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A Risk-Based Strategy for Evaluating Mitigation Options for Process-Formed Compounds in Food: Workshop Proceedings

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Abstract

Processing (eg, cooking, grinding, drying) has changed the composition of food throughout the course of human history; however, awareness of process-formed compounds, and the potential need to mitigate exposure to those compounds, is a relatively recent phenomenon. In May 2015, the North American Branch of the International Life Sciences Institute (ILSI North America) Technical Committee on Food and Chemical Safety held a workshop on the risk-based process for mitigation of process-formed compounds. This workshop aimed to gain alignment from academia, government, and industry on a risk-based process for proactively assessing the need for and benefit of mitigation of process-formed compounds, including criteria to objectively assess the impact of mitigation as well as research needed to support this process. Workshop participants provided real-time feedback on a draft framework in the form of a decision tree developed by the ILSI North America Technical Committee on Food and Chemical Safety to a panel of experts, and they discussed the importance of communicating the value of such a process to the larger scientific community and, ultimately, the public. The outcome of the workshop was a decision tree that can be used by the scientific community and could form the basis of a global approach to assessing the risks associated with mitigation of process-formed compounds.

Keywords

process-formed compounds, food, risk, mitigation, exposure

Introduction

The North American Branch of the International Life Sciences Institute (ILSI North America) Technical Committee on Food and Chemical Safety (referred to hereafter as the committee) developed a draft framework, in the form of a decision tree, to assess the true impact on risk caused by process-formed compounds in food and to proactively evaluate the impact of mitigation procedures. The draft framework was discussed at a May 2015 ILSI North America workshop on the risk-based process for mitigation of process-formed compounds. The workshop aimed to seek alignment on the proposed strategy recognizing that, as a practical matter, the workshop could not necessarily encompass all considerations around the issue. This article highlights the discussion and outcomes of that workshop. As the name implies, process-formed compounds are substances formed as a result of food processing, particularly cooking or heating (eg, Maillard reaction products).[1] Accordingly, exposure to many of these compounds is not a modern phenomenon; rather, it has occurred throughout human history. Awareness of such compounds dates back to at least the 1960s.[2] In the 21st century, increased interest was spurred by the unexpected discovery of acrylamide in many foods in 2002.[3,4] Acrylamide is an industrial chemical considered likely to be carcinogenic in humans by agencies such as the US National Toxicology Program,[5] the European Food Safety Authority (EFSA),[6] and the International Agency for Research on Cancer.[7] The subsequent recognition of other process-formed compounds (eg, furan, 4-methylimidazole, and monochloropropane diols [MCPDs] and their esters) present in some foods, and efforts to reduce exposures to these compounds via various mitigation efforts, has led to the realization that a more forward-thinking process is necessary to evaluate the need for mitigation of such compounds. The objectives of the workshop were to identify (1) criteria that must be established to objectively assess the impact of mitigation and (2) opportunities for additional research needed to support this process.

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Table 1. Risk-Based Process for Mitigation of Process-Formed Compounds Workshop Program.

Welcome *Alison Kretser, ILSI North America, Washington, DC*
Introduction to Process-Formed Compounds *Paul Hanlon, PhD, Abbott Nutrition, Columbus, OH*
Risk Is the Product of Hazard and Exposure *Joseph V. Rodricks, PhD, DABT, Ramboll Environ, Arlington, VA*
The Importance of Exposure in Safety/Risk Assessments *Michael DiNovi, PhD, FDA, College Park, MD*
Regulatory Approaches to Process-Formed Compounds *Nega Beru, PhD, FDA, College Park, MD*
Introduction to the ILSI North America Decision Tree *Alan R. Boobis, OBE, PhD, CBiol, FSB, FBTS, Imperial College London, UK*
Panel Discussion Facilitator: *Paul Hanlon, PhD, Abbott Nutrition, Columbus, OH* Panelists: *Roxi Beck, Center for Food Integrity; Nega Beru, FDA; Alan Boobis, Imperial College London; Michael DiNovi, FDA; and Joseph V. Rodricks, Ramboll Environ*
Summary and Discussion of Communication Strategy: Why "Just the Science" Misses the Mark *Roxi Beck, Center for Food Integrity, Gladstone, MO*

Abbreviations: FDA, Food and Drug Administration; ILSI, International Life Sciences Institute.

The workshop provided a unique forum and brought together scientists from government (US Food and Drug Administration, National Cancer Institute, Health Canada, and Spanish National Research Council), academia, and industry to discuss different criteria for strengthening the framework and to gain consensus on the path forward. The workshop began with several introductory presentations by members of an expert panel designed to provide background on the issue (Table 1; workshop agenda with list of speakers and panelists). This was followed by a presentation of the draft decision tree developed by the committee, describing a risk-based process for mitigation of process-formed compounds. A panel then provided further discussion and obtained real-time feedback from participants on the draft decision tree and ideas for the development of decision criteria and identification of data gaps. The workshop ended with a presentation and discussion of communication strategies, with the recognition that the ultimate success of the proposed process depends on effectively communicating its value to the larger scientific community and, ultimately, the public. Following the workshop, the committee updated the decision tree and solicited further feedback from workshop participants. This article presents a summary of the workshop proceedings and provides an introduction to the final version of the decision tree. This decision tree is expected to serve as the foundational document for the scientific community and potentially regulatory agencies for addressing process-formed compounds.

Problem Definition: Focusing on Risk Rather Than Hazard

In its simplest form, risk is the product of hazard (ie, toxic potency of a chemical) and exposure (or dose); as exposure increases, the risk of the hazards occurring also increases.[8] This concept formed the original basis for what is known as "risk-based" decision-making. An example of a risk-based decision would be estimating exposures at which the risk of the hazards occurring is negligible and thus could be considered "safe." In contrast, "hazard-based" decision-making is based solely on hazard without any consideration of exposure. An early example of a hazard-based decision is the Delaney Clause, which states that any chemical that is an animal or human carcinogen cannot be deliberately added to food (72 Stat. 1784; 1958), regardless of whether the amount of the chemical in food presents any risk to consumers.

