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Threshold of Toxicological Concern for Chemical Substances Present in the Diet

Report of a workshop held in October 1999

Organised by the ILSI Europe
Threshold of Toxicological Concern Task Force

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Report on Threshold of Toxicological Concern for Chemical Substances Present in the Diet

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THRESHOLD OF TOXICOLOGICAL CONCERN FOR CHEMICAL SUBSTANCES PRESENT IN THE DIET

REPORT OF A WORKSHOP HELD ON 5-6 OCTOBER 1999 IN PARIS, FRANCE

ORGANISED BY THE ILSI EUROPE THRESHOLD OF TOXICOLOGICAL CONCERN TASK FORCE

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BACKGROUND

The Threshold of Toxicological Concern (TTC) is a principle which refers to the possibility of establishing a human exposure threshold value for all chemicals, below which there is no significant risk to human health. The concept that exposure thresholds can be identified for individual chemicals in the diet, below which no appreciable harm to health is likely to occur, is already widely embodied in the practice of many regulatory bodies in setting acceptable daily intakes (ADIs) for chemicals whose toxicological profile is known. However, the TTC concept goes further than this in proposing that a *de minimis* value can be identified for any chemical, including those of unknown toxicity, taking the chemical structure into consideration.

This concept forms the scientific basis of the US Food and Drug Administration (FDA) 1995 Threshold of Regulation for indirect food additives. The TTC principle has also been adopted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in its evaluations of flavouring substances.

The establishment of a more widely accepted TTC would benefit consumers, industry and regulators. In precluding extensive toxicity testing and safety evaluations when human intakes are below such a threshold, it would focus limited resources of time, cost and expertise on the testing and evaluation of substances with greater potential to pose risks to human health and contribute to a reduction in the use of animals.

The European Commission's Scientific Committee on Food (SCF) has also been considering the application of the TTC principle. It has raised the question of whether neurotoxic, immunotoxic, endocrinologic and developmentally toxic events would be covered by a threshold based on carcinogenesis data, or whether for some of these endpoints lower thresholds might be needed.

ILSI Europe established an Expert Group on TTC to address the questions raised about the applicability of the TTC to chemicals present in the diet. The goals of the group were to examine current proposals for a TTC, to expand previous analyses of this concept, to develop and analyse additional updated databases for specific endpoints that may potentially induce important low-dose effects, and to investigate the applicability of the TTC concept to flavours and packaging migrants, as well as to a broader range of chemicals present in the diet (such as food additives, contaminants, and naturally occurring substances). The report of the expert group's work entitled "Threshold of Toxicological Concern for Chemical Substances Present in the Diet: A Practical Tool for Assessing the Need for Toxicity Testing" has been published in *Food and Chemical Toxicology*, Vol. 38, Nr. 2-3, pp. 255-312, 2000.

OBJECTIVES OF THE WORKSHOP

The aims of this two-day interactive meeting of invited experts were:

- To communicate principles and assumptions of the TTC concept to a wider audience;
- To review the results of the expert group's work;
- To provide additional scientific input supporting the validation of the concept;
- To consider the applicability of such a concept to other chemicals present in foods in small concentrations (such as contaminants and naturally occurring substances).

INTRODUCTION TO THE WORKSHOP

The chairman, Prof. J. Bridges, University of Surrey (UK), welcomed participants and introduced some broad issues to bear in mind during the workshop. He found the concept very important because the adoption of the TTC concept could bring a number of benefits, including more effective use of toxicological testing and evaluation resources, reduction in the use of animals, a better focus for chemical analytical work and providing a simple basis for legislation. Thought should also be given, he suggested, as to whether the concept could be applied more widely than just to food toxicology.

There were, however, disadvantages to the concept. In particular, he drew attention to the likelihood that the very use of the word "concern" might, instead of implying reassurance, suggest to those unfamiliar with the process that any exposure above a TTC could give rise to health concerns. Perhaps a more neutral term was needed. The loss of potentially valuable substances might also result if industry took the view that certain chemicals present in food above the TTC should be abandoned. In applying a TTC to any particular situation it also would be necessary to take account of other potential sources of exposure to the chemical, other than in the diet. In some regulations on chemicals, such as the EU Drinking Water Regulations, limits lower than the US Threshold of Regulation value for indirect food additives (0.5 µg/kg in the diet) are already prescribed.

There was also a need to consider the extent of scientific data that would be necessary to adequately support the TTC concept and any decision to put it into regulatory policy and practice. No matter how much general support there was for the concept, exceptional substances that are active below any suggested threshold cannot be excluded. Thus the presentation of any TTC policy to the public would need to take account of this.

SESSION 1 – INTRODUCTION TO THE CONCEPT OF THRESHOLD OF TOXICOLOGICAL CONCERN (TTC)

In the first introductory session, Dr. A. Rulis, Food and Drug Administration (USA), presented the FDA concept of Threshold of Regulation applied to food contact materials. The second contribution was on TTC in relation to three structural classes of chemicals presented by Dr. I. Munro, CanTox (CDN), followed by Prof. A. Renwick, University of Southampton (UK), presenting the TTC approach used for the evaluation of flavouring substances by JECFA.

