



A Risk-based Strategy for Controlling Chemical Contaminants as Relevant Hazards in Food Ingredients

ABSTRACT

The global sourcing of ingredients and distribution of products has dramatically increased over the past decade and so have challenges of food safety. While regulatory values for chemical contaminants can be a guide, formulating a comprehensive program to address chemical contaminants can be complex because of differences in priorities between regulatory agencies. Factors such as the source of contamination, the origin of ingredients, production of contaminants through manufacturing processes and adulteration of food for economic purposes, necessitate considerable effort to control contaminants. Establishing criteria that use scientific principles could be the basis for development of a risk-based program to manage chemical contaminants in ingredients. This would allow for compliance to global regulatory requirements and ensure the production of safe products. Therefore, this paper outlines the use of scientific principles to define the criteria associated with the severity of toxicity caused by chemical contaminants and the probability that a chemical contaminant would be present. Furthermore,

the application of science-based criteria to generate rationalized target lists of chemical contaminants specific to ingredient categories can guide the development of analytical methods critical for the control of chemical contaminants. Fundamentally, this is the first publication of its kind that provides a science-based approach that can serve as an assessment tool to measure, modify and improve management strategies for chemical contaminants in food ingredients and ultimately ensure food safety and regulatory compliance.

INTRODUCTION

Chemical contamination of food can occur through multiple mechanisms, including those resulting in naturally-occurring chemicals such as mycotoxins (34) and heavy metals (13); contaminants produced via manufacturing processes such as acrylamide (32) and 3-monochloropropane-1,2-diol (3-MCPD) (12); and intentionally-added economic adulterants such as melamine (33). Regulatory agencies around the globe have recognized the risks that chemical contaminants pose to the food supply

and have therefore established limits for many of these compounds in different categories of food, with the goal of protecting the public from exposure to levels of these contaminants that could result in adverse health effects. Globally, there are over 40 unique chemicals are regulated as contaminants in food (Table 1), not including pesticides and veterinary drugs (of which there are hundreds of unique chemical entities). Beyond regulation, chemicals in food require assessment on a case-by-case basis as part of food safety plans. The vast majority of these chemical contaminants are introduced into products via contribution from ingredients, rather than being created during the manufacturing of food products. Therefore, the control

of chemical contaminants should focus on ensuring that ingredients being used in the production of food products are not contributing sources of these contaminants.

The increasing complexity of the global food trade (15), combined with the patchwork of regulatory requirements, has created additional challenges to ensuring both that the food supply is safe and that it meets regulatory requirements comprehensively. Sourcing of food and food ingredients from different regions of the world dictates that the food industry must understand the unique risks of chemical contamination from each region. This can include awareness of how regional differences can impact the probability of naturally-occurring contaminants, but also how economic

TABLE 1. Examples of chemical contaminants regulated in food (8–11, 16–19, 26–28)

Mycotoxins

| | | |
|--------------|--------------|---------------------|
| Aflatoxin M1 | Aflatoxin G1 | Zearalenone |
| Aflatoxin B1 | Aflatoxin G2 | Deoxynivalenol |
| Aflatoxin B2 | Ochratoxin A | Fumonisin B1 and B2 |

Metals

| | | |
|---------|----------|----------|
| Lead | Tin | Copper |
| Mercury | Nickel | Chromium |
| Arsenic | Antimony | Selenium |
| Cadmium | Zinc | Iron |

Polycyclic aromatic hydrocarbons (PAHs)

| | | |
|-------------------|----------------------|----------|
| Benzo(a)pyrene | Benzo(b)fluoranthene | Chrysene |
| Benz(a)anthracene | | |

Polychlorinated dibenzo-para-dioxins (PCDDs), Polychlorinated dibenzofurans (PCDFs) and Polychlorinated Biphenyls (PCBs)

| | | |
|---------------------------------|--------------------------|---------------------------------|
| WHO-PCDDs (7 compounds) | WHO-PCDFs (10 compounds) | Dioxin-like PCBs (12 compounds) |
| Non-coplanar PCBs (6 compounds) | | |

Solvents

| | | |
|---------------------------|-------------------|-------------------|
| Hexane | Trichloroethylene | Ethylmethylketone |
| Methanol | Propan-2-ol | Methyl acetate |
| Dichloromethane | Dimethyl ether | Diethyl ether |
| Cyclohexane | Butan-1-ol | Butan-2-ol |
| 1,1,1,2-tetrafluoroethane | | |

Other contaminants

| | | |
|---------------|-----------------|--------|
| Melamine | Nitrate/Nitrite | 3-MCPD |
| Acrylonitrile | | |

adulteration can differ between regions. Marketing and manufacturing food in different regions of the world also necessitates that companies ensure that the foods are fit for human consumption and meet regulatory requirements, at a minimum, for chemical contaminants. In some cases, such as in the European Union, regulations also require that companies take steps to ensure that the food ingredients that they are using also comply with all relevant chemical contaminant regulations (17).

