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Carcinogenic Food Contaminants

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Introduction

Cancer is a leading cause of death worldwide and diet is thought to play a substantial role in cancer etiology. The salutatory and detrimental effects of different foods, food components, and food contaminants have been widely studied in the laboratory and in epidemiologic studies. The importance of food contaminants in the link between diet and cancer has been widely studied and formal risk assessments are routinely completed by several governmental and international agencies.

Risk assessments for human hazards typically consist of two components; first, a hazard assessment to determine if a particular exposure can have adverse consequences and second, an exposure assessment to determine if the range of exposures puts an individual or population at risk of adverse consequences. In some instances, a particular exposure will be found to be carcinogenic but the exposure will be so minimal that it is of little concern to the general population. The hazard assessment may be partially based on animal studies. Human epidemiologic studies combine both parts of the typical risk assessment process into a single study by assessing the degree of exposure and the association with the risk of cancer in a single study. These studies are often limited by methods of assessing exposure, a limited range of exposure in any single population under study, confounding by other simultaneous exposures, and the need for confirmation in independent epidemiologic studies, which are often complex and expensive to perform. Both forms of data are useful in the determination of whether specific food contaminants pose a carcinogenic risk to humans.

Two important complementary programs exist that classify whether exposures pose a carcinogenic risk to humans. First, the US National Toxicology Program produces the *Report on Carcinogens* 1 currently in its 11th edition. This biennial report has four primary objectives:

- A list of all substances (1) which either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens and (2) to which a significant number of persons residing in the United States are exposed.
- Information concerning the nature of such exposure and the estimated number of persons exposed to such substances.
- A statement identifying (1) each substance contained in this list for which no effluent, ambient, or exposure standard has been established by a Federal agency and (2) for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in this list, the extent to which such standard decreases the risk to public health from exposure to the substance.
- A description of (1) each request received during the year to conduct research into, or testing for, the carcinogenicity of a substance and (2) how the Secretary and other responsible entities responded to each request.

Second, the International Agency for Research on Cancer (IARC) produces *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (<http://monographs.iarc.fr/>) The stated objective of the IARC Monographs is as follows: “The Monographs represent the first step in carcinogenic risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that certain exposures could alter the incidence of cancer in humans. The second step is quantitative risk estimation. Detailed, quantitative evaluations of epidemiological data may be made in the Monographs, but without extrapolation beyond the range of the data available. Quantitative extrapolation from experimental data to the human situation is not undertaken.” Unlike the *Report on Carcinogens*, the *IARC Monographs* have a worldwide perspective and may address exposures only relevant to communities outside the US. Both programs primary goal is to provide information useful to appropriate regulatory agencies without proposing specific regulations themselves. This is left to the appropriate regulatory bodies of different governmental entities.

The National Toxicology Program (<http://ntp-server.niehs.nih.gov/>) also completes primary research that investigates carcinogenicity of different exposures while the *IARC Monograph* series synthesizes extant information. Both programs rely on published research reports from public and private institutions. Both programs actively search for topics that have sufficient information to draw conclusions.

There are other important independent programs that also assess the human carcinogenicity of substances, such as the one run by the state of California. In 1986, proposition 65 required that the Governor of California to publish, at least annually, a list of chemicals known to the state to cause cancer or reproductive toxicity. The California Office of Environmental Health Hazard Assessment (<http://www.oehha.ca.gov/>) has been tasked with assisting the Governor of California in this and has listed 475 chemicals as carcinogens. Numerous national programs in other countries also provide valuable information regarding the carcinogenicity of different agents in humans, much of which is used in the IARC and NTP evaluations. For the purposes of this review I have included items exclusively covered by either IARC or the NTP.

Carcinogen classifications from NTP and IARC monographs

The National Toxicology Program and the IARC monographs use different categorizations in their conclusions about the human carcinogenicity of substances depending on the quality of the evidence available. The *Report on Carcinogens* classifies substances as “Known to be human carcinogens” or “Reasonably anticipated to be a human carcinogen.” IARC uses a more complex classification scheme which includes substances that have been reviewed but are found not classifiable as possibly carcinogenic to humans: Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, not classifiable as to carcinogenicity in humans; Group 4, probably not carcinogenic.

