Food-Borne Chemical Carcinogens

Subjects: Toxicology

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Food-borne carcinogens span a range of chemical classes and can arise from natural or anthropogenic sources, as well as form endogenously.

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1. Introduction

Foods and beverages are essentially complex mixtures of chemicals consumed for either sustenance or pleasure. The diversity of chemicals found in food is vast, as are their varying properties. It has long been known that chemicals with carcinogenic activity in rodent models can be found in many commonly consumed foods [1][2][3][4][5] from a variety of sources including plants, microorganisms, contaminations, additive uses and reactions which occur during storage, processing and cooking [2] (**Table 1**). In addition, carcinogens can be formed endogenously, from food materials [6][7][8].

Table 1. Sources of detectable carcinogens in food.

Source	Examples [a]	
1. Naturally occurring		
Plant:	**alkenylbenzene derivatives** **aristolochic acid** **cycasin** **ptaquiloside** **d-limonene**	**psoralen** **pyrrolizidine alkaloids** **pulegone** **β-myrcene**
Microbial/Fungal:	**various mycotoxins**	
2. Contaminants		
Introduced before processing:	**daminozide** **dioxins**	**DDT** **flumequine**
Introduced during processing:	**trichloroethylene**	**methylene chloride**
Food contact materials:	**plastics (polyolefins, polyesters, polystyrene, polyamides, etc.)** **polymeric coatings**	**monomers (vinyl chloride, styrene, acrylonitrile)**
3. Additives		
Anthropogenic:	**α,β-aldehydes** **butylated hydroxyanisole and butylated hydroxytoluene**	**hexenal** **saccharin**
4. Formed from food components		
During processing:	**acrylamide** **chloropropanols** **ethyl carbamate (urethane)**	**furan** **various nitrosamines** **alkylated imidazoles**
During packaging:	**bisphenol A** **furan**	**phthalates**
During storage:	**benzene**	
During cooking:	**acrylamide** **benzo[a]pyrene**	**various heterocyclic amines**

Source	Examples [a]	
In the body:	**nitrosamines and nitrosamides** **α,β-aldehydes**	**ethylene oxide**

[a] Many of the agents listed are detectable only at minute levels by highly sensitive analytical techniques.

2. Mechanisms of Carcinogenicity of DNA-Reactive Carcinogens

DNA-reactive carcinogens have structures that permit formation of electrophilic reactants that covalently bind (adduct) to nucleophilic sites in nuclear DNA, as well as in other macromolecules, including RNA and proteins, in the target tissue(s) of carcinogenicity [9][10][11]. In target tissue(s), a single DNA reactant can form different DNA adducts on various nucleophilic sites either on a single base or on different bases. Each adduct can undergo different rates of repair depending upon its location in the genome. For example, adducts in transcriptionally active regions are repaired by a transcription-coupled repair system whereas adducts in transcriptionally silent regions are repaired by a global repair system [12]. The levels of DNA adducts resulting from exposures are a function of several metrics including dose levels, the frequency of exposure, and rates of DNA repair for specific adducts. Each adduct has a characteristic efficiency with which it gives rise to mutations, with those at sites of base pairing being more mutagenic.

Pro-mutagenic DNA alterations are converted to mutations during cell replication [13][14][15]. Mutations in critical growth control genes lead to neoplastic conversion, and subsequent neoplastic development [14][16]. DNA-reactive carcinogens can also exert other cellular effects, such as cytotoxicity, leading to enhanced cell proliferation, which can contribute to their carcinogenic activity [17][18]. DNA-reactive carcinogens can have additive effects with one another in their target organ(s).

Some DNA adducts evidently do not lead to carcinogenicity, since some adducts can be found in tissues where no tumors are induced following administration of a carcinogen [19][20][21][22]. For example, acrylamide, which is discussed below, forms adducts in target and non-target tissues [23]. It could also be the case that epigenetic effects are required to enable neoplastic conversion resulting from some adducts [24][25].

As a result of DNA interactions, DNA-reactive carcinogens are typically genotoxic in assay systems in which appropriate bioactivation is represented [10][26][27][28][29]. Moreover, DNA-reactive carcinogens often produce tumors at multiple sites and with a short duration of exposure, even after administration of a single dose for some. This property underlies their activity in limited short-term bioassays [27].