More recently, there has been increasing pressure for hazard-based decision-making for chemicals, which dictates that all efforts should be taken to reduce chemical exposure.[9,10] Although hazard-based decisions are less resource intensive (only requiring information on hazard), they provide no information as to whether reducing or eliminating exposure actually provides any public health benefit.[11] On their own, the development of hazard characterizations might be adequate for "readily avoidable" substances (eg, food additives) because the exposure to these substances is tightly controlled. However, hazard characterizations alone are inadequate for substances that are "not readily avoidable" (eg, environmental contaminants, naturally occurring chemicals, process-formed compounds) because exposure cannot be easily eliminated and even reducing exposure may involve risk trade-offs and/or technical limitations. Furthermore, hazard-based assessments are not consistent with most legal requirements to consider risk, not just hazard, when promulgating regulations.

Alternatively, risk-based decision models consider the following factors: (1) a hazard characterization that estimates maximum exposure conditions at which adverse effects are unlikely to occur (ie, safe dose such as the acceptable daily intake [ADI]), (2) an exposure assessment that provides an estimate of the amount to which consumers are likely to be exposed, and (3) and a risk characterization that estimates the probability (likelihood) that an adverse effect will occur in a population under various conditions of exposure.[12] Accordingly, better methods are needed to more effectively and efficiently evaluate risk in support of risk-based decisions, while at the same time accounting for and communicating the uncertainties associated with those decisions.

Regardless of the decision model, it is important to recognize that attempts to mitigate one type of risk may also increase another type of risk, given the number of process-formed compounds and other not readily avoidable substances and the complexity of food. Thus, any decision model for evaluating mitigation of these compounds should allow for an assessment of risk trade-offs to minimize the net risk to public health.[13,14]

Refining the Assessment of Hazard and Risk

Hazard Assessment

The fundamental premise of food safety assessment is that all substances purposely added to food are expected to be safe. In practice, this takes the form of establishing target concentrations for compounds in foods. Ideally, this involves establishing a "bright line" that defines an amount of a chemical that can be consumed on a daily basis over a lifetime without appreciable health risk. However, other approaches have been used, such as those that instead use the exposure margin rather than a bright line. The target for risk management can be established in many different ways, depending on the needs of the risk assessment and on the information available for the specific compound. Some of the mechanisms that have historically been used to define this target for chemical contaminants include the ADI, threshold of toxicological concern (TTC), margin of exposure (MOE), and human target dose (HD^{I}_{M}).

Acceptable daily intake. An ADI, also referred to as a reference dose or tolerable daily intake, is defined as an estimate of the amount of a compound that can be ingested daily over a lifetime without appreciable health risk (Environmental Health Criteria No. 70).[15] The ADI approach derives values by estimating a point of departure (eg, no observed adverse effect level [NOAEL] or benchmark dose [BMD]) from an observed dose–response curve and applying factors to account for possible differences between animals and humans and variability within the human population. The ADI approach depends on the ability to define a threshold for the adverse effect and is applicable for most general toxicological end points. The ADI approach is not typically used for end points such as genotoxic carcinogens, where it is assumed there is no threshold. As an example, an uncertainty factor of 100 has historically been applied to a NOAEL to determine the ADI for most compounds directly or indirectly added to food.[16] However, more sophisticated methods can be used to apply uncertainty factors to account for information such as species differences in pharmacokinetics or mechanism of action.

Threshold of toxicological concern. The TTC approach is a de minimis approach that has been used across a number of industries to help prioritize chemicals in cases where the available data are limited and/or insufficient to develop chemical-specific thresholds.[17-19] Rather, the TTC approach takes advantage of the distribution of toxicity data available for hundreds of chemicals for which cutoffs (thresholds) have been developed for broad structural classes of chemicals (eg, Cramer classes, potentially genotoxic compounds). The TTC for a particular category is then used for a chemical that fits into that category. This approach has been applied to certain categories of substances in food.[18,20]

Margin of exposure. The MOE is the ratio of a point of departure (eg, an NOAEL or BMD) to human exposure for a specific compound. Unlike determination of an ADI, in which factors are applied to account for specific uncertainties in the derivation of a safe value, the difference between the point of departure and estimated exposure generated in this approach is a mathematical expression, without consideration of whether this margin is sufficient to ensure safety. Thus, the MOE is not in and of itself a quantitative measure of risk.[21]

A benefit of the MOE approach is that it allows a numerical expression of increased safety (reduced risk) that may accompany a reduction in exposure, with a "significant" increase in the MOE signaling and a significant reduction in risk. However, the challenge is defining the extent of an increase in MOE that is necessary to be considered significant. This approach can still be used for risk management purposes by setting a target of a specific MOE. It is often used in carcinogen risk assessment, in which upper-bound estimates of cancer risk at low doses are derived from the point of departure, and in the absence of evidence to the contrary, a linear no-threshold dose–response curve below the point of departure (ie, 0 risk at 0 dose) is assumed.[22-24] In addition, EFSA has concluded that an MOE of 10,000 or higher (based on the lower confidence limit of a BMD assuming a 10% response rate [BMDL10] from an animal study) for a genotoxic carcinogen present in food would be "of low concern."[25]

Human target dose. The most recent method is the HD^{I}_{M} approach that has been proposed by the International Programme on Chemical Safety.[26] The HD^{I}_{M} approach determines a bright line by setting a goal for the fraction (incidence) of the population that shows an effect of a specific magnitude (severity). For example, a HD^{05}_{10} is the human dose at which 10% of the population shows a 5% change in the effect.[26,27] Like the ADI and MOE approaches, this method also requires compound-specific data; however, this approach is geared toward probabilistic analysis, rather than providing only a single value. The benefit of using this method is the ability to more accurately define the bright line in terms of both the percentage of the population that would exhibit an adverse effect and the severity of that effect.