US FDA Threshold of Regulation

The threshold concept was developed by the FDA as a consequence of the *de minimis* requirement whereby the agency is obliged to set priorities on issues of tangible concern rather than on trivial ones. It was implemented as the Threshold of Regulation, which has been applied to food contact materials (indirect food additives) since 1995. It is based on an analysis of 477 chemical carcinogens from the Gold *et al.* (1984) carcinogenic potency database. The probability distribution of carcinogenic potencies has been used to derive an estimate of the dietary concentration of most carcinogens which would give rise to less than a one in a million (1×10^{-6}) upper bound lifetime risk of cancer. That dietary concentration was estimated to be 0.5 µg/kg, from which a human daily exposure level of 1.5 µg/person was derived, assuming that the whole amount of 1.5 µg is distributed throughout the total diet (1500g of food, 1500g of fluids). An upper bound lifetime risk of 1×10^{-6}, derived by linear proportional extrapolation from the dose causing tumours in 50% of the animals exposed (TD_{50}), is regarded as an extremely conservative estimate – the true risk lying somewhere between zero and the upper bound estimate. Enlarging the database from 477 to over 700 chemicals (Gold *et al*., 1995) did not alter the distribution of the calculated upper bound risks. It should be noted that although this estimate is based on chemical carcinogens, the Threshold of Regulation is not applied to compounds known to be chemical carcinogens, which under US law (the Delaney Clause) are not permitted in food. However, should any untested chemical to which the Threshold of Regulation policy is applied turn out to be a carcinogen, then the consumer should still be protected "with reasonable certainty of no harm". Thus the policy contains elements of both scientific and administrative judgement.

Packaging migrants shown to be present in the diet at levels below the threshold of 0.5 ppb can be exempted from further regulation. The concentration in food qualifying for exemption may be higher if the compound under consideration is present only in a smaller fraction of the total diet. So far, FDA has dealt with around 450 applications under this regulation, and around 300 favourable actions were taken. The main reason for rejection of an application was due to inadequate exposure data submitted to the FDA.

Dr. Rulis concluded that the Threshold of Regulation has been extremely useful for the work of the FDA because it is based on sound science and could be applied rationally, consistently and effectively, case by case.

The main discussion points were centred around the question of how to define "reasonable certainty of no harm" and whether this was limited to adverse effects measured in animal experiments (the basis of the FDA policy) or whether it should extend to alterations measured, for example, at the level of molecular events. Although the FDA does not ask for mechanistic data for an application under the Threshold of Regulation, such data, if available, are used. Similarly, mutagenicity data are not requested by the FDA. However for most industrial chemicals such data are available and if there is a concern about possible mutagenicity, the FDA requests more information unless exposure is very low (e.g. a very low estimated daily intake may override weak positive mutagenicity data).

The question of whether different subsets of carcinogens (e.g. genotoxic versus non-genotoxic carcinogens) should be considered separately was also addressed. As the distribution of exposures estimated to give a lifetime risk of cancer of less than 1×10^{-6} extends over five orders of magnitude, the FDA considers that both types of carcinogens are covered and that the use of different subsets would not be likely to change the estimate substantially. The FDA does not anticipate altering its risk level of 1×10^{-6}. This is regarded as no more than negligible risk; moreover, the estimate used is an upper bound risk, the actual risk lying somewhere between the upper bound value and zero.

TTC in relation to structural classes

Based on the precept that the properties of a substance, including its inherent toxic effects, are influenced by its chemical structure, Munro and colleagues (1996) developed a database of 612 structurally well-defined organic chemicals, divided into three structural classes, as defined by Cramer and colleagues (1978). For these chemicals, 2944 no-observed-effect levels (NOELs) could be derived from non-carcinogenic endpoints in oral rodent or rabbit studies. The most sensitive species, sex and endpoint were chosen for the NOELs. Cumulative distributions of the most conservative NOELs for each chemical in the three structural classes were plotted. Human exposure thresholds of 1800, 540 and 90 µg/person/day were derived by dividing the fifth percentile NOEL for each class by a safety factor of 100. A safety factor of 100 was chosen because of its long history of use in the derivation of ADIs. The use of first percentile NOELs was not considered appropriate because too few data points were available, and because of the "noise" at the lower end of the curve. Class I (137 compounds in the database) are substances with simple chemical structures and efficient modes of metabolism, suggesting a low order of oral toxicity. Class II (28 compounds in the database) are substances which possess structures that are less innocuous than class I substances but do not contain structural features suggestive of toxicity like those substances in class III. Class III (447 compounds in the database) are substances with a chemical structure that permits no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups. Increasing the number of compounds in the database from 612 to 900 did not alter the cumulative distributions. Thus it was concluded that thresholds for non-carcinogenic endpoints were likely to be higher (by one or more orders of magnitude) than any threshold derived from carcinogenic potency data.