Some DNA-reactive carcinogens have been demonstrated to exhibit no-observed-adverse-effect-levels (NOAELs) for carcinogenic effects in animal models [11][17][30][31][32][33][34], although conflicting data have been reported. Based on the steps for tumorigenesis, it is evident that biological thresholds that may influence the likelihood of cancer progression for genotoxic carcinogens exist. Nevertheless, currently, thresholds are not generally accepted for DNA-reactive carcinogens from a risk assessment and management perspective [35]. It is acknowledged that the derivation of NOAELs can be dependent on the study design, and more research is needed in this space. It is outside the scope of this research to discuss thresholds for carcinogens in detail; however, this topic is reviewed elsewhere [11][17][30][31][32][33][34].

3. Mechanisms of Carcinogenicity of Epigenetic Carcinogens

Epigenetic carcinogens do not chemically react with DNA [26][36][37][38][39][40][41]. In the target tissue(s) of carcinogenicity, MoAs of these types of carcinogens involve molecular or cellular effects, which through secondary mechanisms, can either indirectly result in modification of DNA function or cell behavior [26][37]. For example, epigenetic carcinogens can induce oxidative stress, resulting in oxidative DNA damage [42][43][44], leading to either neoplastic conversion or stimulation of cell proliferation, thereby facilitating neoplastic development, often from cryptogenic pre-neoplastic cells. Epigenetic carcinogens can also affect gene expression [45][46], leading to neoplastic conversion. Such effects are often specific for rodents (e.g., d-limonene). Epigenetic carcinogens can enhance carcinogenicity of DNA-reactive carcinogens through interactive effects such as neoplasm promotion (e.g., butylated hydroxyanisole).

Due to their lack of direct DNA reactivity, epigenetic carcinogens, in contrast to DNA-reactive agents, are typically negative in genotoxicity assays, even in the presence of bioactivation, unless some artifact, such as extreme cytotoxicity, mediates mutagenicity. To exert their carcinogenicity, epigenetic agents often require prolonged high-level exposures. Their MoA underlies the fact that in limited bioassays they are negative for initiating activity, but may be positive for promoting activity [27].

Epigenetic carcinogens are well established to exhibit NOAELs for the cellular effect underlying their carcinogenicity in animal models [26][47], as discussed for several of the food-borne carcinogens reviewed herein. Accordingly, thresholds are generally accepted for DNA-reactive carcinogens from a risk assessment perspective [35].

4. Risk Assessment of Food-Derived Carcinogens

4.1. Application of Carcinogenicity Data to Human Risk

Two types of carcinogenicity data are used in the assessment of risk: human epidemiologic data and tumor data obtained in testing in rodent models [48]. The former is considered more relevant for a variety of reasons [49][50][51][52], although such data are often limited in human exposure information and can be poorly controlled [53].

Animal data are usually more robust, but frequently involve findings whose relevance to humans is uncertain [27][54][55], because the tumorigenic effect involves MoAs operational only in rodents. In addition, rodent studies do not mimic real life human exposures with respect to both the concentration and frequency of exposure. The human diet is also composed of mixture of components, which can both enhance and inhibit carcinogenicity.

Thus, in assessing human risk, two considerations are critical, i.e., the MoA of carcinogenicity and human exposure dose [11][56].

Once a chemical has been identified in a food product and its structure determined, it is possible to undertake an in silico analysis to determine, based on structure-activity relationships, the potential for DNA reactivity [57]. While this works well for relatively simple compounds, with the complexity of many natural products, the subtleties of metabolic activation become increasingly difficult to predict. If sufficient material is available, direct testing for DNA reactivity is the preferred approach [27].

This research focuses primarily on chemicals present in food that have sufficient evidence of carcinogenicity in either humans or experimental animals and which were classified by the International Agency for Research on Cancer (IARC) as either carcinogenic to humans (Group 1), probably (Group 2A) or possibly (Group 2B) carcinogenic to humans [48][58]. IARC also recognizes a third group of substances (Group 3) which lack sufficient evidence to be classified as carcinogenic to humans but nonetheless can have the potential to cause carcinogenicity in animals. Moreover, a variety of chemicals has not yet been characterized as to their carcinogenic risk to humans. Where available, evaluations by other expert groups are cited. Data on classification of carcinogens by government agencies and their carcinogenic potencies (TD_{50}) calculated based on the tumorigenicity findings in rodents are provided in **Table 2**.