All of these methods have inherent uncertainties, although some more than others. Regardless, it is imperative that any decision model explicitly acknowledges the inherent uncertainty in the assessment and the impact of that uncertainty on the decision(s) made.[28]

Exposure Assessment

Estimated daily intakes (EDIs), which are based on the food(s) impacted, how much is consumed, and the concentration of the substance in the food(s), can be compared to the ADI to assess safety. Estimated daily intakes well below the ADI (EDI << ADI) are clearly of no concern, whereas EDIs well above the ADI (EDI >> ADI) are clearly of concern. However, when EDIs approach or even slightly exceed the ADI (EDI $\approx$ ADI), it becomes increasingly important to better understand the basis for these values (eg, single food vs foods across the diet, ongoing vs sporadic events, length of dietary survey, acute vs

chronic toxicity, dose response, population-level differences in sensitivity to the chemical, and distribution of exposure across a population).

Examples of dietary exposure assessments for process-formed compounds that have been completed or are ongoing include acrylamide,[6,29-31] furan,[31-33] polycyclic aromatic hydrocarbons (PAHs),[29,34] and MCPDs.[35] In general, process-formed compounds are ubiquitous in many foods in the diet (eg, potentially all cooked foods); thus, the focus has been on evaluating chronic exposure and toxicity. Sufficient data must be available to provide not only a robust assessment but also an understanding of outstanding uncertainties (eg, adoption of mitigation measures is more easily confirmed for institutionally prepared vs home-cooked foods). In addition, unlike the bright-line safety assessments for substances intentionally added to food (readily avoidable), dietary assessment of process-formed compounds should consider the range of possible exposures, not just a single-point estimate, which can be combined with dose–response modeling to evaluate risk. Finally, mitigation measures should not be contemplated without also considering the potential economic and public health impacts (eg, cost of mitigation vs benefit of risk reduction).

Acrylamide and furan are early examples of dietary assessments of process-formed compounds.[30,33] At the time of the discovery of acrylamide and furan in various foods in 2002 and 2003, respectively, multiple agencies across the world quickly assessed dietary intake of these chemicals. Since then, there has been worldwide attention on the presence of acrylamide in various foods, potential for dietary exposure and associated health risks (neurotoxicity, cancer), and possible mitigation measures. Acrylamide is formed from nutrients naturally present in food (asparagine, reducing sugars) as a result of traditional cooking methods (heating) during food processing and at home.[31] The US Food and Drug Administration (FDA) has conducted extensive surveys of acrylamide in food, amassing approximately 2,600 samples by 2006. The FDA exposure assessments in 2003, 2004, and 2006 were essentially the same[30] and generally consistent with assessments conducted internationally.[29] Twenty foods (of 66 food categories included) comprised approximately 90% of the mean acrylamide dietary intake.[30] As noted during the workshop, the FDA collected approximately 1,300 additional samples in 2011 to 2012, which will be added to their database at some point in the future.

The Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) has conducted 2 assessments of the potential health risks associated with dietary exposure to acrylamide,[29,31] with the latter assessment based on updated exposure and toxicity information. Both assessments resulted in similar estimates of the MOE (300-310 for average consumers and 75-78 for high-end consumers), which the JECFA committee considered low for a compound considered genotoxic and carcinogenic in animals and concluded that acrylamide may be a potential human health concern.[29,31] Based on these assessments and those by FDA and others, EDIs of acrylamide have remained fairly consistent even as more information has become available.

As presented at the workshop, the FDA's current dietary assessment for acrylamide also illustrates that potentially dramatic mitigation measures (eg, removing all acrylamide from French fries) would result in only small changes in overall dietary exposure ($\sim$16%-18% reduction at the mean and 90th percentile, respectively). Removing all acrylamide from snack foods, breakfast cereal, or coffee would also not significantly reduce exposure. Less dramatic, more economical mitigation measures would result in even smaller changes to overall dietary exposure, likely so small as to be indistinguishable given the uncertainties in the assessment. The same would be true for mitigation measures to reduce aflatoxin in peanuts and methyl mercury in fish. Thus, rigorous dietary exposure modeling can be useful for evaluating the potential impact of different mitigation plans; however, it is important to recognize that uncertainties in the dietary assessment, as well as in the dose–response modeling, can obscure potential benefits.

The FDA has done some preliminary work on 3 other process-formed compounds: furan, MCPD, and glycidyl esters. Furan was discovered in food not long after acrylamide; in 2004, the FDA recognized that furan was present in a wide variety of foods.[36] Unlike acrylamide, furan is formed by multiple mechanisms,[37,38] making mitigation efforts even more challenging. The FDA has sampled many foods for furan and completed a dietary exposure assessment, with brewed coffee being the largest source of furan in the adult diet.[33] The JECFA conducted an assessment of furan in food in 2010, identifying MOEs that were 3 to 4 times higher than for acrylamide (960 for average consumers and 480 for high-end consumers) but concluded that furan may also be of concern to human health.[31] The Codex Alimentarius Committee on Contaminants in Food concluded that there was insufficient information on mitigation of furan to develop a code of practice.[39]