Types of food contaminants

There are four primary types of potentially carcinogenic compounds that have been examined to determine if they act as carcinogens in humans. The first are natural products that may be present in food and are unavoidable. For example, the process of creating salted fish produces carcinogens which can not be easily avoided. Second, are natural products that might be avoided such as the contamination of grain with the carcinogenic fungal metabolite aflatoxin, which can be reduced or eliminated using best practices for grain storage. Third, anthropogenic chemicals may be present in food. For instance, 2,3,7,8-tetracholordibenzo-p-dioxin has been inadvertently produced during the manufacture of chlorinated hydrocarbons, but it contaminates the environment, resists degradation, and accumulates in certain foodstuffs. A fourth category of concern is anthropogenic chemicals intentionally added to foods, such as

saccharin or food coloring, but these are not addressed in this review because they are not contaminants because they are added intentionally.

Food Contaminants Which Pose A Carcinogenic Threat To Humans

Section 1: Those agents with the highest level of evidence

Aflatoxin—NTP - Known to be a human carcinogen

IARC - Carcinogenic to humans

Aflatoxins are a class of toxic metabolites produced by certain species of fungi. A number of different specific chemical entities make up the class aflatoxins and they are generally present in food as mixtures. The most famous source of aflatoxin is *Aspergillus flavus* that can infect peanuts, but also infects tree nuts and grains. Animals eating infected foodstuffs can produce animal food-products that contain aflatoxins. Women consuming infected foodstuffs can pass on aflatoxin to infants through breast milk.

Laboratory studies have demonstrated the carcinogenicity of aflatoxins in rodents, primates, and fish ². Hepatocellular carcinoma has been seen in numerous species indicating that the liver is an important target organ. Nevertheless, tumors in the colon and kidney are also induced in some species. Initially, ecologic ³ and occupational ⁴ studies suggested an association between excess aflatoxin exposure and the incidence of cancer. Further evidence from a case-control study ⁵ and cohort study ⁶ have confirmed the association and the later sought to disentangle the interaction between aflatoxin and hepatitis on the risk of liver cancer. Recently, chemopreventive trials in endemic liver cancer areas of the People's Republic of China have suggested that interventions can reduce the carcinogenic impact of aflatoxin ⁷.

Alcoholic beverages—NTP - Known to be a human carcinogen

IARC - Carcinogenic to humans

Alcoholic beverages of all types (fermented and those further distilled) can cause cancer in humans. Animal studies have not convincingly demonstrated that ethanol itself is carcinogenic leading to the hypothesis that other contaminants in alcoholic beverages or ethanol metabolites (see acetaldehyde below) are responsible for these effects. The solvent action of ethanol may be relevant for co-carcinogens either in the beverages or in other dietary components ⁸.

Numerous epidemiologic studies have demonstrated an association between alcoholic beverages and cancers of the mouth, pharynx, larynx, and esophagus ⁹, and possibly the breast ¹⁰ and liver ¹¹. The cancer risk appears to be dose-dependent ¹². Many of these studies suggest that the cancer risk from alcoholic beverages is synergistically increased among tobacco users ¹² and confounding by smoking status does not explain the associations.

Alcoholic beverages have been widely studied for health effects other than cancer and important detrimental and beneficial associations have been reported. Alcoholic beverages are the primary cause of liver cirrhosis in the US ¹³ and have been linked to a large proportion of fatal and non-fatal motor vehicle accidents. Conversely, moderate consumption of alcoholic beverages has been linked to a lower overall mortality and reduced risk of coronary heart disease and stroke ¹⁴. Some hypotheses state that the effects may be peculiar to wine and be due to resveratrol or other non-ethanol components of wine ¹⁵, alternatively a host of ethanol effects may be the beneficial agent with regard to heart disease ¹⁴.