In a further analysis of the threshold derived from carcinogenesis data, calculations were presented for the probability of not exceeding a 1×10^{-6} lifetime risk for different human exposure threshold values. For an exposure threshold of 1.5 µg/person/day, this probability is calculated to be 63% if it is assumed that all substances are carcinogenic. However the probability increases to 96% if it is assumed that only 10% of chemical substances in existence are carcinogens, which is the maximum percentage recently estimated by the US National Toxicology Program (NTP)

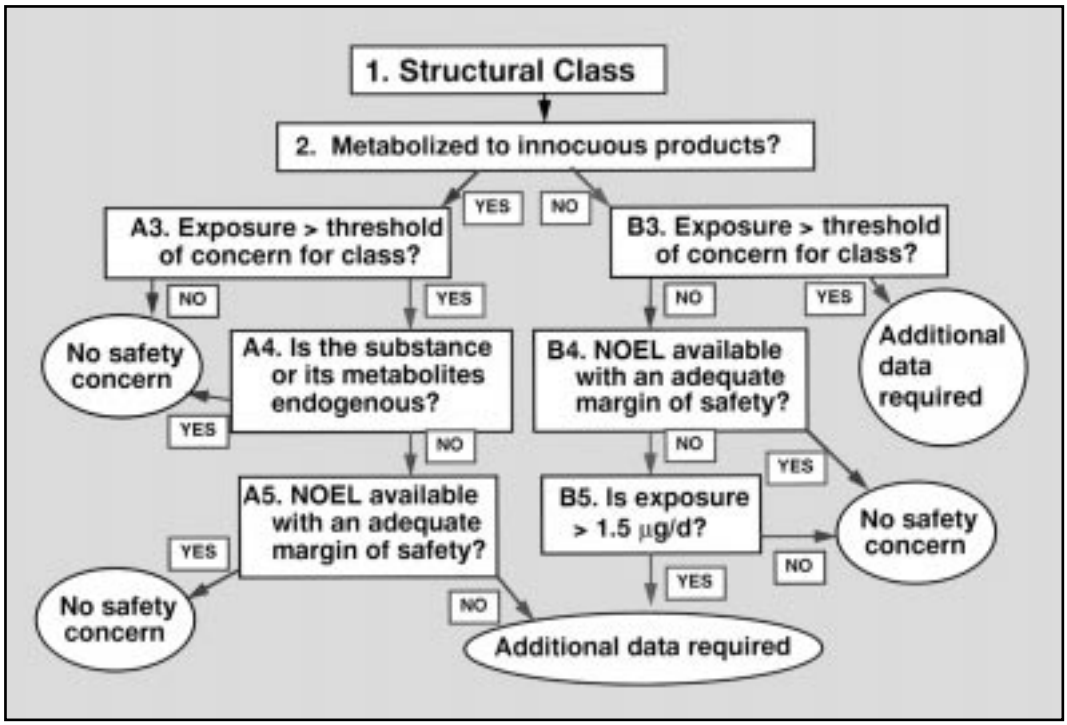
(Huff et al., 1996). By far the most important variable was the percentage of assumed carcinogens entering the procedure. Neither alteration of the exposure level, from 0.5 to 6 µg / person / day, nor alteration of the target risk level, from 1 x 10^{-6} to 1 x 10^{-5}, increased the risk to any significant extent.

The discussion focused on the likely percentage of chemical carcinogens in the "world of chemicals". About 50% of substances positive in the Ames test are also carcinogenic in long-term bioassays. Similarly, 40% of the compounds tested by the NTP turned out to be carcinogenic in one species but only 11% of the compounds are carcinogenic in two species. However, as the NTP selection of chemicals for testing is based on volume of production, human exposure level and genotoxic potential, there is a selection bias and the compounds tested are not representative of the "world of chemicals". If it is agreed that the best estimate of the percentage of chemicals being possibly carcinogenic is 5%-10%, essentially the same probability of not exceeding a 1 x 10^{-6} lifetime risk would result for a TTC of 1 or 5 µg / person / day.

TTC approach used for the evaluation of flavouring substances by JECFA

The TTC concept and the human exposure thresholds derived from the Munro *et al.* (1996) database are applied in principle by JECFA in order to separate flavouring substances for which intakes are not a safety concern from those for which further data are needed. The scheme is outlined in Figure 1.

Figure 1: TTC approach used for the evaluation of flavouring substances by JECFA



Only substances without structural alerts for carcinogenicity are considered for evaluation via the TTC scheme. Furthermore, the question of whether the compound under evaluation can be assumed to be metabolised to innocuous products (i.e. predicted to be harmless at estimated intake) is raised first. Only then is it considered if the estimated exposure is lower than the respective structural class TTC. If so, then the flavouring substance is considered to be of no safety concern. If the anticipated exposure is higher than the structural class TTC, even for a substance assumed to be metabolised to innocuous products, unless the metabolites are endogenous substances, exposure is then compared with the NOEL for the substance to derive the margin of safety (MOS). If the MOS is adequate, the substance is considered to be of no safety concern. If no NOEL is available or the MOS is not considered adequate, additional data may be required for evaluation. If, for a given compound not assumed to be metabolised to innocuous products, exposure is estimated to be lower than the structural class TTC but no NOEL is available, the threshold of 1.5 µg / person / day is considered. If exposure is higher than 1.5 µg / person / day, additional data are required. If exposure is lower than 1.5 µg / person / day, the substance is considered to be of no safety concern.

For the vast majority of flavouring substances, the estimated intakes seem to be generally low, and it has been estimated that intake exceeds the structural class TTC for only 5%, 7% and 3% of the substances considered so far in classes I, II and III, respectively. Exposure is estimated on the basis of the annual production volume and the likely proportion of the population expected to be consumers (10%). Up to 1999, JECFA had evaluated 610 flavours by applying the TTC concept. As an example, at its meeting in June 1999, 137 sulphur compounds were evaluated, 97, 34 and 6 falling into class I, II and III, respectively. Intake of 85 of these compounds was estimated to be less than 1.5 µg / person / day.

