International Association for Food Protection WEBINAR

Food Toxicology Webinar-
Food Chemical Safety and Current Tools and Methods

Organized by: IAFP's International Food Protection Issues PDG

Moderator: Marianne Solomotis, U.S.Food and Drug Administration (FDA)

Sponsored by the IAFP FOUNDATION

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Webinar Housekeeping

- It is important to note that all opinions and statements are those of the individual making the presentation and not necessarily the opinion or view of IAFP.
- All attendees are muted. Questions should be submitted to the presenters during the presentation via the Questions section at the right of the screen. Questions will be answered at the end of the presentations.
- This webinar is being recorded and will be available for access by IAFP members at www.foodprotection.org within one week.

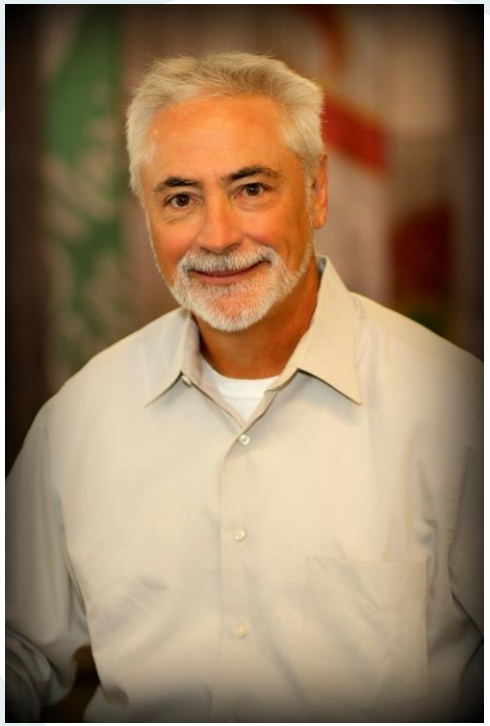
Today's moderator:

Marianne Solomotis Ph.D. FDA

Deputy Director, and Director of Research, Office of Applied Research and Safety Assessment, Center for Food Safety and Applied Nutrition, FDA. As such, she oversees the research in the office, including microbiology and toxicology.

After completing her Ph.D. at the University of the Witwatersrand, South Africa, she was invited to do a Post-Doctoral Fellowship at the University of Maryland School of Medicine, Center for Vaccine Development, Baltimore, MD. She started working at the FDA/CFSAN as a research microbiologist and then changed positions serving as a Risk Assessment Team Lead and/or Project Manager on risk assessments of specific pathogen and/or commodity of concern until she moved on to her current role.

Steve Hermansky



Steven J. Hermansky, Pharm.D., Ph.D., DABT
Senior Science Advisor, Toxicology

Steven J. Hermansky joined FDA in April 2022 to work in the area of chemical food safety and to evaluate and move to New Alternative Methods in their continuing effort to reduce, refine and even replace animal use in toxicology.

Dr. Hermansky left Conagra Brands in April 2022 where he directed & oversaw the corporation's toxicology & product safety risk assessment programs as well as headed the Food Protection, Regulatory Affairs and Analytical and Applied Sciences departments. In this role, Dr. Hermansky led teams of scientists in the Safety Sciences including microbiology, toxicology and analytical chemistry as well as the global regulatory affairs and food safety corporate audit functions. Prior to joining Conagra in 2007, he worked in the pharmaceutical industry as a toxicologist with responsibilities in drug safety clinical trials and adverse event tracking, trending and reporting.

He started his career as a toxicologist conducting contract laboratory animal studies with Union Carbide. Steve has a Doctor of Pharmacy degree as well as Master of Science and Doctor of Philosophy degrees in toxicology from the University of Nebraska. He is a Diplomate of the American Board of Toxicology and has published over 40 textbook chapters, peer reviewed publications and scientific abstracts. He is an adjunct professor at the University of Nebraska College of Public Health and has served on the Advisory or Editorial Boards of several organizations.

George Kass

George Kass, Ph.D., European Food Safety Authority

George Kass was trained as a biochemist. He received his PhD in biochemical toxicology from the Karolinska Institute in Stockholm in 1990. After a post-doc at the Swiss Federal Institute of Technology in Zurich he returned to the Karolinska Institute as Assistant Professor. In 1994 he moved to the University of Surrey in the UK where he became Professor of Toxicology. He moved to the European Food Safety Authority in 2009, where is Lead Expert in toxicology. He is on the UK Register of Toxicologists and is EUROTOX Registered.

He has published over 140 papers in the field of toxicology and chemical risk assessment. A substantial part of his research has focused on the molecular mechanisms of drug toxicity and on liver injury. Currently, he is Associate Editor of Toxicology and Applied Pharmacology. In 2020, he was elected to the Académie d'Agriculture de France.

Introduction to Food Toxicology

Steven J. Hermansky

Pharm.D., Ph.D, DABT

Senior Science Advisor

US FDA CFSAN

Disclaimer

The data and interpretations expressed in this presentation represent that of the author and not necessarily that of the U.S. Food and Drug Administration

Agenda

- Define toxicology and toxicologists
- Regulatory toxicology
  - Food toxicology
  - Regulation of food toxicology
- Methods
  - Traditional
  - NAMS
- Communication challenges

What is Toxicology?