2,3,7,8-Tetracholordibenzo-p-dioxin—NTP - Known to be a human carcinogen

IARC - Carcinogenic to humans

Also known as TCDD or more simply Dioxin, 2,3,7,8-tetracholordibenzo-*p*-dioxin is the prototypical compound of a class of agents (e.g. other dioxins, some halogenated dibenzofurans, some halogenated biphenyls, and some non-halogenated polycyclic aromatic hydrocarbons (see PAHs below)) thought to act through a similar mechanism. These agents serve as ligands of the aryl hydrocarbon receptor (Ahr)¹⁶. 2,3,7,8-Tetracholordibenzo-*p*-dioxin serves as the prototype because of its high potency, high Ahr binding affinity, and because it is more resistant to either environmental or biological degradation than most of the other agents in this class. Both the NTP and IARC name this agent specifically as a human carcinogen, but discuss the use of the Toxic Equivalency Factor to estimate the potency of the other less potent and less well studied members of the class. 2,3,7,8-Tetracholordibenzo-*p*-dioxin was never produced intentionally, except for research purposes, but was created as a by-product in the manufacture of PCBs, chlorinated herbicides (e.g. Agent Orange) and in minute amounts in any process where there is incomplete combustion in the presence of chlorine. Minute amounts are also produced naturally (e.g. by forest fires).

Studies in multiple animal species have demonstrated the carcinogenic potential of 2,3,7,8-tetracholordibenzo-*p*-dioxin in producing tumors of the liver¹⁷, thyroid, the upper aerodigestive tract, and skin¹⁸.

Associations with cancer in human studies have focused on highly exposed subjects in occupational settings. Associations with total cancer, lung cancer, and non-Hodgkin's lymphoma have been noted¹⁹.

2,3,7,8-tetracholordibenzo-*p*-dioxin was originally listed by the NTP as reasonably anticipated to be a human carcinogen in its second annual report. The elevation to known human carcinogen in the Ninth annual report was contested in US Federal court system, but was completed in 2001.

Salted fish—NTP - Not listed

IARC - Carcinogenic to humans

Salted fish are produced in several parts of Asia using a method that appears to result in the production of carcinogenic by products. Several potential carcinogens have been identified including *N*-nitrosodimethylamine (see separate listing below), other *N*-nitroso compounds²⁰.

Minimal work has studied the carcinogenicity of Chinese-style salted fish in animals²¹, but this product does contain agents that are mutagenic²².

Ecologic²³ and case-control studies^{24,25} have demonstrated an increased risk of nasopharyngeal carcinoma in subjects consuming larger amounts of Chinese-style salted fish. The consistency of the association led IARC to classify these preserved fish as a Group 1 carcinogen. Much more limited evidence has linked this product to increased risk of stomach and esophageal cancer as well.

Section 2: Those agents with a moderate level of evidence

Acetaldehyde—NTP - Reasonably anticipated to be a human carcinogen

IARC - Possible carcinogenic to humans

Acetaldehyde is produced in many different geological, industrial, and biological processes and is the first metabolite produced in humans from ethanol after ingestion²⁶. Humans are exposed to naturally occurring acetaldehyde in the air and from numerous foods. Humans are also exposed to it from automobile exhaust, cigarette smoke, fireplaces, and in occupational settings,.

Acetaldehyde has been demonstrated to cause cancer in animals, mainly in the upper respiratory tract.

The evidence of human carcinogenicity is more indirect and has generally been linked to heavy alcohol consumption. Heavy drinkers experience higher rates of oral, pharyngeal, and esophageal cancers⁸ and one hypothesized mechanism is that ethanol is converted to acetaldehyde. Several studies of genetic polymorphisms in the genes which metabolize ethanol and acetaldehyde have shown that subjects who carry one inactive acetaldehyde dehydrogenase 2 allele are at higher risk of alcohol related cancers²⁷. Subjects with two inactive alleles generally cannot tolerate alcohol.

Acetaldehyde may underlie the increase in certain alcohol related cancers (see above). The widespread exposure to acetaldehyde is of concern, but the relevance to cancer of other natural and anthropogenic sources is still unclear.

Polycyclic aromatic hydrocarbons including Benzo[a]pyrene—NTP - Reasonably anticipated to be a human carcinogen

IARC - Probably carcinogenic to humans

Benzo[a]pyrene is a prototypical member of the polycyclic aromatic hydrocarbon family, which also includes benz[a]anthracene, benzo[b]fluoranthene and other similar compounds that show similar toxic profiles. In total, the Report on Carcinogens includes 15 different polycyclic aromatic hydrocarbons. They are produced inadvertently during the incomplete combustion of organic material.