Table 2. Classifications and characteristics of food-borne carcinogens.

Chemical Name	CAS Registry Number	Classification		Carcinogenic Potency (TD_{50}, mg/kg/d) [c]	MoA
		IARC [a]	NTP [b]		
1. Human carcinogens					
Aflatoxins		**1**	**1**	**0.343 (mouse) 0.0032 (rat)**	**GTX**
Aristolochic acid I	**313-67-7**	**1**	**1**	**N/A**	**GTX**
Benzene	**71-43-2**	**1**	**1**	**77.5 (mouse) 169 (rat)**	**GTX**
Benzo[a]pyrene	**50-32-8**	**1**	**2**	**3.47 (mouse) 0.956 (rat)**	**GTX**
Dioxin (TCDD)	**1746-01-6**	**1**	**1**	**0.000156 (mouse) 0.0000235 (rat)**	**EPI**
Dioxin-like compounds (PBCs)		**1**	**N/L**	**N/A**	**EPI**
Ethylene oxide	**75-21-8**	**1**	**1**	**63.7 (mouse) 21.3 (rat)**	**GTX**
Methoxsalen with UV A radiation	**298-81-7**	**1**	**1**	**32.4 (rat)**	**GTX**
Processed meat		**1**	**N/L**	**N/A**	**GTX**
Salted fish		**1**	**N/L**	**N/A**	**GTX**

Chemical Name	CAS Registry Number	Classification		Carcinogenic Potency (TD_{50}, mg/kg/d) [c]	MoA
		IARC [a]	NTP [b]		
2. Likely to be human carcinogens					
Acrylamide	**79-06-1**	**2A**	**2**	**3.75 (rat)**	**GTX**
2-Amino-3-methylimidazo[4,5-*f*]quinoline	**76180-96-6**	**2A**	**2**	**19.6 (mouse) 0.812 (rat)**	**GTX**
***p*,*p'*-Dichlorodiphenyl-trichloroethane (DDT)**	**50-29-3**	**2A**	**2**	**12.8 (mouse) 84.7 (rat)**	**EPI**
Ethyl carbamate (urethane)	**51-79-6**	**2A**	**2**	**16.9 (mouse) 41.3 (rat)**	**GTX**
5-Methoxypsoralen	**484-20-8**	**2A**	**N/L**	**N/A**	**GTX**
***N*-nitrosodiethylamine**	**55-18-5**	**2A**	**2**	**0.0265 (rat)**	**GTX**
Red meat		**2A**	**N/L**	**N/A**	**GTX**
2-Amino-3,4-dimethylimidazo[4,5-*f*]quinoline	**77094-11-2**	**2B**	**2**	**15.5 (mouse)**	**GTX**
2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoline	**77500-04-0**	**2B**	**2**	**24.3 (mouse) 1.66 (rat)**	**GTX**
2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine	**105650-23-5**	**2B**	**2**	**33.2 (mouse) 1.78 (rat)**	**GTX**
Benzophenone	**119-61-9**	**2B**	**N/L**	**152 (rat) 379 (mouse)**	**EPI**
Bracken fern		**2B**	**N/L**	**N/A**	**GTX**
Butylated hydroxyanisole	**25013-16-5**	**2B**	**2**	**5530 (mouse) 405 (rat)**	**EPI**
3-Chloro-1,2-propanediol	**96-24-2**	**2B**	**N/L**	**117 (rat)**	**Uncertain**
Crotonaldehyde	**4170-30-3**	**2B**	**N/L**	**4.2 (rat)**	**GTX**
Cycasin	**14901-08-7**	**2B**	**N/L**	**N/A**	**GTX**
1,3-Dichloro-2-propanol	**96-23-1**	**2B**	**N/L**	**46.4 (rat)**	**GTX**
Di(2-ethylhexyl) phthalate	**117-81-7**	**2B**	**2**	**476 (rat) 484 (mouse)**	**EPI**
1,4-Dioxane	**123-91-1**	**2B**	**2**	**204 (mouse) 267 (rat)**	**Uncertain/EPI**
Fumonisin B_1	**116355-83-0**	**2B**	**N/L**	**6.79 (mouse) 5.75 (rat)**	**Uncertain/EPI**
Fusarin C	**79748-81-5**	**2B**	**N/L**	**N/A**	**Uncertain/EPI**
Furan	**110-00-9**	**2B**	**2**	**2.72 (mouse) 0.396 (rat)**	**EPI**
Lasiocarpine	**303-34-4**	**2B**	**N/L**	**0.389 (rat)**	**GTX**
Methyl eugenol	**93-15-2**	**2B**	**2**	**19.3 (mouse) 19.7 (rat)**	**GTX**
Methylazoxymethanol	**592-62-1**	**2B**	**N/L**	**N/A**	**GTX**
2-Methylimidazole	**693-98-1**	**2B**	**N/L**	**782 (mouse) 868 (rat)**	**EPI**
4-Methylimidazole	**822-36-6**	**2B**	**N/L**	**387 (mouse) 317 (rat)**	**EPI**
Methyl isobutyl ketone	**108-10-1**	**2B**	**N/L**	**612 (rat)**	**EPI**
Monocrotaline	**315-22-0**	**2B**	**N/L**	**0.94 (rat)**	**GTX**
β-Myrcene	**123-35-3**	**2B**	**N/L**	**15,400 (rat)**	**EPI**

