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Establishing causality and managing uncertainty.

"What evidence is needed to establish a causal relationship? How are uncertainty cause and quantitative uncertainty managed in assuring food safety"?

"Causality is the relationship between an event (the *cause*) and a second event (the *effect*), where the second event is a consequence of the first."

The dose-response relationship, or exposure-response relationship, describes the change in *effect* on an organism caused by differing levels of exposure (or doses) to a stressor (the *cause,* usually a chemical) after a certain exposure time. This may apply to individuals (eg: a small amount has no observable effect, a large amount may be fatal), or to populations (eg: how many people or organisms are affected at different levels of exposure). Exposure may be single/short-term (acute exposure), of intermediate duration, or long-term (chronic exposure). Exposure can be divided into external and internal. External exposure refers to the whole dose to which an organism is exposed. Internal exposure refers only to that fraction of the initial chemical dose that is absorbed and distributed throughout the body via systemic circulation.

Studying dose response, and developing dose response models, is central to determining "safe", "admissible","tolerable", "hazardous" and "toxic" levels and dosages for directly or indirectly added chimical to food, contaminants, persistent pollutants, and other substances to which humans or other organisms are exposed. The setting of accetable limits, based on a scientific approache, is often the basis for management policy.

It should be realized that dose-response relationships will generally depend on the exposure time; quantifying the response after a different exposure time leads to a different relationship and possibly different conclusions on the effects of the *cause* under consideration. This limitation is caused by the descriptive nature of the approach.

Dose-response curve is a simple X-Y graph relating the magnitude of a *cause* (e.g. concentration of a chemical) to the response of the target (e.g. organism under study). The response may be a physiological or biochemical response, or even toxic (mortality).

The measured dose (usually in milligrams, micrograms, or grams per kilogram of body-weight) is generally plotted on the X axis and the response is plotted on the Y axis. Commonly, it is the logarithm of the dose that is plotted on the X axis, and in such cases the curve is typically sigmoidal, with the steepest portion in the middle. The first point along the graph where a response above zero is reached is usually referred to as a threshold-dose. At higher doses, undesired side effects appear and grow stronger as the dose increases. The stronger a particular substance is, the steeper this curve will be. In quantitative situations, the Y-axis usually is designated by percentages, which refer to the

percentage of individuals registering a standard response. Such a curve is referred to as a quantal dose response curve, distinguishing it from a graded dose response curve, where response is continuous.

The risk characterization paradigm (Hazard Identification, Hazard Assessment and Exposure Assessment), the characterization of the causal relationship and the intrinsic uncertainties will be subject of the presentation togheter with the last guidances on the assessent of DNA reactive genotoxins and non-DNA reactive genotoxins.