capita estimates derived from annual production poundage data of flavouring agents obtained from comprehensive region-specific surveys assuming that only 10% of the population are consumers (known as the maximized-survey-derived intake [MSDI]). This method is one of several different models for estimating dietary exposures that are available and has been criticized in the past for potentially under-estimating intakes in the case of high consumers of flavoured products. The European Food Safety Authority (EFSA), which also uses the TTC approach to evaluate the safety of flavouring agents, has incorporated other models of calculating intake (e.g. modified theoretical added maximum daily intake [mTAMDI]) into their evaluations of the safety of flavouring agents. In a recent analysis, Young et al. (2006) compared the relationship between intakes calculated based on the reported volume of production (the MSDI) and intakes calculated based on use-level data (the possible average daily intake [PADI] and the mTAMDI) and determined that the MSDI was a conservative, yet practical method to estimate intake of flavouring substances.

4. TTC values for structural alerts for possible genotoxicity and carcinogenicity and the development of a decision tree for general chemicals in food, including contaminants

The application of the structural class TTC values developed by Munro et al. (1996) to substances other than flavours has been the subject of a number of reviews (Kroes et al., 2000; Barlow et al., 2001); these identified that the distribution of NOAELs for neurotoxins was at lower doses than the Class III distribution, indicating that the Class III TTC value might not be adequate for such compounds. Kroes et al. (2004) undertook additional analyses and expanded the procedure that was initially developed for flavouring substances. They proposed a broader evaluation scheme for low molecular weight compounds present at low levels in the diet.

Kroes et al. (2004) developed a decision tree that incorporated two additional TTCs, one for substances with structural alerts suggestive of potential genotoxicity and one for organophosphates. Analyses were undertaken on the carcinogenic potencies of compounds with different structural alerts for genotoxicity. The estimated lifetime cancer risks for most of the compounds with different structural alerts exceeded 10^{-6} at an intake of 1.5 μg/day: in contrast at an intake of 0.15 μg/day this level of risk was exceeded by only about 5% of aromatic amines, aromatic nitrates, azo compounds, benzidine derivatives, heavy metal containing compounds, highly chlorinated compounds (excluding dioxins), compounds with miscellaneous Ashby alerts (see Cheeseman et al., 1999), nitro-furyl compounds, compounds with strained rings and vinyl containing compounds (Kroes et al., 2004). The estimated risks for the majority of aflatoxin-like, azoxy- and nitroso-compounds exceeded 10^{-6}, even at an intake of 0.15 μg/day and therefore the proposed TTC value was not appropriate for such compounds. The greater toxicity of neurotoxins, compared with Class III compounds, was shown to be due to organophosphate compounds. The distribution of NOAELs for organophosphates was plotted; the 5th percentile was estimated to be 0.03 mg/kg body wt/day and converted to a TTC value of 18 μg/person/day for organophophastes. The decision tree retained the TTC values used in the procedure for flavouring substances, but was organised so that compounds with structural alerts for possible genotoxicity/carcinogenicity were considered first and then other structures with decreasing potential for toxicity. The decision tree excluded compounds for which the

TTC approach was not appropriate (proteins, non-essential metal compounds and dioxin-like compounds).

5. Application of TTC values to cosmetics

Kroes et al. (2007) analysed the appropriateness of the Kroes et al. (2004) decision tree to the safety evaluation of cosmetic ingredients. Topical exposure could affect toxicity in two ways. First, the *stratum corneum* represents a permeability barrier, so that only a fraction of the applied topical dose would reach the systemic circulation. Second, many compounds undergo significant metabolism in the gut lumen, gut mucosa and the liver during their absorption from the gut, which could result in route-specific differences in the ratio of parent compound and metabolites in the body.

The relationship between the external topical dose and the internal dose (systemic uptake) can be estimated based on an empirical relationship between molecular weight and log octanol:water partition coefficient, and the extent to which the concentration of the chemical is present as a saturated solution within the applied cosmetic product. It was proposed that different patterns of cosmetic use, including the frequency of application and the use of rinse-off products, could be taken into account by the application of conservative adjustment factors.