Another aspect which is considered by JECFA for naturally occurring flavours is the ratio of natural occurrence in food compared to intentional addition of the substance to food, known as the Consumption Ratio. Of 499 naturally occurring flavours the ratio is < 1 for 84 substances, between 1 and 10 for 106 substances and > 10 for 309 substances. Thus for the majority of naturally occurring flavours, intake is dominated by the natural content in food and not by the intentional addition of the flavour.

In the discussion, it was made clear that the knowledge that a substance was endogenous does not necessarily equal “no concern”. For hormones and other biologically active compounds with regulatory functions in the body, the TTC concept might need further investigation. Furthermore, for endogenous substances, the substance or its metabolites should not give rise to perturbations outside the physiological range of levels found in the body.

SESSION 2 – APPLICATION OF A TTC TO SOME POTENTIALLY SENSITIVE ENDPOINTS

After taking over the chairmanship for this session, and referring to his plenary lecture at the Conference on International Food Trade Beyond 2000, Science Based Decisions, Harmonisation, Equivalence, and Mutual Recognition, Melbourne (AUS), Prof. A. Somogyi, European Commission, Directorate General SANCO (B), emphasised that the TTC is an intellectually stimulating concept with a potential for far-reaching practical applicability. He felt that despite convincing arguments supported by several thorough studies on large databases, the time for its universal use in safety evaluation of all sorts of chemical substances and practically for all purposes does not appear to have arrived yet. This concept, he suggested, should be submitted to further rigorous scrutiny and extensive peer-review. As recommended at the Melbourne conference, the TTC should remain the subject of an intensive scientific debate, preferably in the framework of an international meeting with the participation of outstanding experts representing the widest possible spectrum of views in this field. Prof. Somogyi considered the current ILSI Europe workshop as such an international meeting, particularly as the organisers have been able to enlist the active participation of many of the best recognised experts worldwide in the area. He expressed his conviction that the outcome of the meeting would find the TTC approach as an appropriate method for setting priorities for further toxicological testing and / or the evaluation of substances in question.

In this session, introduced by Prof. R. Walker, University of Surrey (UK), the Expert Group presented their findings on some potentially sensitive endpoints. These were immunotoxicity, developmental toxicity, neurotoxicity and developmental neurotoxicity, endocrine active compounds and allergenicity. Prof. Walker pointed out that the group had focused on the scientific aspects of applicability of the TTC concept, rather than those aspects involving societal decisions about risk management (e.g. what level of risk is acceptable), and it was emphasised that the TTC concept is a risk management tool.

In addition to consideration of potentially sensitive endpoints, other scientific issues relevant to the TTC concept needed to be considered, such as how to treat chemicals which may be biopersistent or may bioaccumulate, and whether the TTC concept was equally applicable to all types of chemicals found in food or other media. Prof. Walker also pointed out that by selecting specific endpoints, the outcome was no longer representative of the "world of chemicals" because the emphasis is shifted to substances with lower NOELs, making it more conservative.

The Expert Group had developed new databases for developmental toxicity, neurotoxicity, developmental neurotoxicity and immunotoxicity. The aspects of endocrine activity and allergenicity were addressed by a more descriptive approach as special case studies. Ir. L.-A. Tran, ILSI Europe (B), described the highly conservative selection procedure for compilation of the databases, the criteria for selection being decided beforehand:

- The endpoints selected included some that might not routinely be picked up in conventional toxicity tests (e.g. endocrine activity);
- Data were selected only from studies designed to address the particular endpoint under consideration, rather than from indicative parameters in more general toxicity tests;
- Only studies using a relevant route of administration (oral) were considered;

- Compounds with effects of strength and potency for the endpoint concerned were considered (e.g. pesticides with anticholinesterase activity for neurotoxins);
- Studies which identified NOELs, preferably with lowest-observed-effect levels (LOELs) were included;
- The lowest NOEL found was utilised in the further analyses.

This rigorous selection of studies ensured that the databases were highly skewed toward positive substances, such that the proportion of studies showing effects should not be taken as representative of the world of chemicals in general, but rather of worst-case scenarios. In this way, it was thought that any extrapolations made from the databases to reach conclusions about chemicals in general would be reassuringly conservative. It was noted however that the selection process resulted in rather low numbers of substances in some of the databases, compared with the earlier analyses of Munro *et al.* (1996) and the carcinogenic potency database (Gold *et al.*, 1984, 1995).

Immunotoxicity

The immunotoxicity database and its interpretation were described by Dr. E. Corsini, University of Milan (I). She pointed out the difficulties of identifying chemicals for inclusion in this database. There were 37 substances in the database, selected from the 50 or so known or suspected immunotoxins in the Luster *et al.* database (1992, 1993) all of which met the criteria for immunotoxicity and had been identified in Tier I and/or Tier II tests specially designed to elucidate such effects. It should be noted that a Tier I study contains some immune system parameters that are also included in current standard protocols for subchronic and chronic toxicity studies.

Immunotoxicity was the most sensitive adverse effect of the chemical for only 15 of the 37 substances. Nineteen of the 37 had only LOELs and not NOELs, and this was regarded as too few to utilise to plot a distribution curve of NOELs. However, for those substances with a NOEL, it was noted that they were of a similar order of magnitude as those obtained for other non-cancer endpoints. Similarly for substances only having a LOEL, their LOELs were of a similar order of magnitude as the LOELs observed for other non-cancer endpoints. Furthermore, the lowest NOEL found, divided by 100 and converted to an intake in µg/person/day, was equivalent to 6-fold above the US FDA threshold value of 1.5 µg/person/day.