However, there are many challenges to applying a food safety standard ensuring compliance to the various national chemical contaminant regulations. Because of the necessary prioritization of chemical contaminant regulations and the complexity of the number of different foods that are present in the food supply, national regulations do not define limits for all relevant chemical contaminants for every possible category of food. Likewise, this prioritization of chemical contaminants results in different contaminants being regulated in some countries but not others (Table 2). Additionally, countries often define limits for certain chemicals in different categories of food and/or set different acceptable limits within the same food category (Table 3).

The importance of setting limits for chemical contaminants in ingredients and products is especially significant considering that many chemical contaminants (Table 1) are inherent in the environment and therefore will always be present at trace amounts in the food supply. In such cases, it is important to understand that as analytical methods

continue to improve and capabilities of detection increase, contaminants will be found with greater frequency in foods. However, these trace amounts, often at concentrations in the parts per billion or even parts per trillion ranges, may not be relevant to health (23). This brings up the importance of being able to use regulatory limits to demonstrate that the presence of trace amounts of these chemical contaminants is highly unlikely to pose a risk to human health.

The challenge to global food companies is to create a program of controlling chemical contaminants that ensures the safety of products, as well as regulatory compliance. Establishing a scientific, risk-based approach to define target lists and limits for chemical contaminants in food categories would enable companies to reduce the risk of ingredients and products exceeding national regulations. Also, such an approach would increase the public's confidence that the food supply is safe and demonstrate to regulators that the risks associated with contaminants are being addressed. In this paper we define a process for using an objective, risk-based assessment to create target lists of chemical contaminants for categories of ingredients. Establishing this process will allow companies to use the same concept to develop target lists for the ingredient categories that are relevant to them.

A RISK-BASED APPROACH TO IMPLEMENTING CONTAMINANT TESTING

The risks that individual chemical contaminants pose to food products are highly dependent upon the ingredients

TABLE 2. Global chemical contaminant regulations for foodstuffs

| | Codex ⁽⁹⁻¹¹⁾ | European Union ⁽¹⁶⁻¹⁸⁾ | India ⁽¹⁹⁾ | China ^(8, 26-28) | Brazil ⁽³⁻⁶⁾ |
|------------------|-------------------------|-----------------------------------|-----------------------|-----------------------------|-------------------------|
| Aflatoxin M1 | X | X | X | X | X |
| Other mycotoxins | X | X | X | X | X |
| Heavy metals | X | X | X | X | X |
| Other metals | X | X | X | X | X |
| Melamine | X | X | | X | |
| Nitrates | | X | | X | X |
| 3-MCPD | X | X | | X | |
| Dioxins and PCBs | | X | | X | |
| PAHs | | X | | X | X |
| Pesticides | X | X | X | X | X |

TABLE 3. Categories of food ingredients referenced for Ochratoxin A

| | EU ⁽¹⁷⁾ | Codex ⁽⁹⁾ | India ⁽¹⁹⁾ | China ⁽²⁶⁾ | Brazil ⁽⁶⁾ |
|---|--------------------|----------------------|-----------------------|-----------------------|-----------------------|
| Aromatized wine | 2 ppb | | | | |
| Barley | | 5 ppb | 20 ppb | | 10 ppb |
| Beans | | | | 5 ppb | 10 ppb |
| Cocoa and chocolate products | | | | | 5 ppb |
| Dietary foods for special medical purposes specifically for infants | 0.5 ppb | | | | |
| Dried vine fruit | 10 ppb | | | | 10 ppb |
| Grains | | | | 5 ppb | 10 ppb |
| Grape juice | 2 ppb | | | | 2 ppb |
| Processed cereal-based foods for infants and young children | 0.5 ppb | | | | 2 ppb |
| Products derived from unprocessed cereals | 3 ppb | | | 5 ppb | 10 ppb |
| Raw wheat | | 5 ppb | | | |
| Roasted coffee beans | 5 ppb | | | | 10 ppb |
| Rye | | 5 ppb | 20 ppb | | |
| Soluble (Instant) coffee | 10 ppb | | | | 10 ppb |
| Spices | 15–80 ppb | | | | 30 ppb |
| Unprocessed cereals | 5 ppb | | | | |
| Wheat | | | 20 ppb | | |
| Wheat gluten | 8 ppb | | | | |
| Wine | 2 ppb | | | | 2 ppb |

that are being sourced as well as what products are being manufactured, and it would be difficult to create an appropriate, risk-based list of chemical contaminants that is applicable to the entire food industry. Therefore, rather than defining a static list, similar to what might be typically constructed for microbiological hazards of food, the purpose of this paper is to define the process that companies could subsequently use to develop target lists that are appropriate to their business.