Chemical Name	CAS Registry Number	Classification		Carcinogenic Potency (TD_{50}, mg/kg/d) [c]	MoA
		IARC [a]	NTP [b]		
***N*-nitrosodiethanolamine**	**1116-54-7**	**2B**	**2**	**3.17 (rat)**	**GTX**
Ochratoxin A	**303-47-9**	**2B**	**2**	**6.41 (mouse) 0.136 (rat)**	**GTX/EPI**
Pickled vegetables		**2B**	**N/L**	**N/A**	**GTX**
Pulegone	**89-82-7**	**2B**	**N/L**	**232 (mouse) 156 (rat)**	**EPI**
Riddelliine	**23246-96-0**	**2B**	**2**	**1.97 (mouse) 0.119 (rat)**	**GTX**
Safrole	**94-59-7**	**2B**	**2**	**51.3 (mouse) 441 (rat)**	**GTX**
***trans,trans*-2,4-Hexadienal**	**142-83-6**	**2B**	**N/L**	**176 (mouse) 62.2 (rat)**	**GTX**
3. Unknown carcinogenic potential					
Agaritine [d]	**2757-90-6**	**3**	**N/L**	**N/A**	**GTX**
Butylated hydroxytoluene	**128-37-0**	**3**	**N/L**	**653 (mouse)**	**EPI**
Carrageenan (native) [d]	**9000-07-1**	**3**	**N/L**	**N/A**	
Chlorate (sodium salt) [d]	**7775-09-9**	**3**	**N/L**	**69.1 (mouse) 0.865 (rat)**	**EPI**
Eugenol [d]	**97-53-0**	**3**	**N/L**	**N/A**	
Furfural [d]	**98-01-1**	**3**	**N/L**	**197 (mouse) 683 (rat)**	**Uncertain**
Hydroquinone	**123-31-9**	**3**	**N/L**	**225 (mouse) 82.8 (rat)**	**EPI**
Isatidine [d]	**15503-86-3**	**3**	**N/L**	**0.716 (rat)**	**GTX**
d-Limonene [d]	**5989-27-5**	**3**	**N/L**	**204 (rat)**	**EPI**
Malondialdehyde	**24382-04-5**	**3**	**N/L**	**14.1 (mouse) 122 (rat)**	**GTX**
Patulin [d]	**149-29-1**	**3**	**N/L**	**N/A**	**Uncertain**
Ptaquiloside	**87625-62-5**	**3**	**N/L**	**N/A**	**GTX**
Quercetin [d]	**117-39-5**	**3**	**N/L**	**10.1 (rat)**	**EPI**
Retrorsine [d]	**480-54-6**	**3**	**N/L**	**0.862 (rat)**	**GTX**
Senkirkine [d]	**2318-18-5**	**3**	**N/L**	**1.7 (rat)**	**GTX**
Sodium saccharin [d]	**128-44-9**	**3**	**N/L**	**2140 (rat)**	**EPI**
Symphytine [d]	**22571-95-5**	**3**	**N/L**	**1.91**	**GTX**
Zearalenone [d]	**17924-92-4**	**3**	**N/L**	**39 (mouse)**	**EPI**
4. Not classified by IARC/NTP					
Daminozide [d]	**1596-84-5**	**N/L**	**N/L**	**1030 (mouse) 2500 (rat)**	**EPI**
Estragole	**140-67-0**	**N/L**	**N/L**	**51.8 (mouse)**	**GTX**
Genistein [d]	**446-72-0**	**N/L**	**N/L**	**27.1 (rat)**	**EPI**
***N*-methyl-*N*-formylhydrazine [d]**	**758-17-8**	**N/L**	**N/L**	**1.37 (mouse)**	**GTX**