In discussion it was questioned whether the limited data available were sufficient to draw a clear conclusion that immune effects would not be more sensitive than other non-cancer endpoints. For example, focusing on the 15 chemicals that had immunotoxicity as their primary effect at low doses, it could be seen that the NOELs for these were generally lower than those for the remaining chemicals. Although not likely, it also was not known whether the 19 chemicals for which there were only LOELs would yield lower NOELs than those identified for the other chemicals in the database. It was noted that the majority of information in the database was from subacute studies on young, inbred, female mice. Lack of data from chronic studies and from studies involving perinatal exposure might also mean that the approach was not sufficiently conservative. A further problem was that, at present, there are no structural alerts for immunotoxicity. However, it was suggested that since cancer would be one of the anticipated effects from impaired immune system function, perhaps the inclusion of carcinogenicity data in determining any TTC would cover immune sensitivity. This might warrant further consideration.

Luster and colleagues (1992) have noted that there is as yet no accepted definition of an immunotoxic agent in rodents, and there are difficulties in interpretation of immune system changes in rodents in relation to the human clinical situation. However, there were encouraging aspects regarding the ability to identify immunotoxicants in rodents. For the substances in the database, a combination of three tests (plaque forming cells, surface markers and delayed hypersensitivity reaction) had been shown to identify all 37 as affecting immune structure and/or function. Identifying immunotoxicants is of particular importance as no structural alerts for immunotoxicity are available yet. Host resistance models were also considered very promising, but there is no consensus yet on their predictivity.

Developmental toxicity

As background, Prof. R. Kroes, Utrecht University (NL), mentioned that the Munro *et al.* (1996) database had included 100 substances causing developmental abnormalities, from which a fifth percentile NOEL of 3.5 mg/kg bw could be estimated, giving a human exposure threshold of around 2000 µg/day if the fifth percentile NOEL was divided by 100. The developmental toxicity database developed by the Expert Group contained 81 substances, 71 of which were also included in the Munro *et al.* (1996) database. However, for the new database, more conservative criteria had been employed. This included focusing on effects other than teratogenic effects, including those identified in multigeneration studies in which test animals were exposed prenatally as well as postnatally through to sexual maturity. The cumulative distribution of NOELs divided by 100 was similar to that of Class III compounds in the Munro *et al.* (1996) database, i.e. developmental toxicity was not more sensitive than other non-cancer endpoints. The distribution of NOELs divided by 100 for developmental toxicity was about three orders of magnitude higher than the distribution of 1×10^{-6} upper bound lifetime risk estimates derived from carcinogenicity data.

In discussion this wide margin between the cancer and developmental toxicity distributions was noted. The Expert Group confirmed that they had taken into account pup body weight at birth, which is generally regarded as a sensitive marker of effects in multigeneration studies. They had not taken into account pup weights at other times during the studies because of the difficulty of secondary effects from maternal toxicity.

To set this question into a broader perspective, attention was drawn to recently published work from the US FDA (Cheeseman *et al.*, 1999) that had examined information on over 3000 substances in the RTECS (Registry of Toxic Effects of Chemical Substances) database for which there are oral reproductive toxicity data. By applying an uncertainty factor of 1000 to the lowest low-effect level for each substance, a range of "pseudo-acceptable daily intakes" (PADIs) was derived. The most likely (median) value for the PADI was 8300-fold above the threshold value derived from the carcinogenic potency database.

Neurotoxicity and developmental neurotoxicity

Dr. B. Schilter, Nestlé Research Centre (CH), described the development of the neurotoxicity and developmental neurotoxicity databases. The Munro *et al.* (1996) database, which did not include specific neurotoxicity studies, had consequently identified few neurotoxicants from general toxicity studies. Nevertheless, from these a tentative human exposure threshold of

18 µg / person / day could be calculated, for example, for 31 organophosphorus compounds. In the database developed by the Expert Group, a search was therefore made for studies specifically designed to address neurotoxicity. After exclusion of studies describing only acute effects, there were 40 substances in the adult neurotoxicity database and 30 substances in the developmental neurotoxicity database. The conservative criteria employed included consideration of functional as well as neuropathological observations and the inclusion of any effect whether it would be interpreted as adverse or not.

For developmental neurotoxicity, the cumulative distribution of NOELs was similar to that of Class III compounds in the Munro *et al.* (1996) database, i.e. developmental neurotoxicity was not more sensitive than other non-cancer endpoints. For adult neurotoxicity, the distribution of NOELs was lower (by about one order of magnitude) than those for other non-cancer endpoints, including developmental neurotoxicity. However, the distribution divided by 100 was still at least two orders of magnitude higher than the distribution of 1×10^{-6} upper-bound lifetime risk estimates derived from carcinogenicity data. It was further noted that only 6 out of the 40 NOELs were lower than the fifth percentile NOELs for Class III compounds from the Munro *et al.* (1996) database and that a TTC of 1.5 µg / person / day derived from carcinogenicity data should comfortably cover neurotoxicity endpoints.

