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The influence of thresholds on the risk assessment of carcinogens in food☆

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ABSTRACT

The risks from exposure to chemical contaminants in food must be scientifically assessed, in order to safeguard the health of consumers. Risk assessment of chemical contaminants that are both genotoxic and carcinogenic presents particular difficulties, since the effects of such substances are normally regarded as being without a threshold. No safe level can therefore be defined, and this has implications for both risk management and risk communication. Risk management of these substances in food has traditionally involved application of the ALARA (As Low as Reasonably Achievable) principle, however ALARA does not enable risk managers to assess the urgency and extent of the risk reduction measures needed. A more refined approach is needed, and several such approaches have been developed. Low-dose linear extrapolation from animal carcinogenicity studies or epidemiological studies to estimate risks for humans at low exposure levels has been applied by a number of regulatory bodies, while more recently the Margin of Exposure (MOE) approach has been applied by both the European Food Safety Authority and the Joint FAO/WHO Expert Committee on Food Additives. A further approach is the Threshold of Toxicological Concern (TTC), which establishes exposure thresholds for chemicals present in food, dependent on structure. Recent experimental evidence that genotoxic responses may be thresholded has significant implications for the risk assessment of chemicals that are both genotoxic and carcinogenic. In relation to existing approaches such as linear extrapolation, MOE and TTC, the existence of a threshold reduces the uncertainties inherent in such methodology and improves confidence in the risk assessment. However, for the foreseeable future, regulatory decisions based on the concept of thresholds for genotoxic carcinogens are likely to be taken case-by-case, based on convincing data on the Mode of Action indicating that the rate limiting variable for the development of cancer lies on a critical pathway that is thresholded.

1. Introduction

The key principle underlying food safety policy at European and international level is that consumers have a right to expect that the food that they eat is both safe and nutritious. Food safety may however be compromised by the presence of chemical contamination. There are also concerns about foods derived using new technologies, such as genetic modification or nanotechnology, and about the introduction of novel foods, previously not consumed to a significant extent by the human population. In order to ensure the safety of food, potential chemical contaminants in foods, compounds released from food contact material, as well as deliberately added substances (food additives, flavourings, vitamins, etc.) and new technologies must undergo a science-based risk assessment in order to reach a conclusion on their potential risk for consumers. Following this assessment, appropriate measures can be taken to manage the risk, including the derivation of health-based guidance values for chemical contaminants in food. Science-based risk assessment and risk management are two of the three cornerstones of risk analysis, the third being the process of risk communication to consumers and other stakeholders.

This paper outlines the approaches applied by risk assessors and risk managers to ensure that food does not contain unsafe levels of chemical contaminants, including approaches to the derivation of health-based guidance values in food for contaminants such as non-genotoxic carcinogens that are considered to show a threshold below which the toxicological effects are unlikely to occur. In contrast chemicals that are both genotoxic and carcinogenic are traditionally regarded as being without a threshold, and their presence in food presents particular difficulties in relation to risk assessment, risk management and risk communication. Approaches to assessing

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their potential risk described in this paper include low-dose linear extrapolation from animal carcinogenicity studies or epidemiological studies [1,2], the Margin of Exposure approach, which has been applied by both the FAO/WHO Joint Expert Committee on Food [3] and the European Food Safety Authority [4,5], and the Threshold of Toxicological Concern (TTC) approach [6]. The paper also explores the possible impact of emerging scientific evidence that there may be a threshold for genotoxicity, at least for some genotoxic agents [7–9].

The Scientific Committees of the EC Directorate General for Health and Consumer Protection (DG-SANCO), namely the Scientific Committee on Health and Environmental Risks (SCHER), the Scientific Committee on Consumer Products (SCCP) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), have recently issued a preliminary report, for consultation, on risk assessment methodologies and approaches for mutagenic and carcinogenic substances [10]. The report of the Scientific Committees provides a comprehensive overview of the approaches in use to assess the risk of substances that are carcinogenic, both genotoxic and non-genotoxic [10], as also discussed in this paper.

2. Derivation of health-based guidance values for chemicals in food

The normally applied approach to derivation of health-based guidance values for non-genotoxic chemicals in food is the determination of a No Observed Adverse Effect level (NOAEL) from a pivotal toxicological study in laboratory animals for assessment of risk to humans [11,12]. If more than one such study exists, then the lowest reliable NOAEL is used as a point of departure. Alternatively, if there are valid data in humans showing a clear dose:response relationship allowing derivation of a NOAEL, then such data may be used in preference to laboratory animal data. Application of an uncertainty factor (e.g. 100) to the NOAEL allows the derivation of an Acceptable Daily Intake (ADI) for the chemical in question. This approach is used, for example, for chemicals added deliberately to food for a particular technological function, such as food additives and flavourings and also for residues of pesticides in food. There are usually extensive toxicological data on these chemicals, the assessment factor applied ensures a conservative, precautionary approach and consequently a reasonable degree of confidence can be placed in the ADI derived as being protective of human health.