Finally, MCPD and glycidyl (both free and ester) can be formed during thermal processing of edible oils. Although it remains unclear how the potency of consumed esters compares to that of consumed free MCPD,[32] assessment of these compounds is ongoing at multiple national risk assessment agencies.[35] 3-Monochloropropane diol and glycidol are considered possible and probable human carcinogens, respectively,[40,41] although 3-MCPD does so through a nongenotoxic mechanism. Early FDA efforts focused on the development of a suitable analytical method, which was followed by a limited survey in retail and industrial samples covering 25 different plant/animal sources.[42] Higher levels were found in refined versus unrefined oils, with the highest levels found in palm oils. The FDA conducted a feasibility study for safety assessment of 3-MCPD and glycidyl esters in refined oils.[43] These compounds are also on JECFA's priority list of contaminants and naturally occurring compounds,[44] with a request for both a hazard assessment and an exposure assessment. Other international efforts are primarily focused on the collection of occurrence data; however, there are also ongoing projects

addressing the toxicology and analytical measurement of these compounds.[44]

Assessing Approaches for Mitigation of Process-Formed Compounds

The ultimate goal of mitigation is to reduce consumer exposure to a process-formed compound in a manner that reduces risk to consumer health. There are many processes available that can be used in efforts to reduce consumer exposures to process-formed compounds, some of which target reduction in the concentration of the compounds in foods and some of which reduce the probability of consumers being exposed to foods that contain significant amounts of those compounds. In some cases, the most effective approach could be a combination of multiple approaches. Available methods include (1) setting regulatory limits for these compounds in specific food types, (2) setting action levels or indicative values, (3) developing guidance on the production of foods at high risk for containing significant amounts of these compounds, or (4) providing consumer guidance. Acrylamide provides a good example of many of these types of efforts to reduce dietary exposure.

Setting Regulatory Limits

Many regulatory agencies have set specific regulatory limits for the concentrations of not readily avoidable compounds in foods.[45] These regulatory limits define acceptable concentrations of substances within individual food categories, and many regulatory agencies have adopted this approach for a number of substances, including the European Commission,[46] Health Canada,[47] Codex Alimentarius,[48] and the China Ministry of Health.[49] Although some process-formed compounds (PAHs, MCPD) have been controlled through this mechanism, acrylamide and a majority of process-formed compounds are not controlled this way.

Setting Action Levels or Indicative Values

As opposed to regulatory limits, which represent levels of substances in food above which the food becomes noncompliant with the regulations of a country, action levels or indicative values represent concentrations of substances in foods that, when exceeded, trigger the need for further investigation. The result of this investigation could be that additional action should be taken, but exceeding an action level or indicative value in and of itself is not the definitive indication that action is necessary. This approach has been taken by some regulatory agencies. For example, the European Commission has adopted indicative values for acrylamide in a number of food categories.[50] Although process-formed compounds have not been specifically addressed in this manner, the FDA has used this approach to mitigate other not readily avoidable contaminants such as aflatoxins and polychlorinated biphenyls (PCBs).[51]

Developing Guidance on the Production of Foods at High Risk for Containing Significant Amounts of Process-Formed Compounds

The approach of establishing regulatory limits or action levels/indicative values can be used either proactively as a target for researchers or manufacturers for changing manufacturing practices/processes to produce food that contains lower levels of process-formed compounds or reactively to address foods that have already been produced and are in the marketplace. The former approach has been used extensively for acrylamide, in which there have been international research efforts from academia, government, and industry to develop recommendations for process changes as a means of reducing exposure. For example, FoodDrinkEurope, a trade body representing Europe's food and drink industry (formerly known as the Confederation of the Food and Drink Industry of the European Union), developed and has continued to update a "toolbox" that identifies the most effective means for reducing acrylamide in a variety of food products.[52] In addition, Codex Alimentarius, which is part of FAO/WHO, has issued a Code of Practice for the Reduction of Acrylamide in Food.[53] These guidelines address raw products, agronomy, ingredients that can be added to food, and food processing techniques to reduce acrylamide levels in the final consumed product. In the late 2000s/early 2010s, both Health Canada and the European Commission initiated monitoring programs to assess whether these industry practices were making a difference.[54,55]

In 2013, the FDA issued a draft guidance for industry that provides information to help growers, manufacturers, and food service operators to reduce acrylamide in certain foods (eg, potato and cereal-based foods).[56] This guidance is intended to provide a range of possible approaches, but it does not recommend specific mitigation measures nor identify any specific maximum allowable level or action level (eg, the indicative levels) for acrylamide in food.[56]

Providing Consumer Guidance

Another mechanism available to reduce consumer exposure to process-formed compounds is to provide guidance directly to consumers as to how they can minimize their exposure to these compounds. This mechanism is especially important for process-formed compounds that are created through processes consumers themselves use, such as preparing, cooking, or frying food. This is an approach that has been taken by the FDA for acrylamide, including publication of "questions and answers," last updated in 2013, as well as a 2013 Consumer Health Information pamphlet.[57,58] In both cases, the FDA suggests ways for consumers to reduce acrylamide in their diet (eg, storage and cooking methods for potatoes, color end point for potatoes, and toast) but also recommends against reducing intake of healthy grains. The FDA has also taken this approach for other not readily avoidable compounds, including guidance on fish consumption as a mechanism to mitigate exposure to methyl mercury.[59]

Summary

Regardless of which approach(s) is used, the goal of these efforts is to reduce the risk to the consumer by reducing exposure to the process-formed chemical(s). An important consideration for gauging the success of mitigation is conducting monitoring of foods to determine whether there is an actual decrease in exposure. In some cases, it may appear that mitigation has not actually decreased exposure, and although this may be interpreted as a lack of effectiveness, it could also indicate a lack of compliance with the implementations of the mitigation efforts.

