Carcinogens in Food: Opportunities and Challenges for Regulatory Toxicology

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Abstract: The risk of developing cancer from carcinogens occurring in food is of widespread interest to scientific researchers, food policymakers and food surveillance institutions, as well as to the general public. When evaluating the risk of carcinogenic food contaminants or carcinogenic foodstuff per se (e.g., alcoholic beverages), the level of scientific evidence should be reflected more clearly. In the past, interest often focused on 'fashionable' agents with only moderate levels of evidence of their carcinogenicity (e.g., acrylamide or furan); whereas agents with the highest level of evidence (e.g., substances classified by the International Agency for Research on Cancer (IARC) as group 1, being 'carcinogenic to humans') were sometimes disregarded. For example, important carcinogens such as arsenic (a contaminant in drinking water), cadmium and other heavy metals, but also benzene, were not even mentioned in a recent review article about carcinogenic food contaminants. Research, control and prevention strategies for carcinogenic agents in food should comprise a risk-oriented approach and should not lose sight of agents that pose an immediate and scientifically quantifiable threat. Suitable strategies include the use of quantitative risk assessments, for example the use of the Margin of Exposure (MOE) approach.

Key Words: Carcinogens, food contamination, risk assessment, regulatory toxicology.

INTRODUCTION

It is notable that the interests of researchers, food policymakers, food surveillance institutions and consumers in carcinogens in food are often concentrated on agents with a lower level of evidence for their carcinogenic effects as well as a relatively low level of exposure (e.g. acrylamide). Of course, public health authorities respond – and have an obligation to respond – to consumers' questions and concerns. But being responsive to public and political concerns may require much time and effort, even though any risk appears small on scientific grounds [1]. More cynical views maintain that by acting on such precautionary principles significant costs are spent on what is a potentially erroneous action [2], or even that putting large amounts of money into small hypothetical risks damages public health by diverting resources and distracting the public concern from major risks [3]. However, we agree with Tomatis *et al.* [4] that a complete dismissal of carcinogens with weaker evidence cannot be a prudent public health policy. The research community's help is often needed to clarify a situation, and research funding for studies on 'fashionable' contaminants is often available. Finally, attention to 'weak-evidence contaminants' appears justified for the sole reason that it is best to respond before weak evidence becomes strong evidence; i.e., it is better to act early than too late.

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Nevertheless, due to this general focus, agents with the highest level of evidence are not the subject of commensurate regard from either the scientific community or the public. Underlying reasons for this may be a lack of funding for grant proposals to study these agents. The public at large, in particular, the younger generation, often seems uninterested in 'established carcinogens' that are part of everyday life, such as alcohol and tobacco.

The best example of an underrated cancer risk factor appears to be 'alcoholic beverages', which the International Agency for Research on Cancer (IARC) classified as carcinogenic to humans (group 1) already in 1988 [5]. More recently, the IARC has identified ethanol as the underlying carcinogenic principle (which was a matter of debate before) and classified 'ethanol in alcoholic beverages' as a group 1 carcinogen [6, 7]. Despite this evaluation, research on alcoholic beverages appears to be partially misfocused on their beneficial health effects, as a recent review article about carcinogenic food contaminants correctly pointed out [8]. Even if moderate alcohol consumption would provide protective health effects, an association that is still debated (see, e.g., the meta-analysis by Fillmore *et al.* [9]), it has been proven that alcohol consumption's detrimental effects by far outweigh its benefits [10, 11]. Especially the combination of two major lifestyle-related factors in developed societies (alcoholic beverage consumption and tobacco smoking) seems to be responsible for a significant burden of disease [12]. For example, alcohol consumption and smoking are the major risk factors for cancers of the upper aero-digestive tract, accounting for approximately three-quarters of cases in

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developed countries [13]. The carcinogenic effect of combined exposure to alcohol and tobacco appears to be multiplicative [6].

Despite this unambiguous scientific proof, we have noticed that the carcinogenic properties of alcoholic beverages are largely unknown to the public; whereas both the press and the consumers widely appreciate the possible harm of the 'fashionable' contaminant acrylamide.

