An Evidence-Based Approach to Reviewing the Science on the Safety of Chemicals in Foods

In considering the safety of chemicals added to foods, or present in foods due to environmental circumstances, we wish to answer the question, "Is there a causal relationship between dietary exposure to the chemical and adverse health effects in humans?". There is often insufficient or inadequate evidence to make a definitive judgement on this and we are often confronted with an array of diverse and often conflicting scientific information on which to assess the likelihood of a causal relationship. Each piece of information (a single study employing a particular study design) can be viewed as 'evidence' and, as with a court of law, the body of available evidence must be sorted and assessed to arrive at a sound judgement.

An evidence-based approach is a process of systematically reviewing, summarising and assessing the quality of published research on a particular topic. The process should be documented, transparent and reproducible (Agency for Healthcare Research and Quality, 2002).

A major US study reviewing systems to rate the strength of scientific evidence identified two major components of the assessment (Agency for Healthcare Research and Quality, 2002):

- Systems for rating the quality of individual articles; and
- Systems for grading the strength of a body of evidence.

These components will be considered separately.

Systems for Rating the Quality of Evidence

Not all evidence is judged to be of equal value in assessing a body of information. This has lead to the development of the concept of a 'hierarchy of evidence', with study designs near to top of the hierarchy being considered to be of greater quality or weight than study designs at lower points in the hierarchy.

While there is continuing debate on the hierarchy of evidence concept (McQueen, 2002; Petticrew and Roberts, 2003), a reasonably consistent hierarchy of study designs for clinical investigations has been reported (Agency for Healthcare Research and Quality, 2002; Petticrew and Roberts, 2003). The hierarchy, in descending order of quality, is usually presented as:

- Systematic reviews and meta-analyses
- Randomised controlled trials
- Non-randomised trials
- Cohort or case-control studies
- Cross-sectional studies
- Case series
- Individual case reports

In some circumstances, anecdotal evidence (e.g. non-clinical individual case reports) may be considered in an assessment of evidence. However, in the absence of higher

quality supporting evidence, anecdotal case reports will usually be considered as very low quality evidence.

While most publications on this topic are concerned with human clinical research, a more generalised version of the 'evidence pyramid' has also been promulgated, with three further (lower) study designs:

- Ideas, editorials, opinions
- Animal research
- *In vitro* research

See: http://phpartners.org/tutorial/04-ebph/2-keyConcepts/4.2.7.html

This expanded hierarchy of evidence is applicable to assessment of the safety of chemicals in food, where available evidence is usually a combination of clinical medicine, epidemiological and toxicological studies, and exposure assessment. An excellent example of this is the highly structured assessment approach adopted by the International Agency for Research on Cancer (IARC), which may include weighing evidence from most tiers of the evidence pyramid (see http://www.iarc.fr).

Indeed, safety assessment of chemicals in the food supply is often entirely dependent on animal and *in vitro* studies. In such cases the focus of an assessment of the information will be more focussed on the strength of the body of toxicological evidence (see below) than the quality of evidence (Guzelian *et al.*, 2005). For cancer-causing chemicals in particular there is a substantial history of causal relationship being established in animals prior to sufficient evidence being accumulated to establish causation in humans (see http://www.iarc.fr).

Systematic reviews use explicit and rigorous methods to identify, critically appraise, and synthesise relevant studies. This will include assessment of the methodologic quality of included studies and an evaluation of the overall strength of the body of evidence. Many of the safety assessments for chemicals in food carried out by international and national bodies meet the criteria for systematic reviews and can be viewed as high quality evidence.

Systems for Grading the Strength of a Body of Evidence

The Agency for Healthcare Research and Quality's review of systems to rate the strength of scientific evidence identified three main elements for systems to grade the strength of scientific evidence (Agency for Healthcare Research and Quality, 2002):

- Quality: the aggregate of quality ratings for individual studies, predicated on the extent to which bias was minimised;
- Quantity: numbers of studies, sample size or power, and magnitude of effect; and
- Consistency: for any given topic, the extent to which similar findings are reported using similar and different study designs.

These elements are consistent with more wide-ranging sets of elements proposed for considering whether experimental evidence can provide a case for concluding a causal relationship. While much discussed in the intervening 40 years, the elements proposed by the English epidemiologist and statistician Sir Austin Bradford Hill are still considered to be pertinent (Hill, 1965). These are:

- Strength. Strong associations are more likely to be causal than weak ones.
- Consistency. Similar results from different studies in different populations are more likely to represent a causal relationship than conflicting outcomes.
- Specificity. A unique relationship exists between the exposure and the effect. This is considered to be one of the weaker elements, as multifactorial causation and multi-effect exposures have been characterised.
- Temporality. For an exposure to be causal it must precede the effect.
- Biological gradient. Evidence of causation is strengthened if an increasing exposure dose increases the risk of the effect.
- Plausibility. The existence of a biological plausible mechanisms strengthens the case for causation.
- Coherence. The association does not conflict with other current knowledge.
- Experiment. Experimental studies to directly test the association are strong evidence for causation, but are often ethically impractical.
- Analogy. Is a similar exposure known to cause a similar effect?

Assessing Evidence on the Safety of Chemicals in Food

In preparation of fact sheets on chemical or groups of chemicals in food the principles discussed above will be applied in assessing which information to include and how to weight information included. In particular, assessments carried out by the organisations listed below will be considered to constitute systematic reviews of the evidence and will be given primacy as information sources:

- Joint FAO/WHO Meeting on Pesticide Residues (JMPR);
- Joint FAO/WHO Expert Committee on Food Additives (JECFA);
- International Agency for Research on Cancer (IARC);
- Expert panels for the European Food Safety Authority (EFSA) or preceding organisations, such as the Scientific Committee on Food (SCF)
- United States Food and Drug Administration (FDA)
- United States Environmental Protection Agency (EPA)
- International Program on Chemical Safety (IPCS)
- Food Standards Australia New Zealand (FSANZ)
- Advisory committees to the UK Food Standards Agency

Where the chemical has not been assessed by these or equivalent agencies or where significant additional information is available, the quality of evidence will be considered with reference to the evidence pyramid outlined above, while the strength of evidence will be considered on the basis of quality, quantity and consistency of the available evidence to decide further the information is suitable for inclusion in the fact sheets.

On occasions weaker or lower quality information may be included in fact sheets, if this is felt to significantly contribute to the communication of risks. The status of such information will be clearly identified.

References

Agency for Healthcare Research and Quality. (2002). Rating the strength of scientific research findings. Accessed at: http://www.ahrq.gov/clinic/epcsums/strenfact.htm. Accessed: 8 September.

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