A scientifically-founded, risk-based process for defining target lists of chemical contaminants can be broken down into the following four stages:

1. Defining the categories of ingredients
2. Defining the chemical contaminants that are in scope for these ingredients

3. Defining criteria for the severity of toxicity of chemical contaminants

4. Defining criteria for the relative probability of presence of a chemical contaminant

This process can be used to develop customized, risk-based target lists of chemical contaminants that allow for prioritization of the testing for the greatest potential health risk posed by various chemical hazard and ingredient pairings. The process can also be directional toward defining residual limits for target chemicals on a case-by-case basis.

Defining the categories of ingredients

Creating categories of food ingredients (e.g., proteins, fats and oils, grains, refined carbohydrates) is an important process when hundreds or thousands of ingredients are being sourced.

Categorization of the food ingredients allows for a generalized risk assessment process, simplifying the processes while still providing a conservative approach for ensuring ingredient and product safety as well as compliance to regulations. If sorted appropriately, ingredients in the same food category will have the same risks of chemical contaminants because of factors such as similarities in the source of starting materials or similar manufacturing processes.

Refined sugars such as glucose, sucrose and fructose are likely to have equivalent contaminant risks, as would refined oils such as canola, soy and safflower oil. However, the contaminants likely to be present in refined oils would be very different from those likely to be present in refined sugars, because of differences in source, manufacturing process and chemical properties of these two categories of ingredients. Grouping multiple ingredients together also has the benefit of using a consistent approach across multiple ingredients. However, the weakness of creating categories is that ingredients within a group could have specific contaminants that present a risk and therefore either could be missed because they are part of the category, or exceptions would need to be created to ensure they are adequately tested. Therefore, particular care must be taken to ensure that ingredients are categorized appropriately.

Since the general approach for grouping ingredients that are agriculturally similar has been followed by many regulatory agencies when setting limits for chemical contaminants, reviewing chemical contaminant regulations can be a good resource for developing ingredient categories that group together foods that are likely to have similar risks for individual chemical contaminants. For example, ochratoxin A is regulated in many different categories of foods by different regulatory bodies (*Table 3*), and these categories of food could be used to group together similar ingredients. Aligning the creation of ingredient categories with categories established by regulatory agencies will also aid in the process of defining limits on concentration for specific residuals.

When developing categories of ingredients, the criteria used to determine whether ingredients can be grouped into the same category should include details such as:

1. The source of the material (grain, fruit, milk, marine oil, etc.)
2. Ingredient manufacturing process (solvent extraction, chemical synthesis, fermentation product, etc.)
3. Chemical properties (lipophilic vs. polar, dry vs. liquid, etc.)

While it is possible that soy oil, corn oil, canola oil, sesame oil and sunflower oil have some differences in the contaminants present, because they are similar agricultural ingredients that undergo similar processing, a single target list could be developed. Ultimately the granularity of the

ingredient categories will depend on a particular company's portfolio of ingredients. It should also be noted that the consideration of chemical contaminants differs from the consideration of microbiological contamination from a food category perspective.

Ingredient categories should be well defined to aid in the identification of the proper category for new ingredients in order to reduce the possibility of ingredients being assigned to improper categories. Since category-specific target lists are established to ensure appropriate testing of all ingredients, assignment of ingredients to an improper category could result in testing the ingredient for the wrong contaminants and therefore creating a gap in the food safety system. Additionally, distinct categorization may be necessary in consideration of chemical contaminants resulting from economically motivated adulteration. Periodic evaluation of the ingredient categories to ensure that all ingredients are still appropriately grouped is also an important aspect of ensuring a sustainable program.

Defining the chemical contaminants that are in scope for these ingredients

A comprehensive list of chemical contaminants relevant to any of the ingredient categories identified in Stage 1 should be compiled, along with any chemical contaminants that are relevant to a firm's products that could be introduced through the use of sub-ingredients or processing aids. At this point in the process, it is not important to differentiate which chemical contaminants are relevant to each individual ingredient category, as that takes place during risk assessment. The list of possible chemical contaminants should be as comprehensive as possible in order to ensure that no contaminants were overlooked and in order to document the rationale as to whether a particular chemical contaminant was included in the target list for a particular ingredient category and not for another.