CARCINOGENIC AGENTS IN FOOD WITH HIGHEST LEVEL OF EVIDENCE

Table **1** gives a selection of agents evaluated in the IARC monographs program, which may pose a carcinogenic threat to humans and are likely to occur as exposure in the food chain. The IARC classifications clearly point out the different levels of scientific evidence for the carcinogenicity [14, 15]. Among the agents with the highest level of evidence (IARC group 1), aflatoxin, alcoholic beverages, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin and salted fish (Chinese style) were recently reviewed by Abnet in the context of food contamination [8]. However, this review article did not mention several important IARC group 1-agents that also are likely to occur as food contaminants: arsenic and arsenic compounds (and especially arsenic in drinking water), benzene, benzo[*a*]pyrene (recently upgraded to IARC group 1), and cadmium and cadmium compounds. In particular, heavy metal contamination of drinking water poses some concern [16]; and health policymakers (e.g., the WHO or the EU) provide maximum limits for these important carcinogens in drinking water and some other foods [17, 18].

Concerns about benzene contamination of food arose in the early 1990s. Several sources can contribute to the occurrence of benzene in foods. Benzoic acid, a widely used food preservative, may decarboxylate to benzene in the presence of ascorbic acid [19]. The formation of benzene from benzoic acid is influenced by the presence of transition-metal catalysts (e.g. Cu(II) or Fe(III) ions) and depends on pH, UV light or temperature [19-22]. We have recently identified benzene as heat-induced contaminant in carrot juices intended for infants [23]. Benzene can also be introduced into foods through leaching from various packaging materials or storage environments, from contamination of water supplies, or it may be formed during irradiation processes [20]. Another source of benzene in soft drinks and beer was the use of contaminated carbon dioxide [24, 25].

Although the IARC monographs evaluations emphasize hazard identification, and further data (i.e., dose-response analysis, exposure assessment and risk characterization [26, 27]) have to be considered to characterize the actual cancer risk; we think that it is a prudent public health policy to limit human exposure to the above mentioned 'IARC group 1' agents, for which a causal relationship clearly has been established between exposure to the agent and human cancer.

CARCINOGENIC AGENTS IN FOOD WITH MODERATE LEVEL OF EVIDENCE

Among the agents with a moderate level of evidence of carcinogenicity (i.e., IARC groups 2A and 2B), acrylamide, some nitrosamines, mycotoxins and pesticides were previously reviewed [8]. Another recent review stressed the importance of nitrates and nitrites, which are not intrinsically carcinogenic but can be endogenously transformed into *N*-nitroso compounds [28, 29].

Table 1. Selection of IARC-Evaluated Carcinogens Likely to Occur in Food or as Contaminants of Food, Grouped According to Level of Scientific Evidence (this List is Not Exhaustive, Please Refer to http://monographs.iarc.fr for Complete List of Approx. 900 IARC Evaluated Agents)

1. IARC Group 1: Carcinogenic to Humans
Aflatoxins (naturally occurring mixtures of)
Alcoholic beverages, ethanol in alcoholic beverages
Arsenic and arsenic compounds, arsenic in drinking water
Benzene
Benzo[*a*]pyrene
Cadmium and cadmium compounds
Salted fish (Chinese style)
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin
2. IARC Group 2A: Probably Carcinogenic to Humans
Acrylamide
Ethyl carbamate (urethane)
High-temperature frying, emissions from
Hot mate
Nitrate or nitrite (ingested under conditions that result in endogenous nitrosation)
N-Nitrosodiethylamine, *N*-nitrosodimethylamine
Some pesticides (e.g. captafol)
3. IARC Group 2B: Possibly Carcinogenic to Humans
Acetaldehyde
Acetamide
Aflatoxin M_1
Caffeic acid
Coffee (urinary bladder)
Fumonisin B_1
Furan
Lead
Nickel, metallic
Ochratoxin A
Pickled vegetables (traditional in Asia)
Safrole
Some pesticides (e.g. chlordane, heptachlor, DDT, dichlorvos, PCP, atrazine)
Some polycyclic aromatic hydrocarbons
Some heterocyclic amines

Additional food contaminants and exposure circumstances in this group include ethyl carbamate (urethane), emissions from high-temperature frying, furan, lead, and nickel (see Table **1**).

Of those, the importance of ethyl carbamate must be stressed because it is a typical contaminant formed during fermentations. Its highest concentrations occur in certain alcoholic beverages [30-34]. This may contribute to carcinogenicity due to the synergistic effects between ethanol, ethyl carbamate and other possible carcinogenic contaminants of alcoholic beverages, or of foods that are co-ingested with alcoholic beverages [35]. As an underlying mechanism, the cytochrome P450 system plays an important role because it activates not only ethyl carbamte, but also a considerable number of other carcinogens [36]; and the activity of cytochrome P450 increases with chronic ethanol ingestion [37].