- The study of the adverse effects of chemicals on living organisms and the environment
- Toxicologists
  - study and evaluate the nature of adverse effects
    - consider cellular, biochemical and molecular mechanisms
  - assess the probability of occurrence
- Regulatory Toxicology
  - Bring the science of toxicology to practical applications
  - Many applications

Toxicologist

- Many roles in society: Occupational, Drug Development, Academia, Forensics, Environmental, Clinical
- The primary responsibility of the toxicologist is the **protection of human health**
  - Regardless of role in society
  - Prevention *and mitigation* of disease caused by chemical exposure
    - How to prevent or minimize harmful exposure
    - How to prevent disease occurrence or treat effects after exposure has occurred
  - Populations, individuals and environment
  - Toxicology is *a "vocation of luxury"*

Regulatory Toxicology

- Profession of Toxicology
  - Must adequately understand all scientific data
  - Making decisions is required
    - Hard for everyone
    - Often required with incomplete or conflicting information
    - Which is harder? Personal, family, unknown individual, or population?
  - Clear, concise risk communication is an absolute requirement
    - Failures of toxicology/toxicologists often occur due to poor or unclear communication
    - Today's world of rapid information, social media and self-proclaimed "experts" requires even more attention to communication

Regulatory Toxicology

- Exactly what are we protecting?
  - Individuals?
  - Populations?
  - Cells?
  - Organs?
  - Genetic information?
    - Heritable mutations

Food Toxicology

- "Why do we need toxicologists in food – food shouldn't be toxic."
  - Chemicals as contaminants have always been a component of food
  - In our efforts to improve public health, we are asking good questions to better manage food chemicals and substances
  - New innovation has improved
    - Shelf life (preserving freshness and nutrition)
    - Palatability
    - Microbial resistance

Food Chemical Regulation in US

- Food and Drug Administration (FDA)
  - Center for Food Safety and Applied Nutrition (CFSAN)
    - Food contaminants
      - Closer to Zero
      - Process formed contaminants
      - Mycotoxins
    - Food ingredients regulated one of two primary ways
      - Food Additive Petition
        - » Significant toxicology data required
          - Required for certain ingredient types (e.g. artificial sweeteners, artificial colorants)
      - GRAS – Generally Recognized as Safe
        - » Standard of Safety is the same as Food Additive Petition
        - » Use experts and history to replace or augment testing

Food Chemical Regulation in US

- Food Additives
  - Direct
    - Intentionally added to food for specific purpose
      - Colorants, sweeteners, etc.
  - Indirect
    - Enters the food supply by various mechanisms
      - Packaging (monomers of polymers)
      - Processing aids (antifoamers)
      - Incidental contact (oil from equipment, gasket components)

Food Chemical Regulation in US

- GRAS
  - Regulatory system developed to account for the vast array of food ingredients due to long history of safe use
    - With the new food and drug law (1958), Congress and FDA perceived a need for approving most food ingredients recognized by experts to be safe
    - Basis of GRAS review is “recognition of safety by experts qualified by education and experience”

- January 2014

Guidance for Industry

Considerations Regarding Substances Added to Foods, Including Beverages and Dietary Supplements

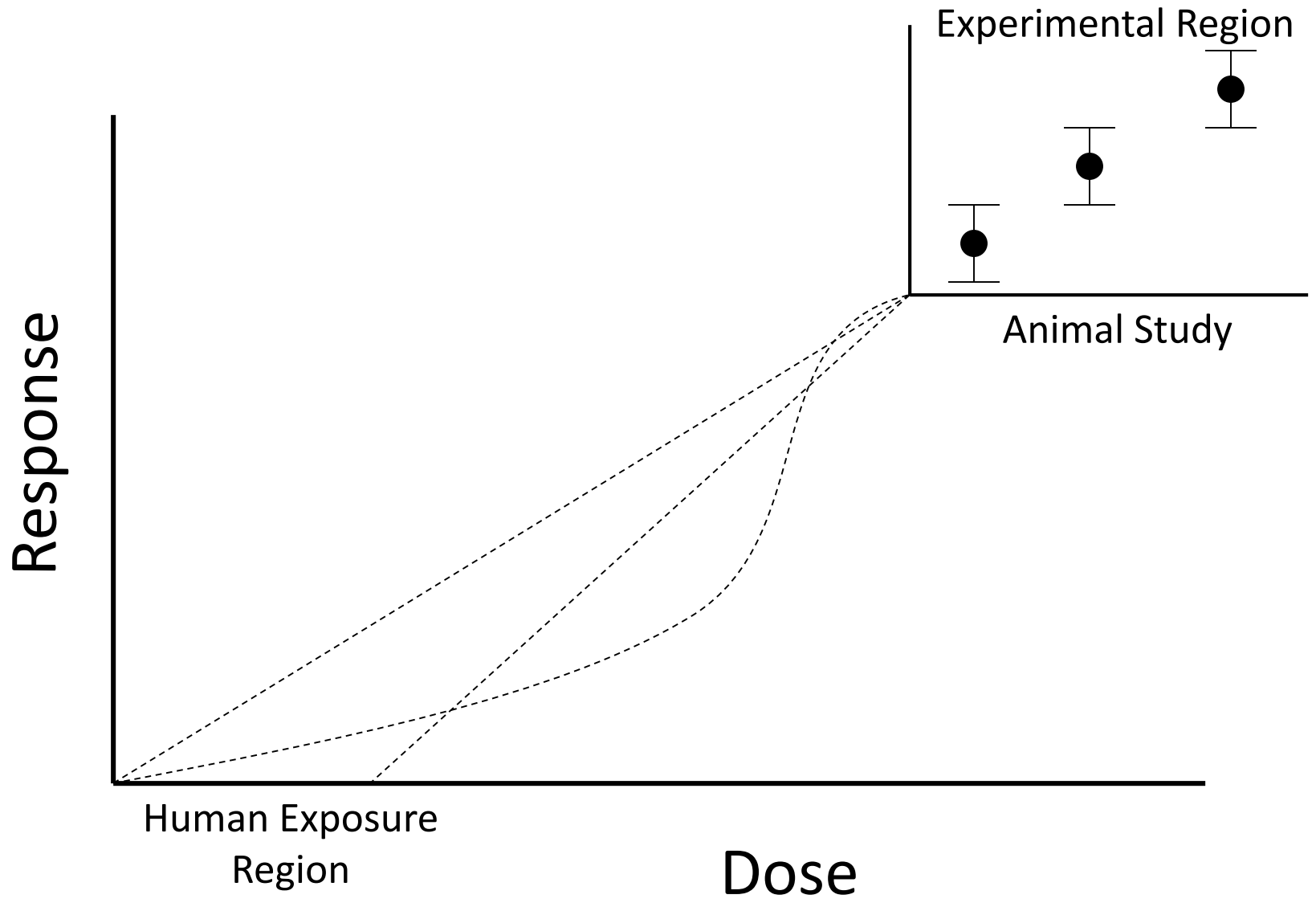
Additional copies are available from:
Office of Food Additive Safety, HFS-200
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740
(Tel) 240-402-1200
http://www.fda.gov/FoodGuidances