However, as discussed later, a reduction in exposure does not necessarily result in a reduction in risk. In addition, it can also be difficult to predict the success of these efforts. For example, surveys conducted before and after the acrylamide guidance published in Europe in the early 2000s[60] indicated relatively little change in acrylamide levels in most foods, prompting the European Commission to issue the aforementioned indicative levels to trigger further investigation by the manufacturer when exceeded.[50]

Introduction to the Decision Tree Developed by the ILSI North America Technical Committee on Food and Chemical Safety

Prior attempts at developing a decision tree to address process-formed compounds have been reactive in nature (ie, mitigation efforts are contemplated only after a particular compound of concern has been identified[61]). Conversely, the goal of the framework in the form of a decision tree developed by the committee is expressly intended to be proactive, addressing process-formed compounds, known and unknown, encompassing all compounds including those with established threshold effects as well as compounds where the effects are assumed to have no threshold. Accordingly, the decision tree represents a multistep process that will require the cooperation of multiple technical disciplines, as well as risk managers and policy makers.

Not surprisingly, workshop participants, including the panel members, provided substantial feedback regarding the decision tree. Although the discussion was wide ranging, there was clear consensus that a "proactive" process such as that being proposed would be a significant improvement over the more "reactive" process currently being used to address process-formed compounds. There was also the recognition that the proposed process was complex and that the decision tree represented a major step forward in providing a better mechanism to assess the true risk posed by process-formed compounds and the protection of public health.

Several steps of the decision tree rely on criteria to determine whether a compound proceeds to the next step in the evaluation process. Workshop participants recognized that these criteria will be challenging to develop, not only from a technical perspective but also because of the need for acceptance by risk managers. Even once these criteria are developed and agreed upon, there will be additional challenges in using them to make decisions, given the relative uncertainty inherent in any risk assessment. For example, when comparing premitigation to postmitigation exposures, reducing exposure that was originally estimated to be above a bright line (eg, an ADI) to below the bright line is more easily concluded to be a significant reduction in risk versus a case in which the postmitigation exposure is lower but still above the bright line. In the latter case, although any reduction in exposure above a bright line could be construed significant, consideration of only exposure in this context ignores the more important factor of whether the reduction in exposure actually impacts risk. When potential mitigation does not reduce exposure below the bright line, more complex discussions are warranted that consider factors such as the importance of a change in the magnitude of MOE or how close the EDI is to the ADI (the closer the EDI is to the ADI, the less likely that a reduction in exposure would be significant). It was also recognized that these interim decision points represent important opportunities for interactions between risk assessors and risk managers, rather than waiting until the end of the process.

Finally, although not necessarily an overt component of the decision tree, both the panel members and the workshop participants recognized the importance of communicating the intent of this proposed process to the larger scientific community and, ultimately, the public. The workshop concluded with a presentation emphasizing the challenges of communicating scientific information to a nonscientific audience, particularly the importance of communicating the entire story (eg, what we know, what we don't know, not just what we want them to know) while making the information as relevant as possible.

Decision Tree for a Risk-Based Process for Mitigation of Process-Formed Compounds

The result of the workshop was the development and refinement of a proactive decision tree that could be used to guide decisions as to whether mitigation efforts would be effective, and if so, which mitigation efforts are likely to be the most effective (Figure 1). The decision tree is arranged into 5 components: prioritization (boxes 1-3), assessment of current risk (boxes 4-6), development of mitigation plans (boxes 7-9), evaluation of secondary effects of mitigation (boxes 10-12), and recommendations (boxes 13-15). Each component of the decision tree is discussed below.

Prioritization (Boxes 1-3)

Box 1: Risk-based ranking of process-formed compounds. This component entails identification of process-formed compounds and prioritization of the identified compounds for purposes of progressing through the remaining steps of the decision tree. In general, the goal of prioritization is to ensure that compounds that are most likely to pose a risk to consumers are addressed before compounds that are less likely, or unlikely, to pose a risk. Compounds that have a high hazard (such as