The list of potential chemical contaminants should include compounds covered by both relevant global food regulations as well as other food-related issue monitoring. A review of contaminant regulations found globally for food categories relevant to ingredients and products should identify a large percentage of relevant chemical contaminants (such as those in *Table 1*). However, to ensure that the process is both sustainable and as proactive as possible, the list of contaminants should include chemicals that might not be specifically regulated. Other resources include Web sites for national surveillance programs, such as the FDA Total Diet Study (<http://www.fda.gov/Food/FoodScienceResearch/TotalDietStudy/ucm184293.htm>), importation alerts, such as the EU Rapid Alert System for Food and Feed (<https://webgate.ec.europa.eu/rasff-window/portal/index.cfm?event=SearchForm&cleanSearch=1>) and known adulterants, such as the USP Food Fraud database (<http://www.foodfraud.org/>). Risks posed by chemical contaminants

are the subject of considerable ongoing research, and to ensure product safety, some chemical contaminants should be considered within food safety programs regardless of whether regulations have been established by regulatory agencies. This approach also allows incorporation of chemical contaminants that are relevant only to specific food ingredients, which may never reach a level at which they become a priority to regulatory agencies.

Creating a sustainable program requires that the list of chemical contaminants that are in scope be flexible and allow for the addition of new chemical entities. Again, at this point in the process the focus should be on identifying any contaminant that could be possible. This does not mean that all newly identified contaminants would necessarily be added to the target lists of all ingredient categories. Periodic review of this list would need to be carried out to ensure that the chemical contaminant program is sustainable.

Defining criteria for the severity of toxicity of chemical contaminants

Prior to assigning a severity rating to each of the chemical contaminants identified in Stage 2, criteria need to be established by which subject matter experts can objectively assign a severity rating to each contaminant. For over a decade, pharmaceutical manufacturers have used these criteria to create occupational exposure limits (29). While

the intent of these criteria is to create control limits for occupational exposure within the pharmaceutical industry, the criteria they use to create the groups may also be applicable to creating categories of severity of toxicity of known chemical contaminants of food (Table 4).

The number of categories can be expanded or contracted to fit the needs of the assessment. Within the realm of food safety assessments as categorized through Hazard Analysis Critical Control Point (HACCP)-type programs, consideration of severity may be reduced to a simple yes or no classification. Hence, Table 4 could be modified to accommodate the intended application of assessment. The table should be used as a guide only, and professional toxicological judgment should be used with a “weight of the evidence” approach. For example, a single response in the severe column should not automatically determine that a contaminant should be assessed as severe; instead, this would be determined by the overall weight of evidence, using these criteria as a guide that results in the classification of each contaminant.

In the case of aflatoxin B1, this mycotoxin is not acutely toxic to humans, but the weight of evidence would dictate assigning it to the severe toxicity category because of its action as a genotoxic carcinogen (20). In contrast, in the case of metallic tin, while exposure can result in moderate acute toxicity (2, 31), the amount of tin exposure needed to produce that toxicity, as well as the reversibility of

TABLE 4. Criteria for assessing the severity of toxicity of a chemical contaminant

| Criteria | Categories of severity of toxicity | | | |
|---------------------------------------|------------------------------------|-------------------------------|---------------|--------------|
| | Severe | High | Medium | Low |
| Typical acute toxic dose | < 0.1 mg/day | 0.1–10 mg/day | 10–100 mg/day | > 100 mg/day |
| Severity of acute effects | High | Moderate | Low–Moderate | Low |
| Toxicity medically treatable | Unlikely | Possible | Yes | Yes |
| Sensitizing potential | Potent | Moderate | Low | Low |
| Carcinogenic | Known in humans | Shown in animals | Unlikely | No |
| Reproductive / Developmental toxicity | Known in humans | Shown in animals | Unlikely | No |
| Mutagenicity | In vitro/ In vivo positive | In vitro/ In vivo positive | Unlikely | No |
| Chronic effects | Probable | Possible | Unlikely | No |
| Reversibility of toxicity | Unlikely | Possible | Probable | Probable |

that toxicity, would dictate assigning tin to the medium toxicity category.