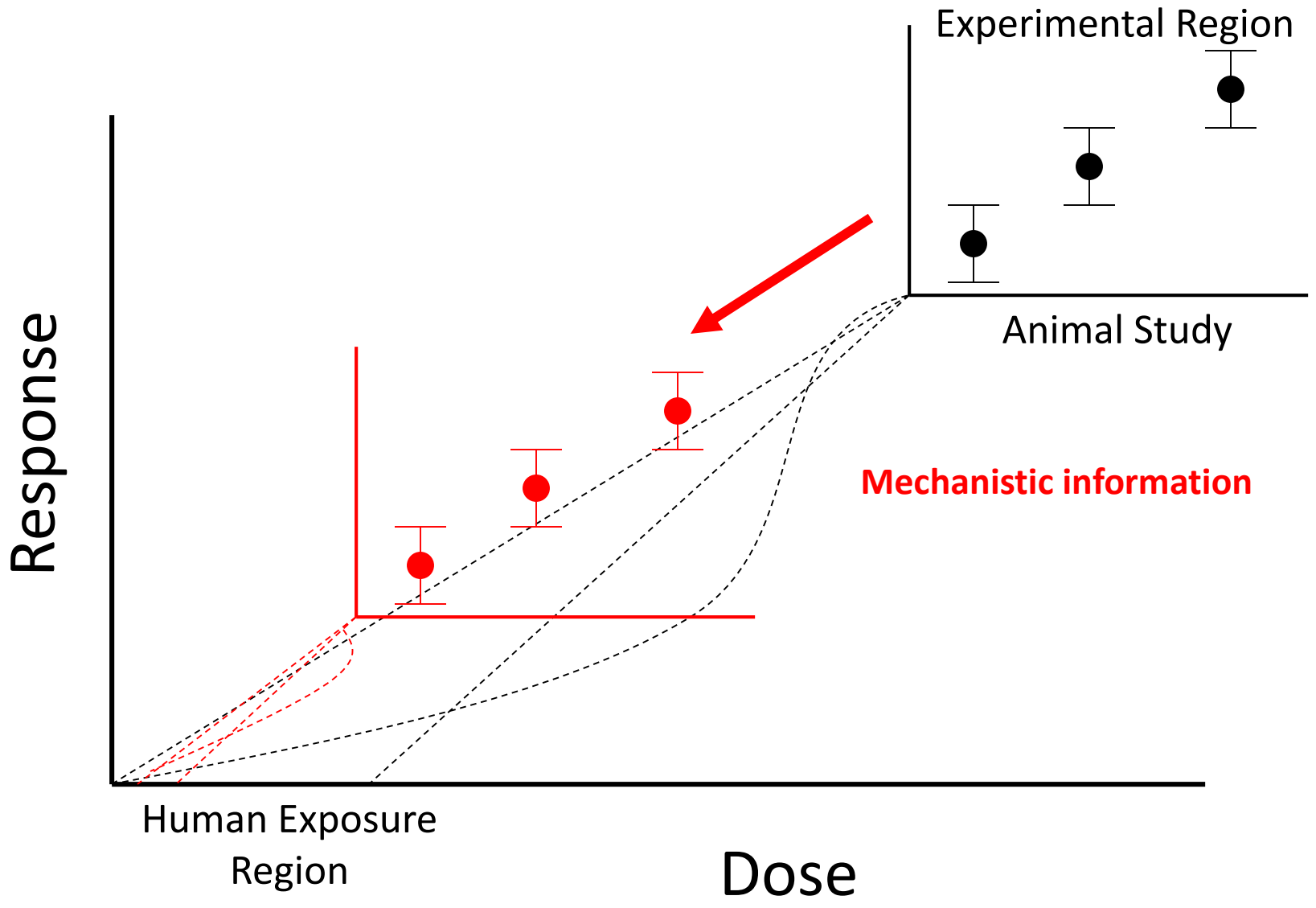
- “It is your responsibility to ensure that substances added to foods you manufacture or distribute, including non-dietary ingredients in dietary supplements, comply with all applicable regulatory requirements for substances added to food.”