Human exposure occurs through many routes including food. Intentional exposure comes through the therapeutic use of coal tar for certain skin conditions. Many people are exposed to PAHs occupationally and through exposure to smoke from tobacco, automobile exhaust, forest fires, and other sources. Food is contaminated with PAHs during smoking, barbecuing, grilling, and is also present at low concentrations in oils, coffee, sausages, etc. In areas of the world that cook their food using coal, the uncooked food can be contaminated from the cooking smoke^{27,28}.

In experimental animals, different specific PAHs and exposures routes lead to different tumors in different species. Gavage leads to forestomach, lung, and liver tumors, intraperitoneal injection to mammary and uterine tumors, and topical application to skin tumors. The site of exposure is often the site of tumor development.

PAHs are present in tobacco smoke, but evidence for PAH carcinogenicity in other exposure routes is less well developed in humans. Occupational exposed cohorts have shown elevations in lung, skin, and bladder tumors²⁹. Epidemiologic studies are hampered by the difficulty in assessing individual PAH exposure.

N-Nitrosodimethylamine and some other nitrosamines—NTP - Reasonably anticipated to be a human carcinogen

IARC - Probably carcinogenic to humans

N-Nitrosodimethylamine and some related nitrosamines were only briefly produced intentionally for purposes beyond research. These compounds are formed during rubber processing, are present in metal working fluids and are inadvertently present in foodstuffs including smoked foods, preserved meats, and some alcoholic beverages³⁰. This agent may also be present in some pharmaceuticals and in tobacco smoke.

A significant source of exposure to N-nitroso compounds, especially in non-occupationally exposed non-smokers, is internal formation in the gut³¹⁻³³. About 25% of dietary nitrate is recycled to the salivary glands. Oral and gut bacteria can reduce dietary nitrate to nitrite and this nitrite can react with amines to form nitrosamines spontaneously.

N-Nitrosodimethylamine produces tumors in experimental animals through many different exposure routes. Most studies have shown that this agent produces liver tumors of several different histologies and sometime tumors in the bile duct, kidney, lung, and nasal cavity.

No adequate human studies have demonstrated that this agent is a human carcinogen. As for many other agents the conduct of epidemiologic studies of this agent are hampered by the inability to assess exposure. Despite this short coming, the overwhelming carcinogenicity in animals suggests that this agent is carcinogenic in humans.

Hot Maté—NTP - Not listed

IARC - Probably carcinogenic to humans

Maté is an herbal infusion of the plant *Ilex paraguariensis* drunk in Argentina, Uruguay, and southern Brazil. Minimal use outside this geographic area precludes its evaluation by the US NTP. The infusion is typically drunk, often at very high temperatures, through a metal straw in a special apparatus.

The carcinogenicity of maté has not been studied in animals but multiple case-control studies have demonstrated an association between hot maté and oral, oropharyngeal, head and neck, and esophageal cancer³⁴⁻³⁷. Most studies have found a dose dependent increase in cancer risk with increased consumption of maté. Quantities greater than 1 liter/day are not uncommon and some people report >3 liters/day. Furthermore, the typical temperature of consumption may also effect the association with subjects reporting the highest temperature at the greatest increased risk in some studies.

The interaction between cancer risk and the quantity consumed and the temperature of consumption suggests that thermal injury and not the maté are responsible for some or all of the increased risk of cancer. A similar hypothesis has been studied in a population in Northern Iran at very high risk for esophageal cancer. These subjects consume large quantities of tea, some preferring very high temperatures, sometimes in excess of 65 °C. Further research will be required to disentangle the effects of maté and the temperature at which it is consumed. Alternatively, contaminants such PAHs, which are introduced during preparation of the leaves, may be the carcinogenic agent³⁸.

Section 3: Those agents with a lower level of evidence

Bracken Fern—NTP - Not listed

IARC - Possibly carcinogenic to humans

Bracken fern are common, grow worldwide, and were first identified as a hazard to grazing animals. For humans, the greatest concern is the direct consumption of bracken fern in Japan and a few other areas. Studies in mouse, rat, guinea pig, and quail have examined the fresh and

processed bracken fern products and sufficient evidence has been developed to demonstrate that this agent can be carcinogenic in animals.