Application of the TTC values derived from the oral toxicity database of Munro et al. (1996) to non-oral human exposures requires consideration of possible route-specific differences in metabolism and toxicity. The oral TTC values would not be suitable for the body burden arising from topical exposures if oral administration of compounds in the Munro et al. (1996) database was associated with significant presystemic detoxication (i.e. metabolic inactivation in the gut lumen and during absorption from the gut and passage through the gut wall and liver). The potential for presystemic detoxication of compounds below and close to the 5th percentile for each structural class was analysed by a literature search; although presystemic detoxication would have occurred for a few compounds, in other cases, especially in Class III, oral dosage would have given greater toxicity than topical treatment due to uptake and bioactivation in the liver. It was concluded that the 5th percentile from oral studies would be relevant to the body burden after topical administration.

6. Application of TTC values to household products

Blackburn et al. (2005) evaluated the applicability of the TTC database to ingredients used in personal and household care products, based on comparison of the range of chemical structures with those in the original Munro et al. (1996) database. They also investigated the range of NOAELs for selected ingredients in structural Classes I (21 chemicals), II (2 chemicals) and III (21 chemicals) compared with the NOAELs in the original database. NOAELs from long-term toxicity studies were not available for all of the chemicals and the data were adjusted for subchronic studies (using a 3-fold adjustment factor) and also for when a NOAEL was not found (using a 3-fold adjustment factor). Overall, the means and ranges were similar to those in the Munro et al. (1996) database indicating that the decision tree of Kroes et al. (2004) was appropriate for this group of compounds.

7. Application of the TTC value for potential genotoxicity/carcinogenicity to genotoxic impurities in medicinal products

Although the TTC approach is not intended to be used for compounds for which there are established risk assessment procedures, such as food additives, pesticides and therapeutic drugs, it has been applied recently to develop a method for determining maximum levels of genotoxic impurities in medicinal products (Müller et al., 2006). Analytical testing requirements for pharmaceutical products are usually based on practicability rather than the potential for toxicity. Because the synthetic routes for the production of drugs often involve highly reactive chemicals, it is not surprising that the final product may contain residues of genotoxic reagents or genotoxic reaction by-products. In 2004, the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP)

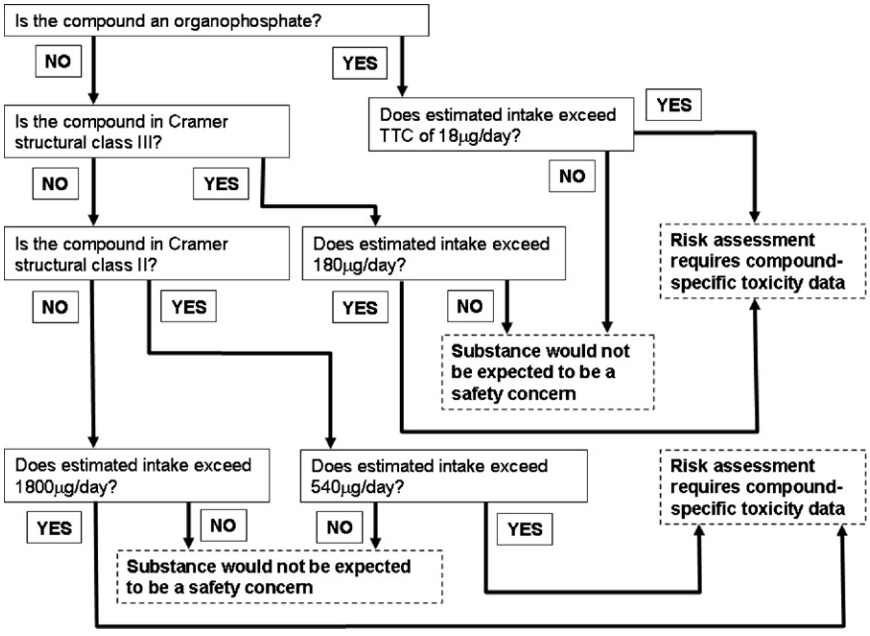

Fig. 3. Modification to the decision tree of Kroes et al. (2004) for compounds without a structural alert for genotoxicity, involving removal of organophosphates from the Class III database and modification of the TTC value (modified from Renwick, 2005). Removal of both organophosphates and organohalogen compounds from the Class III database would give a TTC value of 600 μg/day.

issued a Draft Guideline on the Limits of Genotoxic Impurities based on the TTC developed in the Kroes et al. (2004) decision tree (CHMP, 2004). However, because of the low level of the relevant TTC value (0.15 μg/person/day – see above), direct application of the TTC approach would result in extremely low maximum impurity levels, especially for drugs taken in doses of >10 mg/day. Müller et al. (2006) proposed a staged TTC approach allowing for different periods of exposure, and used a higher cancer risk estimate (10^{-5} lifetime risk) to allow for the fact that exposure is of direct benefit to the exposed individual.