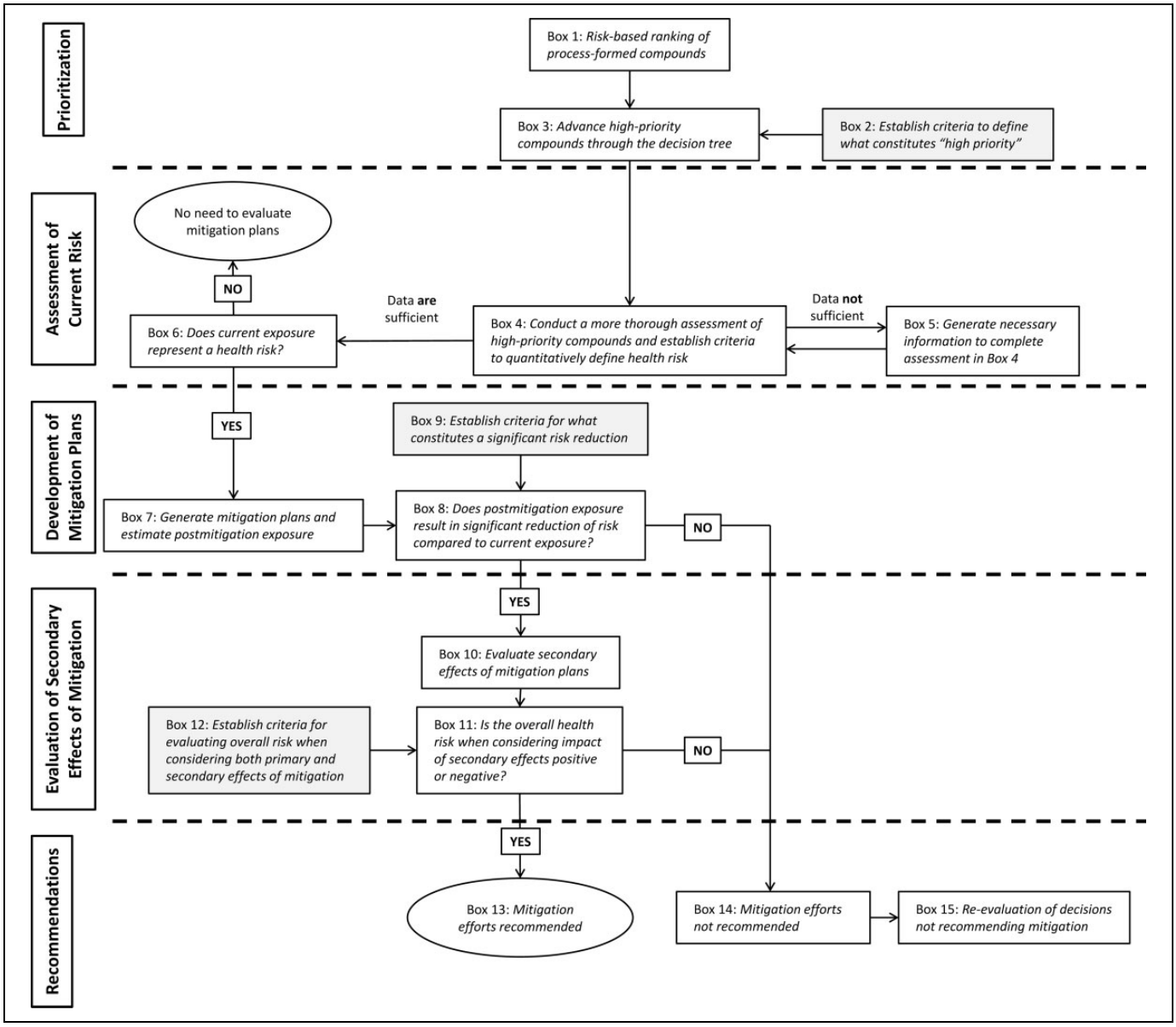

Figure 1. Final decision tree for a risk-based process for mitigation of process-formed compounds in food.

compounds with potential nonthreshold toxicity), high prevalence (such as those present in staple food commodities), or are present at high concentrations should be prioritized above compounds with low potential hazard, low prevalence, and low concentrations.

Importantly, to create a truly risk-based approach, process-formed compounds must be evaluated collectively rather than individually, as is the case today. This will allow for the comparison and ranking of risks across compounds necessary for prioritization. Given the large number of process-formed compounds (eg, there are at least 800 compounds formed during heating of food[62]) and the variable amount of hazard and exposure information likely available for these compounds, this step should utilize existing tools to make it less resource and data intensive. Ideally, this step would be quantitative in nature, recognizing that this might not be possible for all compounds.

Hazard assessment. Tools such as TTCs/Cramer Class,[17] structure–activity relationships/quantitative structure–activity relationships, or read-across, high-throughput screening, and "omics" may be useful for prioritization, especially for compounds with little existing data.[63,64] However, whatever approach is ultimately selected should be applied as consistently as possible across all of the compounds to ensure consistency in the prioritization process.

Exposure assessment. Where possible, exposure assessments should be based on measured concentrations of the compound in food. However, when such data are not available, it may be possible to group compounds into categories representing

similar exposures (eg, when data are available on the presence of a single PAH in a food category, extrapolations could be made for other PAHs) or prioritize compounds based on relative amount consumed (exposure to compounds present in highly consumed foods such as bread is likely to be higher than for compounds present in lesser consumed foods such as spices or herbs).

Box 2: Establish criteria to define what constitutes "high priority". The type and amount of data available may vary substantially across the universe of process-formed compounds. Accordingly, the specifics of this component will depend on whether the risk-based ranking described in box 1 is quantitative or qualitative in nature. If it is quantitative, then possible approaches include the following:

- setting a cutoff as to what "high" priority means,
- picking the top 10 (or 1%) of compounds, or
- creating a tiered approach in which a certain number, or percentage, of compounds is evaluated each year until all compounds have been evaluated.

If there is no way of quantitatively prioritizing compounds, additional discussion or research will be necessary to develop a strategy for selecting compounds to proceed through the decision tree. One concept that could be further explored is something analogous to the Risk21 visual matrix, in which compounds are grouped into categories of low, medium, or high risk, with high-risk compounds being carried forward.[65]

Other information could also be considered during the prioritization step, such as available information pertaining to secondary effects of mitigation or the impact that mitigation efforts are likely to have on exposure/risk. However, it is recognized that although further refinement could lead to more accurate prioritization, it would also require additional resources and time to account for the additional information. Regardless of the approach, the criteria used to prioritize compounds and to select those for further evaluation will need to be agreed upon by risk managers prior to initiation of the process.

Box 3: Advance high-priority compounds through the decision tree. This component simply represents the dividing line between prioritization and mitigation evaluation.

Assessment of Current Risk (Boxes 4-6)

Box 4: Conduct a more thorough assessment of high-priority compounds and establish criteria to quantitatively define health risk. Recognizing that prioritization may be based on limited hazard and/or exposure information, the objective of this component is to more comprehensively evaluate current exposure and define the objective of mitigation based on a refined hazard assessment (eg, achieving a certain ADI, MOE, or TTC). Thus, this box represents the hazard and exposure assessments that are then used in the risk assessment in box 6 to determine whether further action is needed for a compound.

Hazard assessment. The hazard assessment conducted during this step can take advantage of the different approaches to setting targets (eg, ADI, TTC, or MOE) discussed during the workshop and presented earlier in this article. It is not necessary to align on a single approach to apply to all compounds; instead, there may be compounds in which the most effective approach is to use an ADI, whereas it may be appropriate to use an MOE approach for other compounds. As noted by workshop participants, whichever approach is used to assess premitigation risk needs to be the same as for postmitigation risk. For example, it would be inappropriate to use an ADI to assess a compound before mitigation and then assess against the TTC after mitigation. In addition, uncertainties in the process need to be documented to the extent practicable in this and subsequent components in the decision tree.