International Food Chemical Regulation

- Each country/region of the world has regulations on food chemical safety
- CODEX is an international coordinating organization
  - Many functions including food chemical safety
  - US is a member of CODEX
- Lack of harmonization can cause challenges for the regulatory toxicologist

Methods


Experimental Region
Animal Study
Response
Human Exposure Region
Dose


Experimental Region
Animal Study
Response
Mechanistic information
Human Exposure Region
Dose

New Approach Methods (NAMS)

- Novel technologies to improve the predictivity of non-clinical studies and Replace, Reduce or Refine reliance on animal testing
- Refers to a testing strategy that is different from the traditional approach
- May reduce cost and time required for testing and allow testing of more chemicals
- May, at some point, be more relevant to humans

New Approach Methods (NAMS)

- Steadily increasing interest and research in past 20 years
- Multiple international efforts
- Companies and agencies working to develop tools
- Currently only very limited regulatory acceptance for new chemical entities
  - Used as supporting information for animal toxicology
  - Increasing use for structurally very similar chemicals

Challenges for Food Chemical Communication

We are living in a new world with a new reality

- ✓ Increased Consumer Sensitivity to Ingredients
- ✓ Lack of trust in science
- ✓ Changing definition of expert
- ✓ Disagreements within media
- ✓ Distrust of government

Califf, past FDA chiefs look for partners to curb misinformation

Regulatory News | 09 January 2023 | By Mary Ellen Schneider

Past and present commissioners of the US Food and Drug Administration (FDA) say the agency needs partners in combatting public health misinformation, and industry, clinicians, patient advocates and academic leaders all have a role to play.

"Realistically, FDA needs help," Mark McClellan, MD, PhD, who served as FDA Commissioner from 2002-2004, said at the 2023 Innovations in Regulatory Science Summit sponsored by the UCSF-Stanford Center of Excellence in Regulatory Science and Innovation (CERSI).

While there is currently a lack of trust in officials from public health agencies, individuals still have trust in their own physicians, community leaders, and others who are "close to their experience," McClellan said during a panel discussion among past and present FDA commissioners about how to counter the problem of misinformation and restore trust in the agency.

Clockwise from top left: Robert Califf, Mark McClellan, Margaret Hamburg, Scott Gottlieb

INTRODUCTION TO TOXICOLOGY IN FOODS

-CURRENT TOOLS/METHODS-

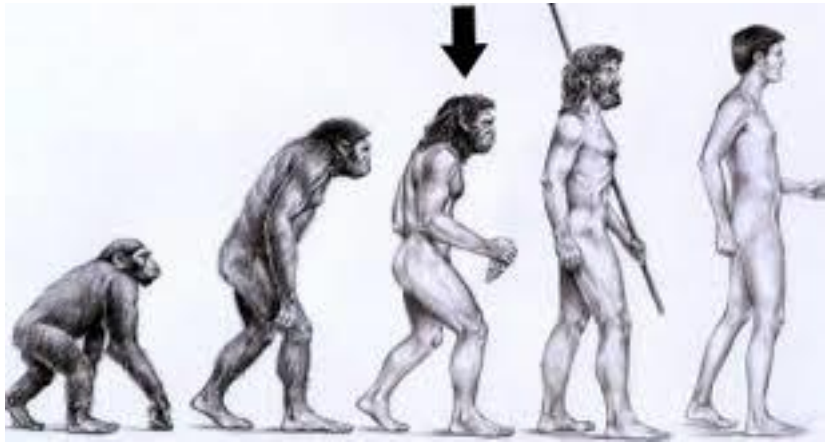
George Kass, PhD, ERT
Lead Expert
Chief Scientist Office

EUROPEAN FOOD SAFETY AUTHORITY

Disclaimer: The views, thoughts and opinions presented are not necessarily those of EFSA

FOOD SAFETY AND HEALTH-BASED GUIDANCE VALUES

- 1953 – WHO: the increasing use of various substances in food has created new public health considerations
- 1956 – First JECFA meeting
- 1961 – JECFA coined the term **acceptable daily intake** (ADI) while evaluating antioxidants and antimicrobials
  - An ADI was defined as the ‘daily intake of a chemical which, during an entire lifetime, appears to be without appreciable risk on the basis of all known facts at the time.’