In discussion comment was made that it was surprising that developmental neurotoxicity targets had not emerged as more sensitive than adult neurotoxicity targets. However, it was pointed out that the sensitivity of the adult neurotoxicity database was driven by the number of compounds included which affected cholinesterase and that developmental studies on these types of compound were limited in number. It was also noted that for some neurotoxicants affecting cholinesterase, acute studies on inhibition would give similar NOELs / LOELs as studies of longer duration, and perhaps acute studies should not have been excluded. It was suggested it might be useful to enhance the database with studies on nerve gases, converting inhaled doses to systemic doses, since these were known to be exceptionally potent in man at low doses.

There were some doubts expressed about the utility of animal data for some neurotoxicants. The example of lead was quoted in which not only is the critical effect observed on cognitive ability (difficult to measure in animals), but the exposures considered to have adverse effects on cognitive ability in children are extremely low. Some doubted, therefore, whether an intake limit of 1.5 µg / day would be low enough for lead. It was also noted that the way in which regular daily intakes might affect body burdens also needed to be taken into account. With regard to these questions, it was argued that the PTWI (Provisional Tolerable Weekly Intake) for lead had been established by JECFA in 1993 and had been allocated a value of 25 µg / kg bw / day, based on data obtained in children. For a four-month old baby weighing 6.2 kg (worst-case scenario) this value corresponds to a total weekly intake of 155 µg. Some, therefore, considered that a threshold of 1.5 µg / person / day would cover the effects of lead. There was also discussion of whether neurotoxicity tests in animals were yet of sufficient sensitivity and appropriate design to draw conclusions about neurotoxicity as a potentially sensitive endpoint in man. It was pointed out, for example, that few, if any, long-term studies have been conducted which specifically evaluated neurotoxicity. The US EPA, however, has concluded that the extrapolation of neurotoxic effects from animals to man is generally good and certainly not worse than extrapolations made for other toxic endpoints (US EPA, 1998).

Endocrine active compounds

Prof. Kroes described the Expert Group's approach to the issue of endocrine active compounds. The Group had focused on oestrogenic activity because this had the potential to be a very sensitive endpoint. The goal had been, through intake analyses, to obtain a general perspective on the intake of oestrogenic chemicals from all sources. The analysis had shown that daily exposure to pharmaceutical oestrogens can be between one and three orders of magnitude greater than the exposure to isoflavones in food (when converted to oestrogen equivalents), while exposure to isoflavones in food is six to seven orders of magnitude greater than estimates of exposure to environmental chemicals with known oestrogenic activity.

In discussion, the question was raised of whether other endocrine endpoints such as thyroid, adrenal and androgen-sensitive effects might present a somewhat different picture. Examples of compounds with very low-dose effects on the thyroid were mentioned, and it was noted as well that the pesticide vinclozolin is as powerful an anti-androgen as some drugs designed specifically for that purpose. Considerable doubts were expressed about the validity of using mass balance comparisons of exposure to oestrogenic substances, particularly comparing dietary oestrogens to powerful pharmaceuticals. It was felt that at present there is still insufficient information about the effects of individual naturally occurring dietary oestrogens on the human body to make such comparisons meaningful.

Doubts were also expressed about the utility of quoting the wide ranges of plasma estradiol levels in men and women, under different physiological conditions, as evidence that perturbations from exogenous sources were unlikely to have a significant effect. While human physiological ranges are evidently very wide, for individuals it was not yet known whether increases, such as a doubling of the individual background levels in males, might have some effect.

Animal studies had also raised the possibility, yet to be confirmed, of U-shaped dose-response curves for endocrine active substances with activity being seen at very low doses. In view of all these reservations, and although endocrine effects at levels of 1.5 µg / day had not been reported, a number of participants considered it was too early to reach firm conclusions about whether endocrine activity would turn out to be a particularly sensitive endpoint. Now that clearer advice was emerging on a screening procedure for detection of endocrine active compounds, it was likely that much more test data would emerge in the near future. It would perhaps be prudent to await the results of such testing before drawing firm conclusions on endocrine activity.

Allergenicity

This was also treated as a special case because of the paucity of data. Dr. H. van Loveren, National Institute of Public Health and the Environment (NL), explained the physiological, cellular and molecular background to the many possible reactions to allergens in animals and man. Major food allergens are usually proteins from common foods such as eggs, milk, fish, etc. He pointed out that because of the diversity of responses, no good models had yet been identified to enable reliable prediction of which substances might be allergenic, though some models showed promise, such as oral sensitisation in the BN rat. Good quantitative models are also lacking. However, the local lymph node assay (LLNA, popliteal or auricular) can now be used to identify critical effect doses with confidence intervals for specific chemicals in sensitised animals, i.e. a range below which allergenicity is not seen in the animal model. These, together with oral sensitisation models, may allow quantitative estimates to be made in the future but a lot more work was required to reach that stage.

In discussion it was agreed that quantitative models both for sensitisation and elicitation were needed because elicitation of an allergic response in humans was clearly dependent on the allergen load, the amount required varying from chemical to chemical. The question of how predictive the LLNA was for man was raised. Human data are fragmentary but where they do exist, the results are not dissimilar to the relative ranking of concentrations needed to elicit an allergic response in the LLNA.