In some cases, groups of chemical contaminants can be assessed together. For example, Polycyclic Aromatic Hydrocarbons (PAHs) all have a similar mechanism of action and similar toxicity characteristics; therefore, instead of classifying a list of dozens of compounds, it may be more efficient to assign PAHs as a group to the same category of severity, especially if the analytical methods used to detect these compounds and the process control mechanisms (e.g., manufacturing mitigation efforts) for these compounds are likely to be the same (1).

Professional expert judgment by individuals with training and experience in toxicology is important for these assessments. Since the severity category for the chemical contaminant (or group of chemical contaminants) is based on the inherent toxicological and pharmacological properties of the contaminant, the severity ranking is not dependent upon the category of food in which the contaminant is found. Therefore, the severity ranking of a contaminant will change only if new data are generated about the inherent toxicity of the contaminant. The addition of ingredients or categories of ingredients would not impact the severity ranking.

As indicated earlier in this manuscript, creating a sustainable process is important for defining the criteria of severity of chemical contaminants. After an initial severity ranking of all of the possible chemical contaminants identified in Stage 2, periodic review of the severity rankings should be established as part of the overall process. For example, identification of new scientifically-relevant data demonstrating additional toxicities for a contaminant could be incorporated into the overall food-related issue monitoring. In addition to periodic review of previously identified contaminants, another important process is to create an objective mechanism to rank the severity of *newly* identified contaminants, using the established criteria.

Defining criteria for the relative probability of presence of chemical contaminant

Likewise, a weight-of-evidence approach and professional expert judgment should be used to evaluate the likelihood that a contaminant would be present in a specific ingredient category. Again, criteria for judging this probability should be established prior to ranking probability, to maximize objectivity. The criteria presented in *Table 5* can be used as a guide for this assessment, although additional criteria or categories should be added as needed to refine and meet the objective of the assessment.

Unlike the severity assessment, the probability assessment is specific to each ingredient category established in Stage 1. To ensure applicability of the ranking to the entire ingredient category, the probability ranking of each chemical contaminant in each ingredient category should reflect the likelihood of occurrence in the ingredient *most likely* to contain the con-

taminant. Thus, the importance of categorizing ingredients appropriately is emphasized, as grouping together ingredients that are very dissimilar could result in the probability ranking for some chemical contaminants to be relevant only to a small subset of the ingredient category, but resulting in high probability for all ingredients in that category. Therefore, grouping dissimilar ingredients could result in a misguided focus on specific chemical contaminants in a particular ingredient category.

Evaluation of the probability of specific chemical contaminants in ingredient categories may result in a reassessment of the ingredient categories established in Stage 1, although redefining ingredient categories at this stage will not affect Stages 2 or 3. For example, while all vitamins could have initially been grouped together at Stage 1, ranking of the probability of occurrence of chemical contaminants at this stage could effectively separate water-soluble from oil-soluble vitamins. Separation of water-soluble and oil-soluble vitamins would avoid unduly conservative ranking of the probability of all contaminants based on the worst-case probability of occurrence in the larger group of all vitamins, and instead would allow for a risk-based ranking that assigns higher risk for hydrophilic contaminants to water-soluble vitamins and higher risk for hydrophobic contaminants to oil-soluble vitamins.

Professional expert judgment should also be used for this assessment, and it is important to involve subject matter experts from multiple disciplines. This will include individuals who are familiar with the sources of the ingredients and the manufacturing process for the ingredients, as well as those who are familiar with the data available either internally or in the peer-reviewed published literature in terms of what chemical contaminants are most frequently found in each food category. When this assessment is implemented by food manufacturers, formation of a cross-functional team may be an effective strategy.

As with the severity ranking, the assessment of probability should use the established criteria as a guide but should use a weight-of-evidence approach when assigning risk. For an ingredient category containing milk and milk products, aflatoxin M1 should be assigned to probable occurrence based on historical data demonstrating its presence and the known source of the contaminant (30). However, available data also demonstrates that aflatoxin B1 is not present in milk (30). Hence, the probability of occurrence of aflatoxin B1 in the milk and milk products category should be assigned to the remote category of occurrence.

Similarly, information about the source and nature of the ingredients within a category can be used to drive the determination of the probability of occurrence. There have been reports of antibiotic residues being identified in crops exposed to manure from treated animals (25). However, this would need to be considered along with the other criteria used to evaluate the probability of occurrence.