8. Future developments of the TTC approach

8.1. Structural class definitions

The approach is based on application of the Cramer et al. (1978) decision tree, which was developed primarily for flavouring substances. Although this has been validated for wider application by the analyses undertaken by Munro et al. (1996), it has not been checked against recent toxicity data or structure-activity relationships. A reconsideration of the decision tree, and revision to exclude questions related to natural occurrence in foods would increase confidence in its wider application.

8.2. Modification of the Kroes et al. (2004) decision tree

The Kroes et al. (2004) scheme introduced an additional TTC value for organophosphate compounds that was lower than the original Cramer Class III threshold. However, the Class III TTC value was not revised; exclusion of organophosphates from the Munro et al. (1996) Class III database gives a 5th percentile NOAEL of 0.3 mg/kg body wt/day, which would give a corrected Class III TTC value of 180 μg/person/day instead of 90 μg/person/day (Fig. 3). In addition, if the unstudied compound is not an organohalogen and such compounds are also excluded from the Munro et al. (1996) database, the resulting 5th percentile NOAEL is about 1.0 mg/kg body wt/day, which would give a corrected Class III TTC value of about 600 μg/person/day instead of 90 μg/person/day. These analyses show the conservatism built into the use of the uncorrected TTC values for the risk assessment of chemicals that do not contain these structural characteristics.

9. Conclusions

Application of the TTC concept in the absence of chemical-specific data is a pragmatic approach that allows the safety evaluation of chemicals to which humans are exposed in food and the environment. A strength of the approach is that unnecessary animal studies are not performed because it identifies those chemicals that need additional testing. Although the TTC approach has been formally applied only in the evaluation of flavouring substances and packaging materials, there are no restrictive criteria that would preclude its use in the evaluation of other substances to which humans are exposed at low levels (Kroes et al., 2005). At its 65th meeting, JECFA considered extension of the TTC concept to other substances present in the diet in small amounts (e.g., processing aid residues, packaging materials, and contaminants) and recommended development of guidelines for the application of the approach in the risk assessment of such substances for which full toxicological datasets are not available or are unnecessary (JECFA, 2005).

In light of the continuing evolution of the TTC approach, regulatory agencies should consider wider acceptance of procedures, such as the ones developed by Munro et al. (1999) and Kroes et al. (2004), as an integral component of the safety assessment process for chemicals that occur at low levels in the diet.

Conflict of interest statement

IM and AGR have been Temporary Advisors at JECFA Meetings that evaluated flavouring agents. AGR was a member of the ILSI-Europe Expert Group on the TTC and of the Colipa Expert Group chaired by Professor Kroes that developed the paper on application of TTC to cosmetics.

References

Barlow, S.M., Kozianowski, G., Wurtzen, G., Schlatter, J., 2001. Threshold of toxicological concern for chemical substances present in the diet. Food Chem. Toxicol. 39, 893–905.

Blackburn, K., Stickney, J.A., Carlson-Lynch, H.L., McGinnis, P.M., Chappell, L., Felter, S.P., 2005. Application of the threshold of toxicological concern approach to ingredients in personal and household care products. Regul. Toxicol. Pharmacol. 43, 249–259.

Cheeseman, M.A., Machuga, E.J., Bailey, A.B., 1999. A tiered approach to threshold of regulation. Food Chem. Toxicol. 37, 387–412.

CHMP, 2004. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), June 2004. Guideline on the Limits of Genotoxic Impurities (draft). Available at http://www.emea.europa.eu./index/indexh1.htm.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard–a decision tree approach. Food Cosmet. Toxicol. 16, 255–276.

