Safety assessment of specialty food ingredients
Consideration of epidemiological observational studies

BACKGROUND

The media often forgets to mention the limitations of the sources of information when discussing the safety of food ingredients. Even when they do, the limitations of epidemiological observational studies are still frequently overlooked. This can create a distorted public perception of their safety.

LET'S RECALL THE BASICS: EPIDEMIOLOGICAL OBSERVATIONAL STUDIES ARE NOT COMPREHENSIVE RISK ASSESSMENT!

EPIDEMIOLOGY "is the study of how often diseases and other health conditions occur in different groups of people and why. It includes the study of health-related measurements (e.g. pesticide exposure or vitamin deficiency) in a population and how they may influence the risk of ill health"[1].
More precisely, "epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems. Therefore, in the broadest sense, epidemiological studies examine determinants of health and disease conditions in defined populations, including humans, animals and plants. **Epidemiological studies include both experimental and non-experimental studies, the latter is often referred to as 'observational' studies"[2]**.

OBSERVATIONAL STUDIES / RESEARCH "involves simply observing the habits or behaviours in large groups of people to investigate the relationship between lifestyle factors and health outcomes. The researcher does not intervene in any way but compares the health outcomes of people who make different diet or lifestyle choices. These studies are used to identify correlations and develop hypotheses for further testing. Because of the presence of confounding factors[3], **observational research cannot prove cause-and-effect.** The

[1] Source: EFSA Glossary: https://www.efsa.europa.eu/en/glossary-taxonomy-terms/e

[2] Source: EFSA Scientific Committee guidance on appraising and integrating evidence from epidemiological studies for use in EFSA's scientific assessments

[3]" For example, researchers observe that people who drink alcohol are more likely to develop lung cancer than those who don't. However, it may also be that people who drink alcohol also tend to smoke more often and that researchers fail to include this factor into their analysis (e.g., it was not measured or not thought to influence the relationship). Here, smoking is a so-called confounding factor: a factor associated with both the exposure (drinking alcohol) as well as the outcome (lung cancer) and therefore could distort the data. In an Randomised Control Trial these confounding factors are evenly distributed across the study groups (assuming randomisation is done correctly), but this is unlikely to be the case in observational research. Source: EUFIC: The levels of evidence in nutrition research

interest of observational studies lies in revealing these relationships in order to address future research."[4]

RISK ASSESSMENT "is a specialised field of applied science that involves reviewing scientific data and studies in order **to evaluate risks associated with certain hazards**. It involves four steps: hazard identification, hazard characterisation, exposure assessment and risk characterisation[5]."

DETERMINATION OF THE SAFETY OF SPECIALTY FOOD INGREDIENTS IS BASED ON COMPREHENSIVE RISK ASSESSMENT

Most specialty food ingredients like food additives, novel food ingredients or sources of vitamins and minerals are subject to a pre-market authorisation. The process requires a **thorough scientific assessment of their safety by EFSA**, based on the consideration by experts of **multiple studies**.

For example, for a food additive, EFSA requires from the applicant[6] many toxicological studies covering toxicokinetics, genotoxicity, carcinogenicity, reproductive and developmental toxicity, immunotoxicity, neurotoxicity etc., as well as exhaustive information on their potential levels of addition or intake in foods and beverages in order to evaluate consumers' exposure.

EFSA GUIDANCE ON APPRAISING AND INTEGRATING EVIDENCE FROM EPIDEMIOLOGICAL STUDIES FOR USE IN EFSA SCIENTIFIC ASSESSMENTS

On 5th July 2024, EFSA has published a guidance on appraising and integrating evidence from epidemiological studies for use in EFSA's scientific assessments.[7]

The guidance considers how evidence from human epidemiological studies can be used in the risk assessment (dose response modelling) and presents several approaches. It also explains the use of uncertainty factors in risk characterization when using evidence from human epidemiological studies is not conclusive or when there are limitations in the available data. It addresses recommendations for EFSA risk assessments, notably emphasizing the risk of bias of such studies and how to apprehend it:

1. Evidence from epidemiological studies in humans should be used in risk assessments to the extent possible.
2. The overall assessment should consider the entire body of evidence.
3. **Judgements on the overall body of evidence should always be made by considering the type, and, if possible, direction and magnitude of potential biases** identified across different studies, for example by using a triangulation approach.
4. To facilitate more structured and time efficient risk assessment, the use of evidence maps and scoping reviews during the planning phase of an Opinion is recommended.

[4] Source: EUFIC: The levels of evidence in nutrition research

[5] Source: EFSA Glossary: https://www.efsa.europa.eu/en/glossary-taxonomy-terms/e

[6] Source: EFSA Guidance for submission for food additive evaluations

[7] Source: EFSA Scientific Committee guidance on appraising and integrating evidence from epidemiological studies for use in EFSA's scientific assessments

5. **Risk of bias tools provide a structured way to identify different biases that may occur to varying degrees in different studies. The key elements to capture within each study are the source, magnitude and direction of possible biases**. That complexity cannot be accurately captured by assigning a numerical score of study quality, which is therefore discouraged.
6. The type of dose-response modelling for risk or benefit characterisation should be selected based on the type and nature of the available data and the objective aimed for (minimising risk, maximising benefits or balancing the two).

Epidemiological observational studies lack control over exposures and confounding variables, and therefore cannot prove cause-and-effect relationships between a food ingredient and human health. They are used to identify correlations and develop hypothesis in order to address further research that proves cause-and-effect.

They can be used in the scientific risk assessment of a food ingredient only under the condition of a robust examination of potential biases.

The safety of specialty food ingredients is based on a comprehensive risk assessment.

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