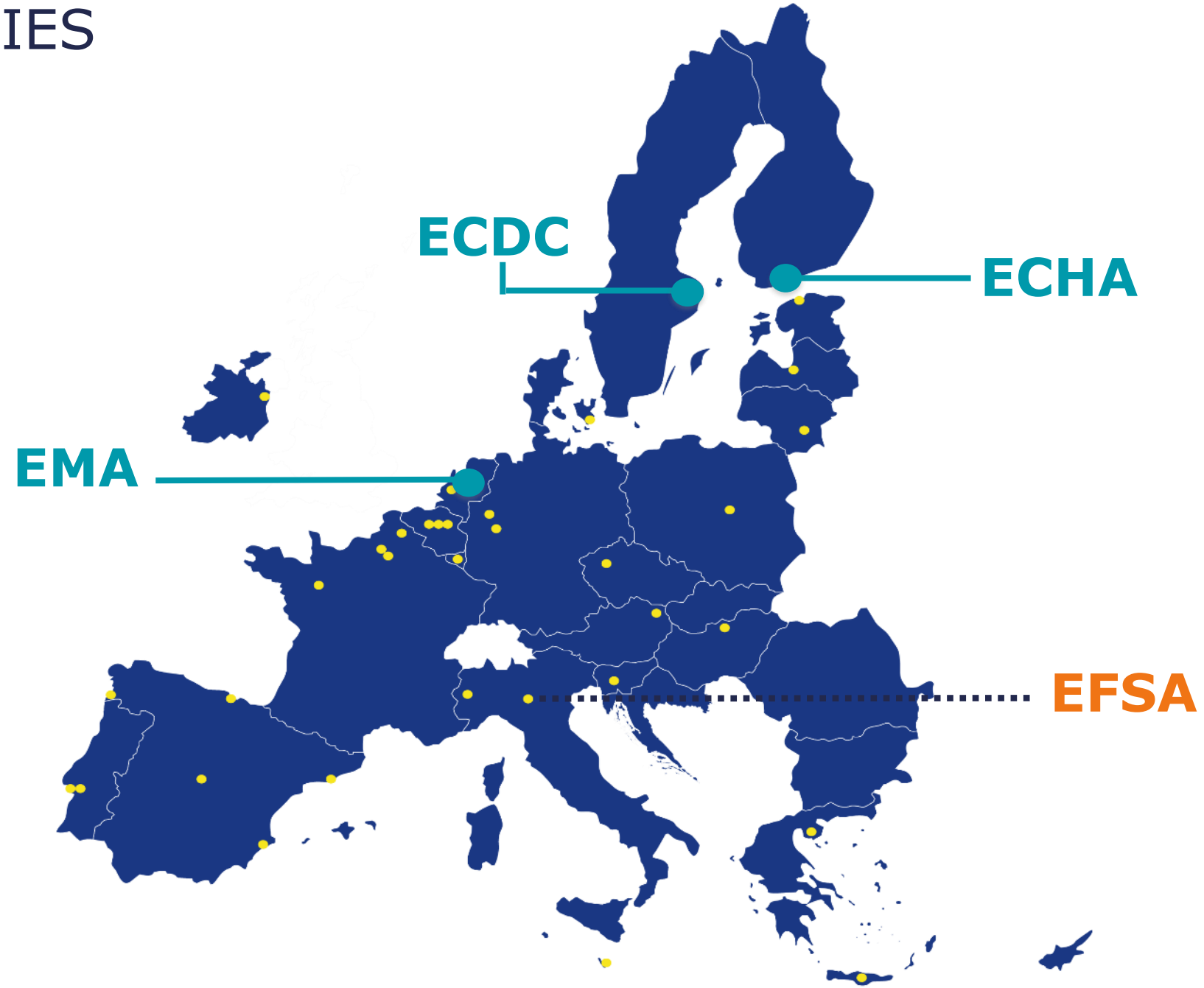


A BRIEF HISTORY

EFSA was established under **EU law in 2002** following a series of food crises as part of a programme to:

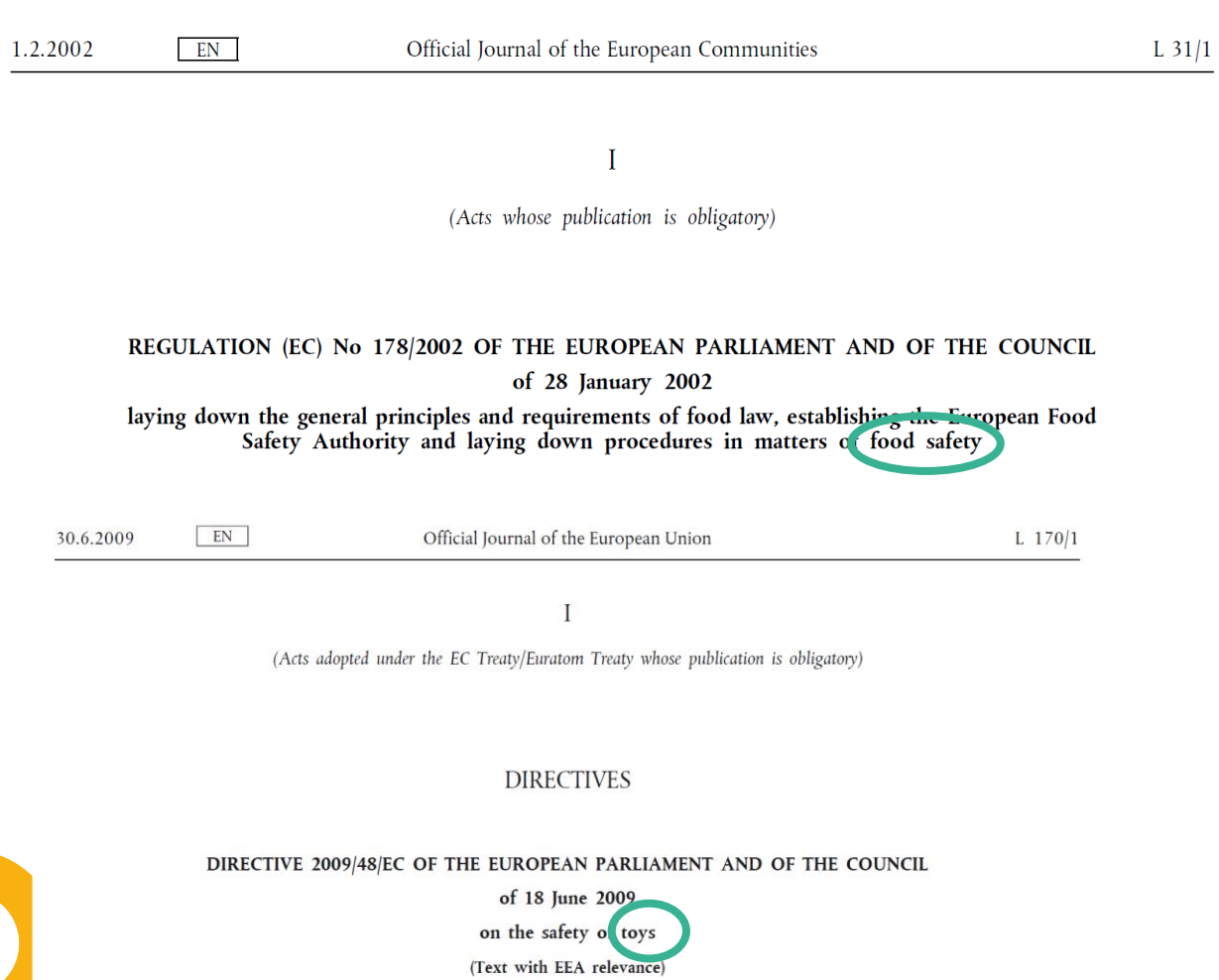
- **improve**
  - the EU food safety system
- **help ensure**
  - a high level of consumer protection
- **restore and maintain**
  - confidence in the EU food supply
- **clearly separate**
  - risk assessment and risk management functions

EU AGENCIES



LEGISLATION AND DATA REQUIREMENTS

FOOD AND CHEMICAL SAFETY IN THE EU



1.2.2002 EN Official Journal of the European Communities L 31/1

I

(Acts whose publication is obligatory)

REGULATION (EC) No 178/2002 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 28 January 2002
laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety

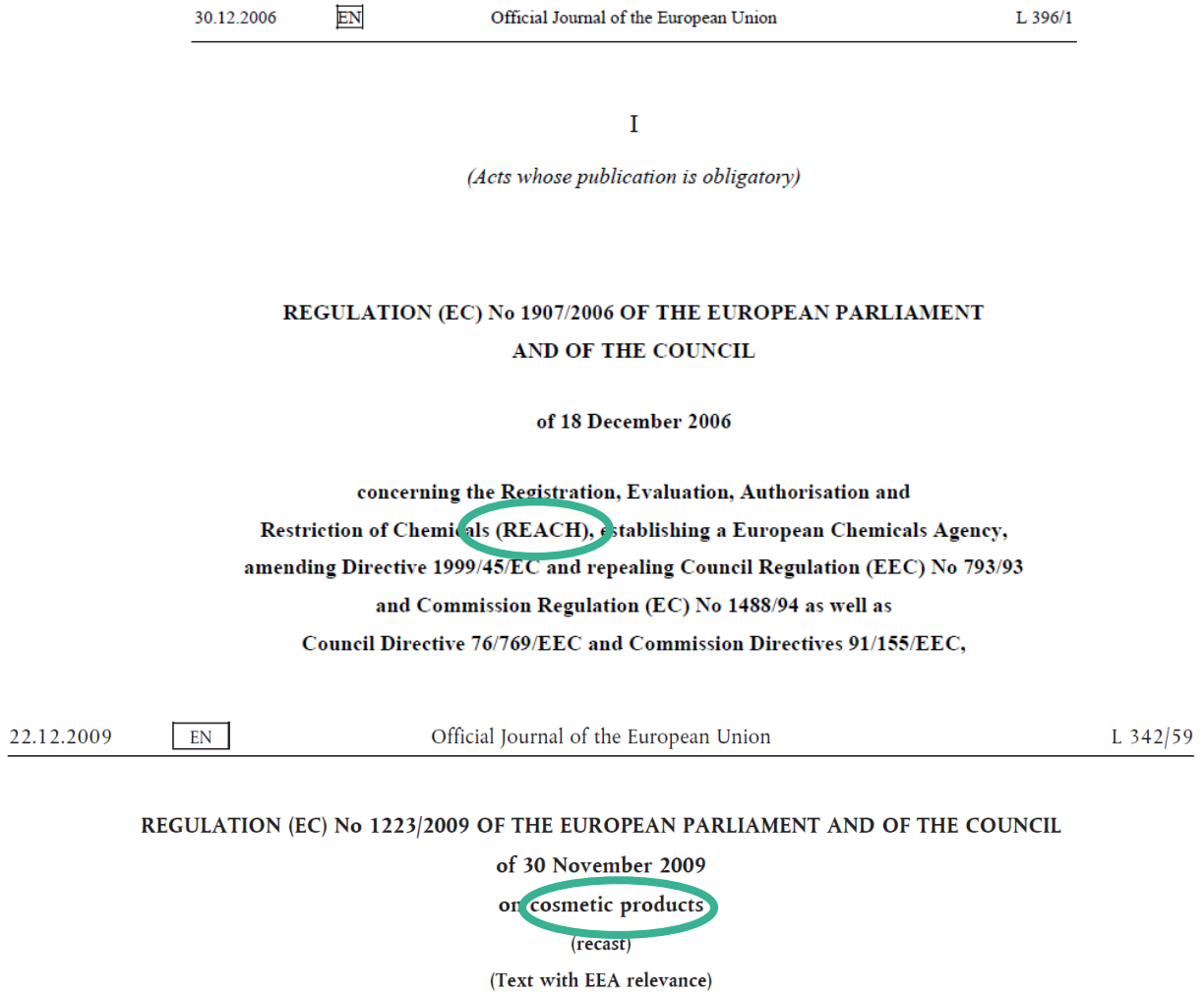
30.6.2009 EN Official Journal of the European Union L 170/1