Furan is important because it could be the successor to acrylamide as a current 'fashionable' contaminant. The formation of furan in food is similar to that of acrylamide because both are heat-induced process contaminants. Furan has been identified in some thermally treated foods, especially canned and jarred foods [38]. Recent studies have shown that several distinct pathways are available for the formation of furan. These are based on the decomposition of ascorbic acid and related compounds, the oxidation of polyunsaturated fatty acids, the Maillard reaction and the pyrolysis of sugars at extreme temperatures [39-41].

CONCLUSIONS

We should not be misunderstood to be advocating a complete refocus on the carcinogens with the highest level of evidence. Of course, research on agents such as acrylamide and furan is necessary and important (and we must admit that we do it ourselves). It is certainly worthwhile to consider food contaminants as underlying risk factors for the increasing incidence of cancers detected since the Second World War [28]. Especially food-processing related compounds that may arise due to new or changed technologies require careful evaluation of potential human health risk [42].

Research should be conducted to provide evidence on the basis of which the IARC could re-evaluate the group 2A/2B agents. For many agents, such data possibly will never be available. For example, the probability that additional epidemiological data will become available in the near future on compounds assigned to group 2B was described to be rather remote. Given the objective difficulties of designing adequate studies capable of credibly demonstrating risks of low or medium level and the access of the results of such studies only to journals with low impact factors, agents assigned to group 2B have not raised the interests of epidemiologists [43]. Therefore, the additional evidence required for re-evaluation is expected to predominantly come from toxicological and mechanistic studies, not from epidemiology.

Food policymakers nevertheless need to address those 'probably/possibly carcinogenic' substances. Pragmatic approaches for prioritization of resources for assessment and management of carcinogens in food can include an assessment of the carcinogenic hazard to humans combined with estimations of intakes per person and of the proportion of the population exposed [1]. An interesting procedure for qualitative assessment of carcinogenic risk was recently developed by Stewart [44]. From the discussed food-related carcinogens only alcoholic beverages and arsenic in drinking water were categorized as risk with proven carcinogenic outcome [44].

The preferred quantitative approach for risk assessment appears to be the so-called margin of exposure (MOE), which can be used to compare animal dose-response data with human exposure scenarios [45-47]. The MOE can be used for prioritization of risk management actions, but is was described being difficult to interpret in terms of health risk [46]. Only relatively few MOE assessment can be found in the literature (e.g. for acrylamide, aflatoxin B_1, benzo(*a*) pyrene, dimethylnitrosamine and some other compounds in a summary by O'Brien *et al.* [45], as well as some separate evaluation for acetaldehyde [48], ethyl carbamate [49, 50], or furan [51]). Hopefully, new forms of internet publication such as the "Open Toxicology Journal" will facilitate the dissemination of MOE studies, which are often difficulty to place at traditional journals.

From a public health standpoint, it is certainly justifiable to acquire human exposure data about these 'weak-evidence' substances, and limit their concentrations in food according to precautionary toxicological evaluations. According to the Codex Alimentarius general standard for contaminants and toxins in food, contaminant levels in foods shall be as low as reasonably achievable (ALARA) [52]. This ALARA-principle was often criticized because it provides advice based solely on hazard identification and does not take into account either potency or human exposure [46]. However, we think that the presence of carcinogens in foods should be always regarded as undesirable, so that the ALARA-principle still appears to be valid for the contaminants discussed in this article. This is especially true as exposure levels completely devoid of risk cannot be identified with certainty at present [53]. The actual role of a long series of risk factors in increasing the cancer burden is also still poorly known, and the noxious effects of low or very low concentrations have only begun to be elucidated [43].

Over the discussion about the long list of probable or possible carcinogenic substances, however, we should not forget the substances with the highest level of evidence. From a risk-oriented approach food policy and food control should not lose sight of those agents that pose an immediate and scientifically quantifiable threat. From a global viewpoint, we should start with the following to reduce food-related carcinogenic risk:

- reduction of the consumption of alcoholic beverages (and, especially, the combined risk factors alcohol and tobacco) using policy measures (e.g., by controlling their availability; see Framework for Alcohol Policy in the WHO European region [54] and Rehm *et al.* [55]).
- prevention of aflatoxin contamination by improved procedures and control in countries that produce foods that may be contaminated with aflatoxins; strict control of imported foods (see, e.g., Commission Decision 2006/504/EC [56]).
- control and prevention of carcinogenic heavy metals (arsenic, cadmium, nickel and lead) in drinking water (especially in emerging countries).

- control and prevention of all other carcinogenic food contaminants using a risk oriented-approach (i.e., the level of scientific evidence should be reflected in the control frequency and depth) [57].
- prioritization of actions using quantitative risk assessment approaches, e.g. the MOE approach.

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