by Roger Clemens, A. Wallace Hayes, and Claire Kruger

Understanding the Difference Between Hazard and Risk

There is growing awareness of the relationship between food and health. There is, unfortunately, little understanding of the fundamental concepts of hazard and risk as it is applied to the safety of our food supply. Dietary guidelines advise consumers to follow a plant-based diet for improved health, however, it is interesting to note that such foods contain a broad spectrum of toxins, carcinogens, and mutagens. For example, prussic acid, carotatoxin, and glycoalkaloids are found in cherries, carrots, and tomatoes, respectively (Ames et al. 1990; Crosby and Aharonson 1967; Friedman 2015). A number of mycotoxins have been identified in a variety of crops (Marin et al. 2013). In isolation, such substances are typically associated with adverse health events, yet they are ubiquitous to the plant kingdom. Importantly, these substances and the concentrations of these substances within a food matrix do not necessarily present a risk. Why is this?

To answer the "why" question, we are reminded of Paracelsus, a 16th century physician and father of toxicology, who is credited with proclaiming, "all things are poison and nothing is without poison; only the dose makes a thing not a poison" (Lane 2014). For example, insufficient doses of fat-soluble nutrients, such as vitamins A and D, can lead to frank deficiencies, whereas doses of 5,000 IU and 400 IU, respectively, are required for healthy adults. On the other hand, doses in excess of 1–2 orders of magnitude of these requirements may be neurotoxic or contribute to hypercalcemia, respectively (de Oliveira 2015; Araki et al. 2011).

These dose-outcome associations illustrate two important concepts. Those concepts are dose-response and hazard/risk relationships. An example of a dose-dependent transition is acetaminophen, the common analgesic in *Tylenol*. When consumed in excess, depletion of glutathione occurs and the normal pathway of excretion is overloaded with the production of the toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQ1), which induces liver damage (Holt and Ju 2006; Kane et al. 2015). To understand hazard/risk relationships, there is a need to recognize four basic principles: dose matters, timing is critical, people differ, and things change. The fat-soluble vitamin example previously noted illustrates the dose matters principle. All vitamins have Dietary Reference Intakes (DRIs) and Tolerable Upper Intake Levels (ULs). There is ample evidence that chronic exposure to excessive intakes of vitamins, particularly fat-soluble vitamins, can lead to harmful effects. Thus, the Institute of Medicine established a UL for many vitamins (IOM 2011).

Another interesting example is warfarin and *Coumadin*. Warfarin is an anticoagulant originally isolated from sweet clover that is used in many rodenticides to kill household and farm pests, such as rats and mice. The same chemical used at lower doses is a common drug administered to protect people against heart attacks, strokes, and thrombosis. The optimal dosing for these intended effects is complicated by dietary components, such as cruciferous vegetables that contain higher amounts of vitamin K1. This is important since warfarin antagonizes vitamin K1 recycling, which can lead to depletion of this nutrient (Holford 1986).

Coffee provides another example of dose relationships. Other than water, a cup of java is the favorite beverage in the global beverage market, including the United States. Coffee is chemistry in a cup. It contains almost 2,000 identified compounds, including caffeine and a spectrum of potential carcinogens. In the late 1970s, some investigators suggested an association between coffee, tea, and cola consumption (sources of methylxanthines) and the development of benign fibrocystic disease among women. This association was later rejected by many epidemiological data and case-control studies (Marshall et al. 1982). More recent studies indicate coffee also contains an array of substances that support health, including a reduced risk of diabetes and some forms of cancer (Higdon and Frei 2006).

Our understanding of reproduction biology provides a foundation of the "timing is critical" concept. For example, thalidomide, originally marketed in Germany nearly 60 years ago, was approved to reduce nausea associated with morning sickness. Shortly after its introduction as an over-the-counter medication, approximately 7,000 infants were born with phocomelia (malformation of the limbs). In this case, it is important for us to remember that during fetal development, arm and leg buds presentation occurs around 5–7 weeks of gestation. Maternal exposure to the developmental toxicant thalidomide during this sensitive stage of arm and leg development causes phocomelia. Recent clinical investigations with thalidomide support its use in treating several maladies, such as multiple myeloma (Rajkumar 2015) and colorectal cancer (Huang et al. 2015), symptoms associated with HIV/AIDS (Brunel et al. 2012), rheumatoid arthritis (Sathe and Khubchandani 2013), and a number of skin conditions that are not responsive to traditional care (Sharma and

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Kwatra 2015). These findings illustrate that when thalidomide is administered at the right dose and outside a critical period of human development, it does not produce phocomelia.