In contrast, derivation of health-based guidance values for contaminants such as environmental pollutants, mycotoxins, chemicals migrating from food contact materials and process contaminants that may be present in food is often more difficult, as there may be fewer toxicological data from which to derive a NOAEL. Nonetheless the same approach can be taken, in order to derive a Tolerable (as opposed to Acceptable) Daily or Weekly (TDI, TWI) Intake for the contaminant in food. TDIs or TWIs have been established for a large number of contaminants in food, including heavy metals such as lead [13] and chemicals that have the potential to migrate into food from food contact materials such as bisphenol A [14].

The risk assessment of carcinogens in food, and whether a safe level of intake can be derived, has long been a controversial topic in food safety. It has been recognised that consumption of certain foods is associated with an increased risk of cancer, an example being liver cancer caused by consumption of aflatoxin-contaminated nuts and grain. The systematic toxicological testing of many food chemicals, not only food contaminants but also occasionally some food additives, has led to the recognition that a number of these cause cancer in laboratory animals, with consequent concern about the implications for human health. This was articulated in regulatory terms as early as 1958, when the US Congressman James Delaney tabled the following amendment to the 1954 Federal Food, Drug and Cosmetic Act (FFDCA) "the Secretary of the Food and Drug Administration shall not approve for use in food any chemical additive found to induce cancer in man, or, after tests, found to induce cancer in animals." [15].

This regulatory measure still applies in the US and implies "zero tolerance" of carcinogens in food. While applying to the deliberate addition of potential carcinogens to food, it has had a major influence on regulatory approaches to any carcinogen in food. The measure has however been seen as inconsistent with the fact that food can contain natural constituents, e.g. flavouring substances such as safrole and estragole, that have been demonstrated to be carcinogenic in animal tests. It also does not take into account the considerable body of evidence that has built up since the Delaney Clause was introduced, regarding the mode of action (MOA) of carcinogens and the fact that thresholds exist for many non-genotoxic carcinogens, as detailed in the next section.

3. Derivation of health-based guidance values for non-genotoxic carcinogens

Several decades of research into the underlying mechanisms of carcinogenicity, including the demonstration of the *in vitro* and *in vivo* genotoxicity of some carcinogens, has led to the acceptance that carcinogenic chemicals can be divided into two groups, DNA-reactive chemicals and non-DNA reactive chemicals [16–18]. The MOA of the former group in producing cancer is now well understood, involving mutations in key genes controlling cellular processes such as cell proliferation which, if they continue unchecked, lead to cancer. In the case of the latter group, effects on e.g. hormonal balance, cell signalling, DNA repair and other fundamental cell processes lead to enhanced cell replication and promotion or progression of spontaneous tumours or of tumours initiated by genotoxic carcinogens. The key principle in regulating non-genotoxic carcinogens in food, demonstrated in many experimental studies, is that there is a level of exposure below which the cellular events triggering the carcinogenic process are held in a balance in which cellular physiology is not disturbed [19,20]. As long as exposure to the chemical is below this level, then it can reasonably be assumed that an increased incidence of the cancer in question will not occur. Thus a NOAEL can be defined from toxicological studies showing a clear dose:response relationship, and this NOAEL can be used as the point of departure in defining an ADI or TDI for the chemical in question in a similar way to other additives and contaminants in food as outlined above.

4. Risk assessment of genotoxic carcinogens

The default assumptions for chemicals that are both genotoxic and carcinogenic, in the absence of mechanistic evidence to the contrary, are that the mode of action involves direct and potentially irreversible interaction with DNA, that there is a linear dose–response relationship for this interaction, and that consequently there is no threshold for the carcinogenic effect. A further assumption is that exposure to the chemical is usually considered to be continuous, for extended periods up to lifetime exposures. The mutagenic/carcinogenic process may theoretically be initiated by exposure to very low levels of the genotoxic carcinogen and consequently a NOAEL cannot be identified.

These assumptions have underpinned the regulatory approaches to genotoxic carcinogens, with consequent difficulties in assessing and characterising the risk of such chemicals in food, and in applying appropriate risk management measures including derivation of health-based guidance values. While maximum levels for a number of genotoxic carcinogens, e.g. aflatoxins in food, have been established, it is recognised that there may be