The question of whether there was a clear difference between the dose needed to sensitise and the dose required to elicit an allergic reaction was discussed. For clinically detectable responses, the elicitation threshold was generally lower than the sensitisation threshold, but this relationship might not hold true if one looked at changes taking place at the cellular and biochemical levels. In response to the question of whether it was possible to elicit an allergic response with an exposure to a dietary substance at a level of 1.5 µg, it was considered too early to say. Some human case reports on peanut protein allergy had suggested that reactions could occur with challenge doses as low as 10-110 µg / person. However, the dose expressed was for total protein and not the allergenic component(s) which have yet to be identified. These reports do however suggest that caution should be exercised before concluding that a threshold of 1.5 µg / day would also protect against protein-based allergic reactions. It was remarked that for non-protein compounds, allergic responses at such levels were unknown. The current approach of labelling to alert to the presence of potential food allergens was still seen as appropriate. There are also now databases for structural alerts for non-protein allergens that can be used to predict the possibility of reactions. However, for proteins, structural alerts for particular primary, secondary and tertiary structures have not yet been developed.

Summing up of the Expert Group's work

In concluding the session, Prof. Kroes reiterated the main conclusion of the Expert Group, which was that the analyses conducted show that a TTC of 1.5 µg / person / day provides adequate safety assurance and that chemicals present in the diet that are consumed at levels below this threshold pose no appreciable risk. The TTC can never offer an absolute guarantee of safety, but it seems to be soundly based with respect to general toxicity and the particular endpoints examined by the Expert Group. For endpoints for which validated methodology had yet to be developed, the TTC would need to be judged against these in due course. For some of these, such as endocrine activity, Prof. Kroes considered that the large margins of safety built in probably covered them already. For others, such as allergenicity, risk management may have to continue to be by appropriate labelling.

SESSION 3 – GENERAL AND PANEL DISCUSSION

The chairman, Prof. Bridges, introduced a number of topics for discussion.

Definition of TTC

The definition of TTC needs careful consideration if risk managers and the public are to have a clear understanding of when and how the concept can be applied and the strengths and weaknesses of the science behind it. In the ILSI Europe Expert Group paper (Kroes *et al.*, 2000), TTC is defined as "a level of exposure to chemicals below which no significant risk is expected to exist". Perhaps there was a need to be clearer on whether the TTC could be applied to **any** chemical and what is meant by "significant risk". In the discussion, participants agreed that the TTC concept could probably be applied to most chemicals in food if there were appropriate pre-screening to single out chemicals for further consideration (e.g. considering structural alerts for genotoxicity, biopersistence and others). However, for chemical exposures involving routes other than food (such as occupational exposure), different considerations might apply, and these would need to be examined by those with appropriate expertise before any generalisation of the TTC concept to regulatory control of any chemical could be considered.

There is no EU-wide agreement or definition of what constitutes "significant" or "acceptable" risk, though some documents and regulations had used such phrases and even a level of 1×10^{-6} when discussing carcinogenic risks. Terms such as "appreciable risk", "very low probability" and "reasonable certainty" are often used but may convey different meanings to different people. Descriptions of the TTC concept should, however, emphasise that it is probabilities of adverse events which are being discussed, not absolute certainties of absence of harm below particular exposures. Defining levels of tolerable risk involves wider considerations beyond just the science and should involve risk managers and the public. It was emphasised that the application of the TTC concept within the US FDA Threshold of Regulation policy did not mean that indirect food additives with exposures below the threshold were not regulated at all. Rather, it meant that for chemicals with such low exposures, it was justified to regulate them with less expenditure of resources, commensurate with the lesser potential for risk.

Is there adequate scientific support for a TTC of 1.5 µg/person/day ?

If the TTC concept were to be adopted for regulation of chemicals in food, it would be important not only to use all the available data to derive a figure for the TTC but also to give risk managers an idea of the uncertainty around any TTC value. In describing the likelihood of occurrence of outliers, for example, some idea of the size of the tail of the distribution below the TTC would be useful. Further analyses of the databases could be undertaken using tolerance limits, estimated with a 95% confidence level, for the lower percentiles of the distributions of NOELs. This would provide an estimate on the likely size of the tail for all chemicals, including unknowns.

Prof. Bridges suggested a number of reasons why a TTC of 1.5 µg / person / day could be questioned. Some might consider that insufficient chemicals have been studied and that certain endpoints have not been adequately covered. There were some exceptions already to meeting a TTC of 1.5 µg / person / day, and the size of this "tail" was important. Some may consider that more allowance is needed for variations in human sensitivity. The TTC may also be inappropriate, by itself, to deal with chemicals which bioaccumulate.

In discussion, it was agreed that there were already outliers to a TTC of 1.5 µg / person / day and more would be found. However, it was important to recognise that the occurrence of outliers does not discredit the utility of the databases themselves. It was felt that the databases available indicate that, within the whole world of chemicals, the probability of a new chemical being an outlier below a TTC of 1.5 µg / day is very small. However, scientific judgement rather than unthinking application of the TTC concept would, of course, be needed in the case of particular groups of chemicals (e.g. neurotoxic pesticides). The occurrence of outliers should not paralyse decision-making if sufficient evidence exists from the bulk of chemicals that a TTC could be identified that gave reasonable certainty of no harm. It would be important to identify any patterns in the reasons for chemicals being outliers and to develop ways of anticipating them. Whatever TTC was applied, it would be important to use, in exceptional cases, scientific judgement to single out chemicals for further consideration, even if their exposure levels were below the TTC.