TABLE 5. Criteria for assessing the probability of chemical contaminants occurring in an ingredient category

| Criteria | Categories of Likelihood | | | |
|--|--|--|---|---|
| | Probable | Reasonably Probable | Potential | Remote |
| Potential for economic adulteration | Known examples of economic adulteration | Potential for economic adulteration | Unlikely potential for economic adulteration | No potential for economic adulteration |
| Historical data demonstrating presence of a contaminant in a commodity category or safety limits | Data demonstrating consistent exceeding of regulatory or safety limits | Data demonstrating periodic exceeding of regulatory or safety limits | Data demonstrating rare exceeding of regulatory or safety limits | Extensive data demonstrating contaminants are absent or consistently below regulatory and safety limits |
| Chemical properties of the contaminant | Chemical properties are highly compatible with those of the commodity category | Chemical properties are compatible with those of the commodity category | Chemical properties are somewhat compatible with those of the commodity category | Chemical properties are incompatible with those of the commodity category |
| Source of the commodity | The source of the commodity is a probable source of the contaminant | The source of the commodity may be a source of the contaminant | The source of the commodity is unlikely to be a source of the contaminant | The source of the commodity is highly unlikely to be a source of the contaminant |
| Manufacturing process | The manufacturing process is highly unlikely to remove the contaminant from the commodity or is highly likely to produce the contaminant | The manufacturing process is unlikely to remove the contaminant from the commodity or is likely to produce the contaminant | The manufacturing process is likely to remove the contaminant from the commodity and is unlikely to produce the contaminant | The manufacturing process is highly likely to remove the contaminant from the commodity and is very unlikely to produce the contaminant |

Thus, if the source of the ingredients is not of animal origin (e.g., plant-sourced carbohydrates or minerals), then the probability of occurrence of chemical contaminants such as veterinary drug residues at levels relevant to human health is remote.

To establish a sustainable process, the probability rankings for the chemical contaminants in the ingredient categories should be reviewed on a periodic basis, and processes should be implemented to ensure that when new information is identified, a way exists to change the probability rankings to reflect that information. The probability ranking of a category can be adjusted to be more or less probable based on the new information, and the probability ranking is likely to have the most impact on the target lists for ingredient categories. Additionally, with any new contaminant identified in Stage 2, a probability assessment should be conducted for all ingredient categories.

Example of the application of the process

Once the severity of each contaminant has been assigned, and the probability of occurrence of each contaminant has been determined for each ingredient category, the overall risk for each contaminant can be determined for each ingredient category by assessing the product of severity and probability. This is easily demonstrated as a matrix (Fig. 1), with the severity displayed along one axis and the probability displayed across the other.

The target lists for each of the ingredient categories are then created by defining the overall risk score that is required in order to add that contaminant to the target list. Determining the overall risk score required to add a contaminant to a target list should again be based on an evaluation of the data. The determination may require refinement upon evaluation of the initial target lists. The initial target lists created should be evaluated by subject matter experts to ensure that known, high-risk potential contaminants are included. Various national contaminant regulations can again be used as reference for this exercise.

| | | Probability of Contaminant in Commodity Category | | | |
|----------------------|------------|--|-------------------------|---------------|------------|
| | | Probable (4) | Reasonably Probable (3) | Potential (2) | Remote (1) |
| Severity of Toxicity | Severe (4) | High | Medium | Medium | Low |
| | High (3) | Medium | Medium | Medium | Low |
| | Medium (2) | Medium | Medium | Low | Low |
| | Low (1) | Low | Low | Low | Low |
| | | | | | |

FIGURE 1. Determination of overall risk using the product of probability and severity. The overall risk to a food ingredient from a chemical contaminant is the product of the probability of that contaminant being present and the severity of toxicity that contaminant would produce if it were to be present at a particular concentration. When displayed graphically, the combination of probability (columns) and severity (rows) can be used to assess whether the overall risk of the chemical contaminant in that ingredient category is High, Medium or Low.

Figure 1 provides an example of how the determination of overall risk can be conducted. In this example, the overall risk for each contaminant for each ingredient category is divided into high, medium and low risk. In practice, more or fewer categories of overall risk may be desired in order to differentiate testing frequencies or other classifications. Alternatively, instead of a matrix approach, the process can be thought of as a mathematical product, where the categories of severity and probability are assigned numerical values (see case study, below). This mathematical approach can be useful in determining overall risk to large numbers of contaminants or ingredient categories and reinforces a mostly objective, rather than subjective, assessment.

Once the in-depth assessments have been conducted in Stages 1–4, the mathematical process can quickly generate an overall risk assessment without additional technical expertise. An evaluation of risk should be developed to determine a threshold value that would add a potential contaminant to the target list for a specific ingredient category. Using this simplified example, if a particular target list were to include only high and medium risk contaminants (e.g., any contaminant that has scored a 6 or greater as the product of the severity and probability scores), the four hypothetical ingredient categories would each have different target lists (see the case study that follows for an example).