I

(Acts adopted under the EC Treaty/Euratom Treaty whose publication is obligatory)

DIRECTIVES

DIRECTIVE 2009/48/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 18 June 2009
on the safety of toys
(Text with EEA relevance)



30.12.2006 EN Official Journal of the European Union L 396/1

I

(Acts whose publication is obligatory)

REGULATION (EC) No 1907/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 18 December 2006

concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC,

22.12.2009 EN Official Journal of the European Union L 342/59

REGULATION (EC) No 1223/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 30 November 2009
on cosmetic products
(recast)
(Text with EEA relevance)

Overview – different regulations and different data requirements!

- Environmental pollutants – **No Testing**
- Pharmaceuticals, food additives, plant protection products, biocides – **Extensive testing**
- Industrial and consumer chemicals (>30K in the EU) – **Limited testing to extensive testing**
- Cosmetics – **No animal data**

DATA REQUIREMENTS FOR FOOD SAFETY: PPPS

REGULATIONS

COMMISSION REGULATION (EU) No 283/2013

of 1 March 2013

setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market

(Text with EEA relevance)

INTRODUCTION

Information to be submitted, its generation and its presentation

1. The information submitted shall meet the following requirements.

1.1. The information shall be sufficient to evaluate the foreseeable risks, whether immediate or delayed, which the active substance may entail for humans, including vulnerable groups, animals and the environment and contain at least the information and results of the studies referred to in this Annex.

DATA REQUIREMENTS FOR FOOD SAFETY: PPPS

SECTION 5. ***Toxicological and metabolism studies***

Introduction

5.1. Studies on absorption, distribution, metabolism and

5.1.1. Absorption, distribution, metabolism and excretion

5.1.2. Absorption, distribution, metabolism and excretion

5.2. Acute toxicity

5.2.1. Oral

5.2.2. Dermal

5.2.3. Inhalation

5.2.4. Skin irritation

5.2.5. Eye irritation

5.2.6. Skin sensitisation

5.2.7. Phototoxicity

5.3. Short-term toxicity

5.3.1. Oral 28-day study

5.3.2. Oral 90-day study

5.3.3. Other routes

5.4. Genotoxicity testing

5.4.1. *In vitro* studies

5.4.2. *In vivo* studies in somatic cells

5.4.3. *In vivo* studies in germ cells

5.5. Long-term toxicity and carcinogenicity

5.6. Reproductive toxicity

5.6.1. Generational studies

5.6.2. Developmental toxicity studies

5.7. Neurotoxicity studies

5.7.1. Neurotoxicity studies in rodents

5.7.2. Delayed polyneuropathy studies

5.8. Other toxicological studies

5.8.1. Toxicity studies of metabolites

DATA REQUIREMENTS FOR FOOD SAFETY: ADDITIVES

L 354/16 EN Official Journal of the European Union 31.12.2008

REGULATION (EC) No 1333/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 16 December 2008

on food additives

(Text with EEA relevance)

(7) Food additives should be approved and used only if they fulfil the criteria laid down in this Regulation. Food additives must be safe when used, there must be a technological need for their use, and their use must not mislead the consumer and must be of benefit to the consumer. Mis-