Exposure assessment. The objective of the exposure assessment at this step is to refine the assumptions about the compound to more accurately inform the risk decision in box 6. Refinement of the exposure assessment could include additional information about the concentration of the compound in food categories (eg, additional analytical results), more detailed information about consumption of those food categories (eg, refined dietary intake studies), or more sophisticated models of exposure assessment (eg, Monte Carlo simulation of both the concentration of the compound in food categories and food consumption). Sophisticated exposure assessment techniques can be both resource and time intensive; thus, this level of assessment is not recommended during the prioritization phase (boxes 1-3); rather, it is only for those compounds that have advanced into the assessment of current risk phase (Boxes 4–6).

Box 5: Generate necessary information to complete assessment in box 4. One possible outcome of the initial assessment of a high-priority compound is that there is insufficient information to assess current health risks for that compound. Thus, the purpose of this component is to identify missing information (gap assessment) and then undertake the necessary research to generate that information. This component may entail a reassessment of the adequacy of other data sources such as read-across or in vitro or in silico methods before actually undertaking additional research. Once sufficient data are available, the compound would be reevaluated as described in box 4. Any determination that sufficient information cannot be generated for a high-priority compound should be communicated to the appropriate risk manager (or result in reprioritizing the compound to a lower tier).

Box 6: Does current exposure represent a health risk? The purpose of prioritization (boxes 1-3) is to identify the compounds that are most likely to pose a health risk. Although it is likely that high-priority compounds will be shown to represent a health risk, it is possible that the refined assessment in box 4 will result in the opposite conclusion. In this way, box 6 is the decision step based on the hazard and exposure assessments developed in box 4. For example, the estimated exposure can

be compared to a bright line (eg, ADI, TTC) established for that compound to determine whether the compound is likely to result in an appreciable health risk. One challenge of relying on these bright lines is the situation in which a value is slightly above or below the bright line. For example, given the uncertainties in both hazard and exposure, is there a difference in population-level risk for a compound with an ADI of 100 mg/d when the exposure is estimated to be 97 mg/d versus 103 mg/d? Ultimately, these criteria will need to be accepted by risk managers and other stakeholders. Compounds representing a health risk based on current-day exposures will proceed through the decision tree; otherwise, there would be no need to develop mitigation plans for that compound.

Development of Mitigation Plans (Boxes 7-9)

Box 7: Generate mitigation plans and estimate postmitigation exposure. This component entails generation of mitigation plans and assessment of postmitigation exposure. Ideally, this step would include evaluation of multiple mitigation plans/options (or even combinations of options) for reducing exposure to a process-formed compound, recognizing that development of even a single mitigation plan may represent a significant expenditure of resources. As previously described, examples include the following:

- setting regulatory limits for these compounds in specific food types,
- setting action levels or indicator levels,
- developing guidance on the production of foods at high risk for containing significant amounts of these compounds, or
- providing consumer guidance.

Postmitigation exposures would then be estimated for individual and/or reasonable combinations of mitigation options using the same methods as were used to estimate premitigation exposures, including characterization of uncertainties in the exposure estimates.

Box 8: Does postmitigation exposure result in significant reduction in risk compared to current exposure? This determination will be based on the criteria developed in box 9. If multiple mitigation plans appear to provide significant risk reduction, then all of these plans should advance to the next step of evaluating secondary effects, because a plan that appears to provide the most significant risk reduction may also have significant secondary effects (and thus not provide the best overall outcome). If none of the evaluated mitigation plans provide significant risk reduction, based on the criteria developed in box 9, then no mitigation efforts would be recommended (box 14).

Box 9: Establish criteria for what constitutes a significant risk reduction. Similar to box 4, this component will likely rely, at least initially, upon the targets, such as ADI or TTC, established earlier in the process (ie, if premitigation exposure is [presumably] above the ADI, but postmitigation exposure is below, then the mitigation plan [or plans] is predicted to result in a significant reduction in risk). Examples include the following:

- reducing the EDI from greater than the ADI to less than the ADI;
- increasing MOE to >10,000 for genotoxic carcinogenic compounds;
- decreasing exposure to below the TTC value for compounds, based on read across to chemicals with structural similarity; and
- decreasing exposure to below the HD_M^I.

As with prior decision criteria, acceptance by risk managers and other stakeholders will be required. Furthermore, as noted during the workshop, even after agreement has been reached on these criteria, there may need to be consideration of instances in which a mitigation plan does not result in postmitigation exposure falling below a bright line but may still be considered by some to be significant, especially when the premitigation exposure is far from the bright line.

Evaluation of Secondary Effects of Mitigation (Boxes 10-12)

Box 10: Evaluate secondary effects of mitigation plans. As discussed during the workshop, mitigation efforts can have unintended consequences such as increased risk for microbial contamination when decreasing the duration or temperature of thermal processing steps. Therefore, it is imperative that any mitigation plan predicted to result in significant risk reduction be further evaluated for potential secondary effects. This assessment would be conducted in a manner similar to that described for the postmitigation exposure assessment described in box 7.

Box 11: Is the overall health risk when considering impact of secondary effects positive or negative? This determination will be based on the criteria developed in box 12. If the overall effect is positive, then mitigation efforts would be recommended (box 13). Conversely, if the overall effect is negative (or neutral), then mitigation efforts would not be recommended (box 14).

Box 12: Establish criteria for evaluating overall risk when considering both primary and secondary effects of mitigation. This component may be the most challenging part of the decision tree and will likely require substantial additional discussion and/or research to reach consensus on an approach. The goals would be to:

- quantitatively evaluate the combined effect on human health of the proposed mitigation plan and any secondary effects (ie, a composite metric),
- establish objective criteria to determine whether the overall effect is beneficial (positive) or detrimental (negative), and
- compare the net impact of different mitigation efforts.