For this process to be sustainable, mechanisms must be in place that allow for changes in the target lists. The purpose of creating target lists may be to set the direction for testing. Evaluation of the analytical results from this testing can inform the probability ranking and lead to changes in target lists (either addition or deletion of contaminants from specific target lists). If, during the course of testing, a specific chemical contaminant included in a target list for

ingredients in the grain category has never been detected, then the probability ranking should be adjusted downward, which could then result in it being removed from the target list for that ingredient category.

CASE STUDY

Initial establishment of process

A processed food manufacturer is establishing a chemical contaminant testing program to ensure that the ingredients that are being used do not contain chemical contaminants at levels that would pose a food safety concern for consumers.

1. Defining the categories of ingredients

The manufacturer sorts all ingredients used in the manufacture of their products into four categories:

- Grains:
 - Such as flaked oats and barley flour
- Refined sugars
 - Such as glucose and fructose
- Milk-derived ingredients
 - Such as skim milk powder and whey protein concentrate
- Oils and oil-derived ingredients
 - Such as soy oil and monoglycerides

2. Defining the chemical contaminants that are in scope for these ingredients

The manufacturer performs an extensive search to identify all possible chemical contaminants that would be present in these ingredients and would then be introduced into products. Based on this review, four potential classes chemical contaminants were identified that would be relevant to any of these four product categories: heavy

metals (such as lead), mycotoxins (such as aflatoxin B1 and aflatoxin M1), economic adulterants (such as melamine) and process-formed toxicants (such as polycyclic aromatic hydrocarbons). In this example, classes of chemical contaminants (e.g., heavy metals) are identified for the purpose of the risk assessment, which is an option for manufacturers to follow. However, regardless of whether the manufacturer follows this process or conducts a risk assessment for individual chemical contaminants (e.g., arsenic, cadmium, lead and mercury), eventually the analytical target list must contain the list of all specific chemical contaminants.

3. Defining criteria for the severity of toxicity of chemical contaminants

The manufacturer employs a toxicologist who has the education, training and/or experience to be qualified to perform a severity assessment for these potential contaminants. The manufacturer establishes criteria for the severity assessment corresponding to the information in *Table 4*:

- Heavy metals – Severe Toxicity (4)
- Economic adulterants – High Toxicity (3)
- Mycotoxins – Severe Toxicity (4)
- Process-formed toxicants – Severe Toxicity (4)

4. Defining criteria for the probability of presence of a chemical contaminant

The manufacturer assembles a group of subject matter experts who can provide information about the chemical properties, manufacturing process, and historical presence of the chemical contaminants in each ingredient category. Based on a weight-of-evidence approach, the probability that each contaminant would be present in the ingredient category is established:

Heavy metals

- Grains: Reasonably probable (3)
- Refined sugars: Potential (2)
- Milk-derived ingredients: Reasonably probable (3)
- Oils and oil-derived ingredients: Potential (2)

Economic adulterants

- Milk-derived ingredients: Reasonably probable (3)
- Other ingredient categories: Remote (1)

Mycotoxins

- Grains: Probable (4)
- Refined sugars: Remote (1)
- Oils and oil-derived ingredients: Potential (2)
- Milk-derived ingredients: Probable (4)

Process-formed toxicants

- Oils and oil-derived ingredients: Probable (4)
- Other ingredient categories: Remote (1)

Generation of a target list using the process

The manufacturer calculates the overall risk score for all chemical contaminants in each of the ingredient categories by multiplying the severity and probability scores:

Grains

- Heavy metals
 - Severity (4) X Probability (3) = Overall Risk is **Medium** (12)
- Economic adulterants
 - Severity (3) X Probability (1) = Overall Risk is **Low** (3)
- Mycotoxins
 - Severity (4) X Probability (4) = Overall Risk is **High** (16)
- Process-formed toxicants
 - Severity (4) X Probability (1) = Overall Risk is **Low** (4)

The manufacturer determined that contaminants identified as either high or medium risk should be tested in each ingredient category, and that those contaminants identified as high risk should be tested with a greater frequency than those identified as medium risk. Thus, in this example ingredients in the “grains” category would be tested for heavy metals and mycotoxins, and mycotoxins would be tested with greater frequency than heavy metals. The manufacturer determined that contaminants identified as low risk pose an insignificant risk to products and therefore do not require any periodic testing.