The third basic principle is that people differ. While the genetic makeup of humans is conserved, there are genetic variants called polymorphisms, most of which do not impact our health or development (http://ghr.nlm.nih.gov/handbook/genomicresearch/snp). These small changes lead to well-known differences in blood type, and less known responses to food ingredients and medications. With respect to ethanol, many Asians have a polymorphism involving alcohol metabolism that results in the inability to properly detoxify ethanol, which contributes to "Asian flush reaction" and an increased risk of alcohol-related oral cancer (Crow and Batt 1989; Druesne-Pecollo et al. 2009). In the case of the non-nutritive sweetener aspartame (*Equal*), there is a phenylketonuria warning label. This disorder affects approximately 1 in 10,000 babies and about 1 in nearly 13,000 adults in the United States (Berry et al. 2013). These people are unable to metabolize the essential amino acid phenylalanine, which leads to its bioaccumulation. The inability to metabolize phenylalanine to tyrosine results in neurological disorders, organ damage, and structural defects and may compromise pregnancy (Waisbren et al. 2015).

The fourth principle of risk assessment was illustrated by the Grecian philosopher Heraclitus, when he said that the only thing that is constant is change. The fact that things change is fundamental to metabolism. Changes occur in response to substances that we consume. The interplay of drug-food interactions, advanced by the late Daphne Roe, is common. One example is grapefruit juice, which can be part of a healthy diet, and yet several components of grapefruit juice, which contains an array of flavonoids, can alter the metabolism of statin drugs (Bailey and Dresser 2004). The evidence suggests flavonoids increase drug absorption and decrease its excretion. This issue is particularly important among those taking certain statin drugs in that bioaccumulation or altered metabolism of these drugs may elevate the risk of liver damage and kidney failure. Another example is the relationship between folic acid and anti-seizure medications, such as *Dilantin*. Folic acid metabolism involves methyl transport. *Dilantin*, on the other hand, interferes with methyl transport. This illustrates the delicate balance between maintaining nutritive status via folic acid, and reducing the risk of presenting seizures. In the realm of chemotherapy, a similar relationship exists between folic acid and methotrexate, an anti-folate medication. This medication inhibits methylation, a critical reaction in cell division, while the nutrient contributes methyl groups to maintain cellular health, including reducing the risk of developing neural tube defects during gestation.

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As news outlets and scientific publications sensationalize potentially negative aspects of the food supply, food ingredients, and food processing, a fundamental understanding of the risk assessment process, including differentiating between real risk and a perceived hazard, is critical. For example, a 1998 *Lancet* article suggested a link between the MMR (measles, mumps, rubella) vaccine and the development of autism (Wakefield 1998). Ultimately, this paper was retracted in response to the UK General Medical Council's Fitness to Practise Panel, which found the publication represented dishonest and irresponsible research (Dyer 2010).

Germane to the purported vaccine and autism issue, the Institute of Medicine did not discover any evidence that suggests such a link (IOM 2004). Subsequent research supports the absence of evidence of harm from vaccines that contain thimerosal (ethyl mercury) and rejects the previously reported relationship between the MMR vaccine and autism. While MMR vaccination rate experienced a decline following the scandal, current data indicate approximately 95% of children under kindergarten age receive vaccinations as recommended by the CDC (CDC 2014).

As we read and hear about the latest "risks" and "hazards" associated with the food supply and medications, it is important to remember a simple acronym, RITE (Risk Is Toxicity x Exposure). With respect to thimerosal and vaccines, there does not appear to be any plausible hazard. Additionally, thimerosal was never used in the MMR vaccine or in vaccines for chicken pox or polio in the United States. Thus, no hazard plus no exposure means no risk.

As we understand and apply these simple principles of risk assessment, the sensationalistic announcements of potential adverse effects often ascribed to foods, food ingredients, and food processing will be put in proper perspective. As noted above, the understanding of dose, critical timing of exposure, differences among people, and the role of metabolic change is critical in understanding the risk and hazard relationship. **FT**

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