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Advances in assessing ingredient safety

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ABSTRACT

The safety of food ingredients will be assessed in the 21st century by mixture of traditional methods, such as the "safe" dose concept, which is thought to be an accurate but imprecise estimation of dose below the population threshold for adverse effect, and contemporary methods, such as the Benchmark Dose (BMD), Chemical Specific Adjustment Factors (CSAF), physiologically-based pharmacokinetic models, and biologically-informed dose response modeling. New research on the horizon related to toxicology 21 may also improve these risk assessment methods, or suggest new ones. These traditional, contemporary and new methods and research will be briefly described.

1. Introduction

In one sense, risk assessment is preventive medicine. The safety assessment of food ingredients is an example of this. As a result, a multi-disciplined process and one that includes multiple risk assessment approaches, is reasonable. Today's talk is about traditional and contemporary methods, some of which are well known and some of which are not. We are going to touch upon these methods in general and with reference to some of the recent activity by the Food and Drug Administration's (FDA).

2. Traditional methods

Quantitative risk assessment requires calculations of two components of risk: the magnitude of the critical effect, and the probability that the effect will occur. In the context of public health, risk assessment is the process of quantifying the probability of a harmful effect to individuals or populations from certain human activities. Thus, you need a team of toxicologists, epidemiologists and clinicians to determine the critical effect, defined by The US Environmental Protection Agency (EPA) and others as the first adverse event (or its precursor if known) that occurs as the dose rate increases (EPA, 2002). While basic information about environmental risk assessments for the public is provided by the EPA, the Food and Drug Administration (FDA) regulates food safety through risk assessment (Merrill, 1997). In 1973 FDA required that cancer-causing compounds must not be present in foods at concentrations that would cause a cancer risk greater than 1 in a million over a lifetime. Other groups, such as the Stockholm Convention on persistent organic pollutants (POPs), provides a qualitative risk framework for public health from chemicals that display persistence, bioaccumulation, and toxicity (PBT) activity (Szabo and Loccisano, 2012) in both foods and environmental media.

Risk assessment is the determination of an observed or extrapolated value of risk related to a real situation and a recognized hazard. A typical dose-response curve is depicted in Fig. 1. Traditionally the hazard data are plotted versus the percent response and you get a dose-response curve. As you go down the curve until you find some point of departure where the experimental or observational data end; you can call it an 'effect' dose, benchmark dose (BMD) or a no observed adverse effect level (NOAEL). If you use a mathematical modeling approach, you can add in 'lower limits'. Then, if you are EPA (and some other agencies) and you have a carcinogen with a mode of action that is mutagenic, you might plot a linear slope to project a virtual safe dose. This is really a FDA concept going back to Arnold Lehman, an early toxicologist with FDA and on whom the Arnold Lehman award was named by the Society of Toxicology. Arnold Lehman published many articles about chemicals in food for such journals as *Advances*

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in Food Research, *Journal of Nutrition*, and the *Journal of the Association of Food & Drug Officials of the United States*.

To do a risk assessment on a food product, for example, requires the inputs of different disciplines:

1. *Hazard Identification* aims to determine the qualitative nature of the potential adverse consequences of any contamination and the evidence it can have that effect. This is accomplished by results of toxicology and epidemiology studies.
2. *Dose-Response Analysis* determines the relationship between dose and the incidence of effect. This requires extrapolating the results from laboratory animals to humans, and/or from high to lower doses. In addition, the genetic differences between individuals mean that the hazard may be higher for a susceptible population. In developing such a dose-response analysis, there needs to be accounting for the largely unknown effects of animal to human extrapolations, increased variability in humans, or missing data, by including safety factors in the estimate of the 'safe' dose, typically a factor of 10 for each unknown step.
3. *Exposure Assessment*, determines the amount of a contaminant that individuals or populations will receive. This is done by examining different scenarios of exposure at different location, lifestyles and other factors likely to influence the amount of contaminant that is received, especially by susceptible population(s).

Finally, the results of the three steps are combined to produce an estimate of an acceptable daily intake (ADI) and a comparison to the chemical's exposure. The resulting risk will vary within a population because of the different susceptibilities and exposures.

So you get a risk specific dose or virtual safe dose and an acceptable daily intake or a reference dose. The critical effect is the first adverse effect, or its known precursor, that occurs as the dose rate increases. So in this idea of looking at all the data, you want to look at the data that's most relevant. Are we worried about mortality in humans? Yes, but we don't study mortality in rats to find out what an ADI is for humans. We need to look at other kinds of effects; to look at this idea of critical effect, the first adverse effect.