Periodic review of the process

Once the manufacturer has implemented the process, the process must continue to be monitored to ensure that the criteria-based risk assessments and target lists are still valid. Using this example, the manufacturer has an annual review of the process to assess whether:

- new potential chemical contaminants have been identified
- there is new information that would alter the assessment of either the severity ranking of a contaminant or the likelihood that a contaminant would be present in a specific ingredient category

In the annual review of the program, the manufacturer’s subject matter experts reviewed all available information and made adjustments to the risk assessments that were completed at the initiation of the program. This re-evaluation could result in either increasing or decreasing the extent of testing, as demonstrated by the examples on page 99.

If during the course of the year, a number of reports have surfaced of an increasing number of incidents of economic adulteration of vegetable oils, this would result in the probability score for oils to change from remote

to potential, and thus, according to the manufacturer's program, result in an increase in the extent of testing for oil and oil-derived ingredients.

Oils and oil-derived ingredients

Economic adulterants

- Year #1 (prior to re-evaluation)
 - Severity (3) X Probability (1) = Overall Risk is **Low** (3)
- Year #2 (after re-evaluation)
 - Severity (3) X Probability (2) = Overall Risk is **Medium** (6)

Additionally, if over the same period of time the manufacturer generates analytical data demonstrating that mycotoxins were not detected in any grain ingredients, and additionally their grain suppliers provided them with years of historical data also demonstrating a lack of mycotoxins in their materials, this would result in the probability score for grains to change from probable to potential, and thus, according to the manufacturer's program, result in a decrease in the extent of testing of ingredients in the grains category.

Grains

Mycotoxins

- Year #1 (prior to re-evaluation)
 - Severity (4) X Probability (4) = Overall Risk is **High** (16)
- Year #2 (after re-evaluation)
 - Severity (4) X Probability (2) = Overall Risk is **Medium** (8)

DISCUSSION

The proliferation of analytical technology has greatly expanded the capabilities of chemical contaminant detection over the past several decades (22, 24). Development of new analytical methods can help identify sources of risk in the food supply, as well as help refine our understanding of exposure. However, in some cases analytical capabilities are being pursued that provide no additional value in terms of safety and instead generate data that is often misinterpreted in the absence of an understanding of how exposure translates into risk (14).

The process described here can be used to help guide the establishment of testing programs in three ways:

1. Defining which chemical contaminants are of the highest risk for different categories of ingredients
2. Defining the concentration of chemical contaminants that would be safe for consumers for the individual categories of ingredients
3. Ensuring that chemical contaminant testing programs are established that demonstrate compliance to relevant food regulations

Significant resources are required to develop validated methods for the detection of chemical contaminants in each relevant food matrix. Therefore, defining and prioritizing which contaminants pose the highest risk to each ingredient category using this scientific process allows for the allocation of these resources to the areas that can have the largest impact to safety. Similarly, identifying action levels that define safe levels of these chemical contaminants in ingredients is also valuable in guiding analytical method development, both in terms of which analytical methods to use and in terms of the sensitivity needed for those methods.

Especially in the case of chemical contaminants that are inherent in the environment (e.g., heavy metals, dioxins, PAHs, mycotoxins), the establishment of action levels and regulatory limits based on health risk is important, because it puts the objective of limit setting on protecting the food supply. Allowing action levels and regulatory limits to be set to the limit of detection shifts the objective away from ensuring the safety of the food supply and to the development of ever more sensitive analytical methods. However, the importance of setting contaminant limits on safety, and the concept that lowering exposure does not necessarily increase safety if the original exposure is already below the Acceptable Daily Intake (ADI), is a concept that must be carefully communicated to the public, where the prevailing attitude is often the need to reduce exposure to contaminants to zero (7, 21).

CONCLUSION

This paper defines a process for using a risk-based assessment to create chemical contaminant target lists for categories of food ingredients. This process represents a model that can be utilized to prioritize relevant chemical hazards within a food safety plan, ensuring both the safety of the food product and regulatory compliance. The process is not meant to define a fixed list of chemical contaminants that must be tested in each ingredient category, nor is it meant to define a list that cannot be modified. The key concept of this process is that it is a sustainable process that allows for customization of the target lists both to meet the specific needs of the entities that are creating the target lists and to provide room for updating and incorporating new information in the target lists. The challenges of controlling chemical contaminants in the current global marketplace, along with the growing amount of research being conducted in this area, necessitates a flexible approach such as is detailed in this paper. Implementation of processes like this can help ensure product safety and regulatory compliance, but establishment of a scientifically-founded approach to controlling chemical contaminants can also increase consumer confidence in the safety of their food.

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