Federal Register, 1993. Food additives; threshold of regulation for substances used in food-contact articles. Fed. Reg. 58 (195), 2719–52727.

Federal Register, 1995. Food additives; threshold of regulation for substances used in food-contact articles. Final rule. Fed. Reg. 60 (136), 36582–36594.

Frawley, J.P., 1967. Scientific evidence and common sense as a basis for food-packaging regulations. Food Cosmet. Toxicol. 5, 293–308.

JECFA, 1997. Evaluation of Certain Food Additives and Contaminants. Forty-Sixth Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), WHO Technical Report Series (TRS) No. 868. Available from: http://whqlibdoc.who.int/trs/WHO_TRS_868.pdf.

JECFA, 2005. Joint FAO/WHO Expert Committee on Food Additives Sixty-Fifth Meeting: Summary and Conclusions, June 7–16, 2005. Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO); Geneva, Switz., [JECFA/65/SC]. Available from: ftp://ftp.fao.org/es/esn/jecfa/jecfa65_summary.pdf.

JECFA, 2006. Evaluation of Certain Food Additives and Contaminants. Sixty-Fifth Report of the Joint FAO/WHO Expert Committee on Food Additives, June 7–16, 2005, Geneva. World Health Organization (WHO); Geneva, Switz., WHO Technical Report Series, No. 934. Available from: http://whqlibdoc.who.int/trs/WHO_TRS_934.pdf.

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

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

Kroes, R., Kleiner, J., Renwick, A., 2005. The threshold of toxicological concern concept in risk assessment. Toxicol. Sci. 86, 226–230.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45, 2533–2562.

Müller, L., Mauthe, R.J., Riley, C.M., Andino, M.M., Antonis, D.D., Beels, C., Degeorge, J., De Knaep, A.G., Ellison, D., Fagerland, J.A., Frank, R., Fritschel, B., Galloway, S., Harpur, E., Humfrey, C.D., Jacks, A.S., Jagota, N., Mackinnon, J., Mohan, G., Ness, D.K., O'donovan, M.R., Smith, M.D., Vudathala, G., Yotti, L., 2006. A rationale for determining, testing, and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity. Regul. Toxicol. Pharmacol. 44, 198–211.

Munro, I.C., 1990. Safety assessment procedures for indirect food additives: an overview. Regul. Toxicol. Pharmacol. 12, 2–12.

Munro, I.C., Ford, R.A., Kennepohl, E., Sprenger, J.G., 1996. Correlation of structural class with no-observed-effect levels: a proposal for establishing a threshold of concern. Food Chem. Toxicol. 34, 829–867.

Munro, I.C., Kennepohl, E., Kroes, R., 1999. A procedure for the safety evaluation of flavouring substances. Food Chem. Toxicol. 37, 207–232.

Munro, I.C., Kennepohl, E., 2001. Comparison of estimated daily per capita intakes of flavouring substances with no-observed-effect levels from animal studies. Food Chem. Toxicol. 39, 331–354.

Munro, I.C., Hlywka, J.J., Kennepohl, E.M., 2002. Risk assessment of packaging materials. Food Addit. Contam. 19, 3–12.

Munro, I.C., Danielewska-Nikiel, B., 2006. Comparison of estimated daily intakes of flavouring substances with no-observed-effect levels. Food Chem. Toxicol. 44, 758–809.
Renwick, A.G., 2004. Toxicology databases and the concept of thresholds of toxicological concern as used by the JECFA for the safety evaluation of flavouring agents. Toxicol. Lett. 149, 223–234.
Renwick, A.G., 2005. Structure-based thresholds of toxicological concern–guidance for application to substances present at low levels in the diet. Toxicol. Appl. Pharmacol. 207, S585–S591.
Young, K.W.H., Danielewska-Nikiel, B., Munro, I.C., 2006. An evaluation of the maximized survey-derived intake (MSDI) as a practical method to estimate intake of flavouring substances. Food Chem. Toxicol. 44, 1849–1867.
WHO, 1987. Principles for the Safety Assessment of Food Additives and Contaminants in Food. Environmental Health Criteria, No. 70. World Health Organisation, Geneva.
WHO, 1994. Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits. Environmental Health Criteria, No. 170. World Health Organization, Geneva.