This is not a simple binary (yes/no) analysis; rather, it will likely involve some form of risk–benefit or risk–risk analysis. Examples of composite health metrics that may be used in such analyses are quality-adjusted life years and disability-adjusted life years.[66] In cases in which multiple mitigation plans are evaluated, additional criteria may be needed to objectively determine which plan has the greatest net impact. Such assessments are expected to be multifaceted, and agreement will be needed in terms of which parameters are considered (eg, magnitude, incidence, target population, as well as food quality and food safety factors). If quantitative objective criteria cannot be developed, then a process relying on expert judgment could be considered.

Recommendations (Boxes 13-15)

Box 13: Mitigation efforts recommended. If the assessment conducted in box 11 concludes that the predicted net health impact of mitigation is sufficient to justify implementation, then mitigation efforts would be recommended. This recommendation would be for a specific mitigation plan (or combination of plans) and would include a provision to reevaluate the effectiveness of mitigation efforts at some point in the future, as well as how accurately the original assessment model predicted the impact of mitigation.

Box 14: Mitigation efforts not recommended. If the assessment conducted in box 11 concludes that the predicted net health impact of mitigation is detrimental (or neutral), then mitigation efforts would not be recommended, at least at this time. This decision would require development of a communication plan explaining the rationale behind this decision to risk managers and other stakeholders.

Box 15: Reevaluation of decisions not recommending mitigation. It is possible, if not likely, that technological limitations may be part of the rationale for not recommending mitigation efforts (ie, the currently available technologies for mitigation simply do not provide a net health benefit). Accordingly, there is a recognition that the decision tree needs to include a process for reevaluating decisions recommending against mitigation should new technologies become available at some point in the future. Specific criteria as to what would trigger such a reevaluation have not been developed; however, one possibility is to place this responsibility on whoever is developing a new technology, with the decision tree serving as the tool for justifying that mitigation efforts would now be merited. The level of effort required for this reevaluation will vary depending on specific circumstances, but it is envisioned that not all reevaluations will entail going through the entire decision tree (eg, information on premitigation exposures may be sufficiently well characterized). Finally, the earlier stages of the decision tree (ie, changes in hazard identification and/or premitigation exposure assessment) may provide a mechanism for ''monitoring'' the need to reevaluate the merits of mitigation efforts.

Discussion

This workshop provided a forum among academia, government, and industry to discuss a new framework, in the form of a decision tree, for evaluation of process-formed compounds to improve upon current methods that have been less than optimal. Although this article may not account for all considerations around this topic, the decision tree provides the basis for fundamentally changing the process for evaluating the need for and benefit of mitigation of process-formed compounds. Rather than addressing individual compounds in isolation as they are discovered (a reactive process), the proposed decision tree represents an overtly proactive, risk-based process for addressing mitigation of process-formed compounds as a whole. This workshop resulted in a final version of the decision tree reflecting input from workshop participants and an expert panel. It was recommended to evaluate several case studies to demonstrate the utility of the decision tree. Future research in this area would define criteria for some ''yes/no'' decision points and methods for assessing net benefit of mitigation.

Many of the issues and/or questions raised during the workshop were addressed during the refinement of the decision tree, the final version of which is presented here (Figure 1); however, others are beyond the scope of the decision tree. One example is the reality that mitigation plans would be focused on exposure to a single compound via a single route of exposure (ie, oral exposure via the diet). For many process-formed compounds, there is potential for people to be exposed from other sources and/or exposure routes, and in some cases, such exposures may dwarf exposure from food (eg, acrylamide and smoking).[67] Such realities will need to be included as part of any communication plan regarding recommendations for or against mitigation efforts. As noted above, a key component of the decision tree is assessment of potential secondary effects of mitigation. This step will provide the opportunity to evaluate the potential impact of other compounds that may be unintentionally introduced and/or affected by the proposed mitigation plan.

Another reality is that the majority of the discussion on the proposed process was limited to process-formed compounds, whereas many other compounds with potential implications to human health, both beneficial and detrimental, are also found in food. There was also general agreement among the workshop participants that the decision tree is well suited to other not readily avoidable compounds such as naturally occurring chemicals (eg, mycotoxins, heavy metals) and widespread low-level environmental contaminants (eg, PCBs, pesticides). Existing processes for addressing more readily avoidable compounds, such as food additives, are likely sufficient for that purpose.

The purpose of the decision tree is to enable a risk-based, scientific evaluation of the need for and benefit of mitigation of process-formed compounds. The goal of the evaluation is to provide a recommendation as to whether mitigation efforts are warranted, based on whether mitigation will have a significant positive impact on food safety for consumers. However, the

predictive nature of the decision tree will be highly dependent upon the strength of the criteria that are developed to support this process. Those criteria should be developed in a transparent manner to meet the objective of the process gaining wide acceptance by the scientific community, regulatory agencies, and public. Nevertheless, the results of these evaluations will ultimately need to be considered and evaluated in the appropriate risk management context, such as in the creation of regulatory and public health policies.

In conclusion, the proposed risk-based process for mitigation of process-formed compounds is an ambitious effort to fundamentally change the status quo for addressing these compounds, many of which have been present in food for much of human history. The workshop was a significant step forward in efforts to improve public health by discussing a framework and gaining consensus on the final decision tree to effectively evaluate the potential risk posed by process-formed compounds. The workshop confirmed strong support for the decision tree for use within the scientific community and adoption by global regulatory bodies.

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Paul Hanlon contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted the manuscript, and critically revised the manuscript. Gregory P. Brorby contributed to analysis and interpretation, drafted the manuscript, and critically revised the manuscript. Mansi Krishan contributed to design, contributed to analysis and interpretation, drafted the manuscript, and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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