Several studies have suggested that subjects who live in areas where bracken ferns are very common have higher risk of gastric and/or esophageal cancer³⁹⁻⁴¹. One study of bladder cancer found no increased risk associated with fern consumption⁴² and a recent review suggests that bracken fern is unlikely to be a serious health hazard⁴³.

Dichlorodiphenyltrichloroethane (DDT)—NTP - Reasonably anticipated to be carcinogenic to humans

IARC - Possibly carcinogenic to humans

DDT is the nickname for the pesticide dichlorodiphenyltrichloroethane that was used in the United States from 1939 until it was banned for general use, but not manufacture, in 1972. Debate about its use was heightened by the findings of its affect on raptor populations. Because DDT is highly lipophilic it concentrates in fat and bioaccumulates in higher consumers in the food web. In addition to direct exposure to pesticide applicators, all people are exposed to DDT through food, especially but not exclusively through animal products, but also some vegetables.

There is ample evidence that DDT is carcinogenic in animals. The liver appears to be the primary target organ, but lung tumors and lymphomas have also been noted.

The evidence for carcinogenicity in humans remains mixed. No prospective epidemiologic studies have been reported which examine the association between DDT/DDE exposure and incident cancers at any site. Some ecologic and case-control studies have suggested an association with human cancer, especially liver and breast^{44,45}, but no clear associations have been uncovered⁴⁶⁻⁴⁹. In addition, concerns about co-exposure to other organochlorines make the interpretation less clear⁵⁰.

Although banned in most developed countries DDT is still used in some parts of the world. DDT could appear in the food of countries with bans through food imports. Aerial deposition is also a concern as has been demonstrated in the findings of DDT in animals in the arctic and other areas that have little direct use of the pesticides^{51,52}.

Toxins from *Fusarium moniliforme*, Fumonisin, Fumonsin B₁—NTP - Not listed

IARC - Possibly carcinogenic to humans

Fusarium moniliforme (now known as *Fusarium verticillioides*) is a species of fungus that, among others, produces a series of toxic metabolites known as fumonisins, the best studied being fumonisin B₁. This fungus is most closely associated with maize, but can infect other food stuffs as well. Fumonisin produce a broad spectrum of toxic effects in animals including equine leukoencephalomalacia and porcine pulmonary edema⁵³. Occasional inadvertent farm animal poisonings have occurred from moldy grain.

The carcinogenicity of fumonsin B₁ in animals was demonstrated by the NTP after completion of a two-year bioassay in rats and mice⁵⁴. These studies showed an increase in renal tubule adenomas in male rats and hepatocellular tumors in female mice.

Evidence for the carcinogenicity of fumonisins in humans is limited to ecologic associations in the People's Republic of China⁵⁵⁻⁵⁸, in the Republic of South Africa^{59,60}, and in Iran⁶¹. Each of these countries have sub-populations at high risk for esophageal squamous cell carcinoma and these sub-populations appear to have greater exposure to fumonisin than sub-

populations at lower risk for esophageal squamous cell carcinoma. Only a single case-control study has examined the association between fumonisin exposure and esophageal squamous cell carcinoma and it reported no apparent association, but this study used an exposure biomarker of uncertain value ⁶².

Ochratoxin A—NTP - Reasonably anticipated to be carcinogenic to humans

IARC - Possibly carcinogenic to humans

Ochratoxin A can be produced by *Aspergillus*, *Penicillium*, and other molds. Food is the primary route of human exposure, especially from grain but also through animal products from animals consuming contaminated feeds and possibly from processed grain products including beer.

The liver and possibly the kidney are target organs for the carcinogenic effects of Ochratoxin A in laboratory animals.

Little evidence of carcinogenicity in humans exists because few epidemiologic studies of Ochratoxin A have been conducted. An ecologic association between high ochratoxin A contamination and nephropathy has been noted in southeastern Europe^{63,64}.