In order to make good risk assessment decisions, a team of experts (toxicologists, epidemiologists and clinicians) are needed to look at all the relevant data and this can become very complicated. You need clinicians on your team to tell you, no, when you eat potatoes and you get an increase of stomach enzymes, that is a biological effect, it is real, you can record it and you can have

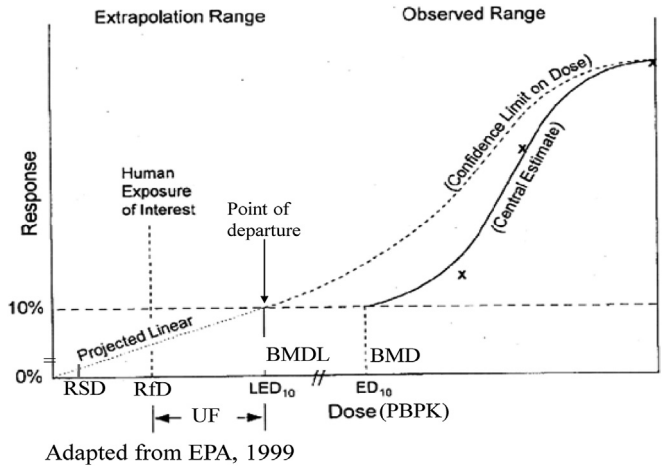

Fig. 1. Traditional method of safety assessment.

statistically significant findings. It doesn't mean anything from an adverse effect point of view, however, and yet you're going to find some toxicologists, and some epidemiologists, that are going to try to make decisions, these risk decisions, on the basis of effects that are not even adverse or of unknown adversity. For example, with an endocrine disruptor, effects might be observable down at very low levels, but this is not to say the effects are adverse. You need to work with teams and come to this decision. Safe exposures, such as the ADI, need to protect again adverse findings, but they need not need to protect against biological effects with no adversity.

To give an example, look at how the National Academy of Science (2004) reviewed perchlorate. Their first critical (adverse) effect was hypothyroidism (Fig. 2). Using the 'critical effect' as a base, the ADI for perchlorate would be the first adverse effect or maybe its immediate precursor (thyroid hypertrophy or hyperplasia). However, NAS did something unconventional and they started with a distant precursor, the inhibition of iodide uptake by the thyroid. This is a non-adverse effect. Yes, this is a safe dose but so is a dose higher or lower dose. In fact, any number of "safe" doses could be estimated depending upon the critical effect chosen. This is why the most appropriate choice of critical effect is the first adverse effect or its known and immediate precursor.

3. Traditional uncertainty factors

Traditional uncertainty factors for within human variability, experimental animal to human extrapolation, LOAEL to NOAEL, subchronic to chronic, and lack of certain data (data gaps) require a tenfold safety factor at each comparison. One common misconception is that variability of the human population is larger than a 10-fold variability, and so is the use of this factor large enough to be protective?

Laboratory animal variability data are very homogenous because they are all the same age, strain, and receive the same feed, water and husbandry. Humans are a much more heterogeneous group. Fig. 3a is a graph of a hypothetical cumulative response as a function of dose for both humans and rats, and Fig. 3b is response of dose for both humans and rats (adapted from Dourson et al., 2002). These data are hypothetical, but approximate real situations. The same human NOAEL or BMD and the animal NOAEL or BMD in Fig. 3a and b are plotted on both graphs; one dose against cumulative response and the other just response.

You get the expected bell shaped distributions of tolerance of adverse response. Each of these points represents some individuals at their low adverse effect level. That's where they started to respond. With the animal data reflecting homogeneity because they are from a laboratory experiment; the humans are more heterogenous, and the data more flattened.

Look at the data curves for sensitive, average and resistant humans in Fig. 3c (also adapted from Dourson et al., 2002). We do not apply a ten-fold safety factor to the most resistant person in the distribution; no, you go down to the low end of the distribution and divide this by ten. Human polymorphisms are 100–1000-fold; therefore, a tenfold safety factor may be enough to account for these polymorphisms, because of the way the 10-fold uncertainty factor is used.

4. Contemporary risk methods

A contemporary method in risk assessment is currently benchmark dose; and it has clear advantages and disadvantages (Casarett and Doull, 2001; Hayes, 2014): It uses responses near the range of observation, includes a measure of variability in the response, determines a consistent measure of response, and accounts for more dose response information of the critical effect. But