The first defensive step in identifying outliers should be to apply the TTC on a case-by-case basis after applying scientific judgement to consideration of other factors and all available information. This would include, for example, structural alerts, knowledge of toxicity of related chemicals and indicators for bioaccumulation and biopersistence. Good schemes for structural alerts for genotoxicity / carcinogenicity have been in use for some time, and a number of structural alerts for neurotoxicity are also well understood. Alerts for other toxic endpoints are improving in scope and the US FDA now uses a number of such schemes in applying its Threshold of Regulation policy. For prediction of bioaccumulation, half-life of a chemical in blood is a valuable indicator but rarely available for low exposure chemicals. The EC Scientific Committee on Food has been using octanol / water partition coefficients as a surrogate indicator for bioaccumulation for some time now when considering reduced-toxicity dossiers for food packaging chemicals. The experience so far is that such data are useful for indicating a low likelihood of bioaccumulation (log Po / w<3) but high values for log Po / w are unreliable for predicting a high likelihood of bioaccumulation, with larger molecules tending to give false positives.

One clearly identified problem is how to identify outlier chemicals that might be immunotoxic, a problem that applies equally to the current regulatory situation with respect to allergenicity. There are too few data available at present to reach firm conclusions on whether 1.5 µg / person / day is a sufficiently low threshold for immunotoxicity. There are as yet no structural alerts for immunotoxicity of non-protein chemicals and no clear indication of what studies should be done if exposures are below a level of 1.5 µg / person / day.

While acknowledging that there would be outliers, there was discussion of whether there was sufficient information within the databases to reach a general conclusion on the use of TTC in the regulation of chemicals and on whether to accept the figure of 1.5 µg / person / day as a TTC. Were smaller databases acceptable for decision-making in the case of chemicals of low anticipated toxicity but not for chemicals expected to be toxic? It was also recognised that the smaller databases constituted a selected subset, and therefore, a worst-case approach. Large databases were available on carcinogenicity and subchronic toxicity which contained a wide diversity of chemical structures and chemical types, but the new databases for the specially selected endpoints were smaller (80 chemicals or fewer) and less diverse. It was agreed that the robustness of the analysis of the structural Class III substances lay in its variety and, for the earlier databases, the addition of further chemicals had not significantly altered the distributions. The recent work of Cheeseman *et al.* (1999) had provided further reassurance that the inclusion of large numbers of chemicals does not radically alter the distributions for non-carcinogenic endpoints. It would be important at least to continue the addition of further chemicals to the newer databases in order to strengthen the statistical basis for any TTC decision and to recognise the possible need to adjust any TTC policy in the light of new data.

The possibility of identifying different TTCs for different toxicological endpoints was mentioned in relation to chemicals for which some data were available. The presence of genotoxicity data was seen as an obvious candidate for consideration. The work of Cheeseman *et al.* (1999) has looked at this question, using the 700 or so chemicals now in the Gold *et al.* (1995) carcinogenic potency database. In the Ames bacterial assay for gene mutations, the difference in potency between carcinogens which were positive and those which were negative was not greatly different, but genotoxic carcinogens did have a slightly higher probability of exceeding a risk of 1×10^{-6} at a given exposure level. However, the view was expressed that since there was so much conservatism built into the derivation of a 1×10^{-6} risk, then this lack of a great difference was perhaps not surprising. Moreover, for non-genotoxic carcinogens, a linear extrapolation might be over conservative.

The value of using structural alerts for genotoxicity before applying a TTC was also questioned, in that the carcinogenic potency databases from which the conservative figure of 1.5 µg / person / day was derived included genotoxic carcinogens. It was important to be clear about the reasons for using such an alert. It might, for example, be appropriate to incorporate it into a decision-tree for reasons of prudence, or in order to increase reassurance of using TTC for all other toxic endpoints, or because there was a desire on the part of risk managers to exclude, where possible, genotoxic carcinogens from the food supply.

CLOSING REMARKS

In his closing remarks, Prof. Bridges summarised some points on which there appeared to be general agreement:

The TTC concept was considered a useful means of concentrating limited resources on chemicals of concern.

Since the TTC is a probabilistic concept, outliers below an adopted TTC cannot be excluded. The lower the TTC, the less likely the outliers; but the lower the figure, the less it would serve to save resources – including animals.

It was generally felt that the databases assembled are probably sufficient to guide the setting of TTC levels in principle. Further efforts are important for investigating particular endpoints, such as immunotoxicity and allergenicity for which only limited data are available. For endocrine toxicity, work is under way and needs to be evaluated before conclusions can be drawn on influence on present thresholds.

The TTC could become more acceptable to both scientists and risk managers if a scientifically based pre-screening assessment is developed, aimed at the early elimination of potential outliers. The pre-screening should take into account the experience already obtained within the FDA in their use of the "Threshold of Regulation" for packaging migrants. Such a pre-screen might include consideration of any information from related chemicals and should include the potential for biopersistence, bioaccumulation, genotoxicity, organophosphorus-type neurotoxicity and allergenicity. Based on the outcome of such a pre-screen, ranges of TTC values might become appropriate, rather than a single figure.

Use of the TTC concept for regulatory purposes should be accompanied by increased sophistication of exposure assessments and considerations for both dietary and non-dietary applications.

In the light of new scientific data the proposed threshold values today might be changed to other and even higher figures.

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