2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and other heterocyclic amines—NTP – Reasonably anticipated to be a human carcinogen

IARC - Possibly carcinogenic to humans

PhIP is an aryl amine that forms during the cooking of meat, especially at high temperatures. The temperature and form of cooking can significantly alter the production of PhIP and two related heterocyclic amines, namely 2-amino-3,4-dimethylimidazo[4,5-f]quinolone (MeIQ) and 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) ⁶⁵.

All three compounds are considered to be mutagenic and cause tumors in animals. The site of tumor depends on the route of exposure include the intestine (small and large), prostate, lymphomas and other sites.

Human data that has specifically estimated heterocyclic amine intake are limited and since the primary route of exposure, cooked meat, is also likely to contain PAHs (and will also be confounded by fat intake, iron, etc.) ⁶⁶. Some recent studies have demonstrated an association between estimated heterocyclic amine intake and cancer risk ⁶⁷.

One method which might help separate the effects of PAHs and heterocyclic amines is the study of genetic variation in the cytochromes P450 which metabolize these agents. Distinct profiles might be drawn with different enzymes being more active towards PAHs than heterocyclic amines and vice-versa. The association of polymorphisms in these genes with the cancers of interest may suggest the importance of particular agents.

Coffee—NTP – Not listed

IARC - Possibly carcinogenic to humans

Coffee is grown and consumed the world over and was listed in 1991 by IARC as possibly carcinogenic to humans. Some evidence had linked coffee to an increase risk of bladder cancer. Subsequent studies suggest that this association is unlikely or very weak ^{68,69}. The association is biologically plausible, but the lack of a dose-response in most studies suggests that residual

confounding could be to blame. An association with pancreatic cancer has been suggested but remains unconvincing ⁷⁰. As later noted by IARC and others, coffee may have an inverse association with the risk of colon cancer ⁶⁸.

Pickled vegetables—NTP – Not listed

IARC - Possibly carcinogenic to humans

Pickled vegetables have been studied for their association with cancer mainly in Asia and especially in the People's Republic of China. The pickling process is different from that used in many parts of the world and uses no salt or vinegar. Instead it relies on natural fermentation and can lead to contamination with mold.

A small amount of laboratory evidence suggests that these vegetables may contain mutagens ^{71,72}. Epidemiologic studies have suggested an increased risk of esophageal cancer in pickled vegetable consumers ^{73,74}. In the highest esophageal cancer risk area of north central China no association between pickled consumption and cancer has been noted in multiple studies ⁷⁵⁻⁷⁷. This population was subject to a public health campaign against the consumption of these vegetables prior to the baseline interview. This may have led to exposure misclassification if subjects recently discontinued consumption or prevarication due to the repeated warnings to stop consuming the pickles.

Acrylamide—NTP – Reasonably anticipated to be a human carcinogen

IARC - Probably carcinogenic to humans

In 2002 Professor Margareta Törnqvist at the University of Stockholm reported that acrylamide is created in the process of high temperature cooking of certain foods such as potatoes and cereals. Acrylamide was previously listed by the NTP as *reasonably anticipated to be a human carcinogen* and by IARC as *Probably carcinogenic to humans*. But, when reviewed neither of the agencies had data on the presence of acrylamide in food due to high temperature cooking and the primary routes of exposure were occupational and possibly in drinking water due to residues from polyacrylamide flocculants.

Since the high profile reporting on this potential new source of contamination, several studies have examined the association between foods that may contain acrylamide (e.g. fried potatoes, coffee) and cancer risk ⁷⁸⁻⁸¹. These studies used exposure estimates derived from dietary data on acrylamide content of different foods and failed to find significant associations with cancer sites studied.

Conclusions

The accumulation of evidence sufficient to render judgment on food contaminants and human cancer risk is a daunting task. This process generally relies on individual investigators demonstrating a potential concern through exploratory analyses in the lab, with animals, or even in epidemiologic studies. Nevertheless, numerous food contaminant concerns exist and several food contaminants have been confirmed as carcinogenic to humans. Possibly the clearest example is the finding that aflatoxin is a major cause of liver cancer, especially in lower resource countries and in populations where infection with hepatitis B is common. Once identified the elimination/reduction of exposure can be initiated through government regulation, food producer initiatives, and individual dietary changes.

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