[a] IARC group 1—carcinogenic to humans; group 2A—probably carcinogenic to humans; group 2B—possibly carcinogenic to humans; group 3—not classifiable as to its carcinogenicity to humans; group 4—probably not carcinogenic to humans.

Source—Agents Classified by the IARC Monographs, Volumes 1–131 [58] . [b] 1—known to be a human carcinogen; 2—reasonably anticipated to be a human carcinogen. Source—NTP Report on Carcinogens, 15th Edition [59] . [c] Only rodent data was included for comparison; Source—Lhasa Carcinogenicity Database, https://carcdb.lhasalimited.org/ (accessed on 9 July 2022). [d] Not discussed in this research. EPI, epigenetic modifications; GTX, genotoxicity; N/A, not available N/L, not listed.

In this research, the evidence for human cancer risk from intake of food borne carcinogens of both the DNA-reactive and epigenetic types is discussed. In the assessment of risk from experimental studies, the greatest weight is given to studies with oral administration since that route of intake is most relevant to human consumption. The demonstration of human carcinogenicity is made in epidemiologic studies, although, the absence of an effect can be due to inadequacy of the studies.

4.2. Risk Assessment of DNA-Reactive Rodent Carcinogens

In order to evaluate possible safety concerns arising from presence of carcinogens with DNA-reactive MoA in the diet, many regulatory and advisory agencies, including the European Food Safety Authority Panel on Contaminants in the Food Chain (EFSA CONTAM) and the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) the Expert Committee on Food Additives (JECFA) use a margin of exposure (MoE) approach [60][61]. MoE is calculated as a ratio between an appropriate Point of Departure for a tumor response, such as NOAELs obtained from animal studies, and a predicted or estimated human exposure level. A number of considerations should be taken into account when a MoE is derived, including the biological relevance of carcinogenic MoAs to humans [55].

Among DNA-reactive rodent carcinogens, only aflatoxins, aristolochic acid I, benzene, benzo[a]pyrene and ethylene oxide, have been found to be associated with cancer causation in humans (**Table 2**). Nevertheless, all materials in this class are genotoxic, indicating an MoA that represents human risk [62].

4.3. Risk Assessment of Epigenetic Carcinogens

The contribution and relevance of epigenetic mechanisms produced by dietary factors leading to the development of cancer in humans is uncertain [63], and the best approach to risk assessment of such carcinogens remains a topic of a debate [64]. Nevertheless, at low intermittent exposures (less than 1 mg/day) epigenetic carcinogens are not considered to pose cancer risks to humans [56]. This may reflect the absence in humans of the processes involved in the MoAs in rodents, e.g., d-limonene alpha 2μ($\alpha_{2\mu}$)-globulin nephropathy in male rats leading to kidney tumors [65], or the much lower exposures of humans, e.g., forestomach irritation in rats caused by butylated hydroxyanisole leading to squamous cell carcinoma [66]. Additionally, the fact that epigenetic changes can be reversible could contribute to lack of human risk. Hence, for epigenetic carcinogens NOAELs are used to derive safety values, such as tolerable daily intake (TDI) [56].

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