DATA REQUIREMENTS FOR FOOD SAFETY: ADDITIVES

efsa
European Food Safety Authority

EFSA Journal 2012;10(7):2760

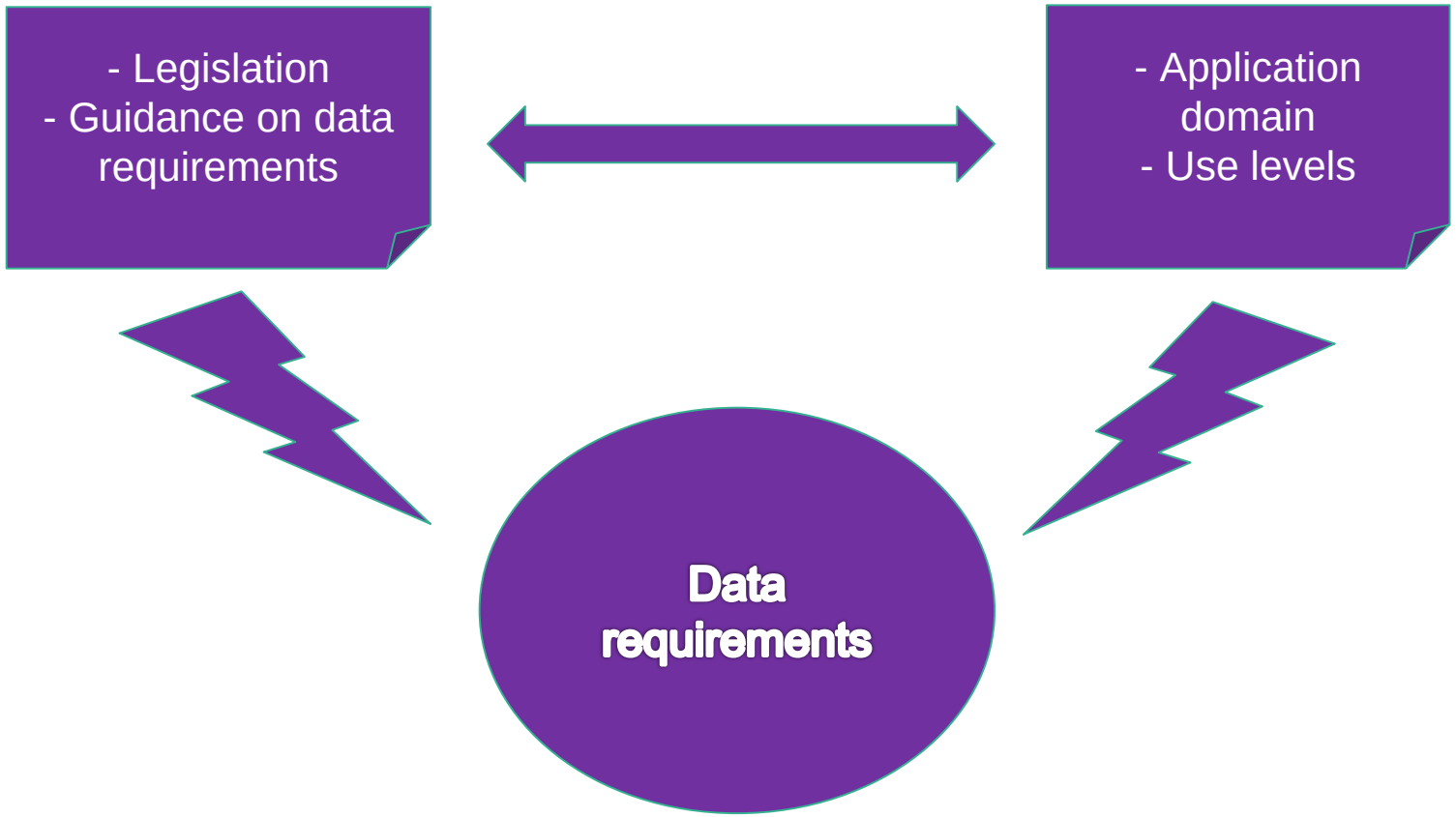
SCIENTIFIC OPINION

Guidance for submission for food additive evaluations[1]

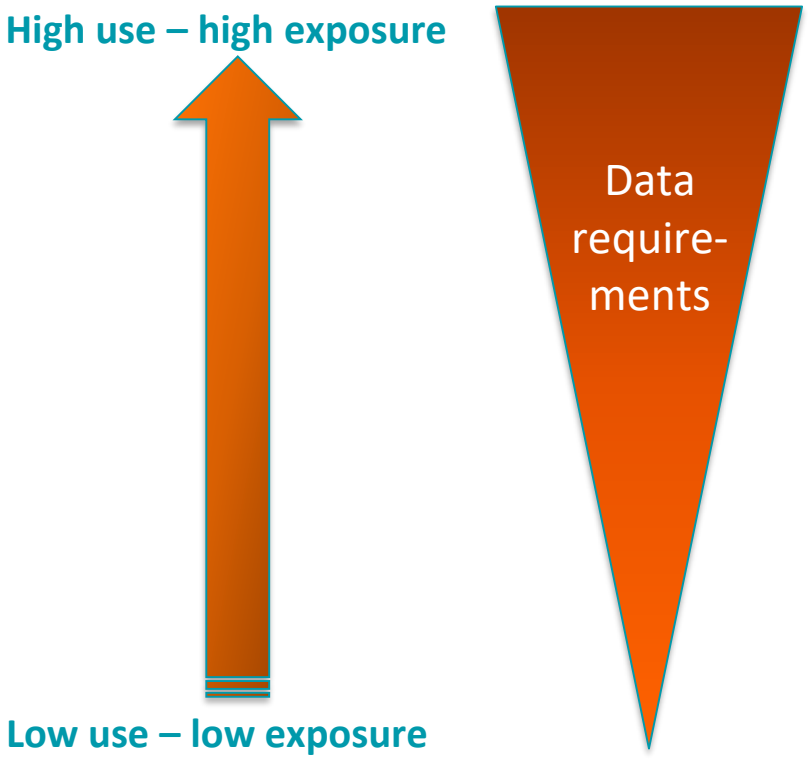
EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

DATA FOR RISK ASSESSMENT: GENERAL CONSIDERATIONS



DATA FOR RISK ASSESSMENT: GENERAL CONSIDERATIONS



2-Year carcinogenicity
Chronic toxicity
Reproductive/ developmental toxicity

Sub-chronic toxicity
Full ADME

Genotoxicity
ADME

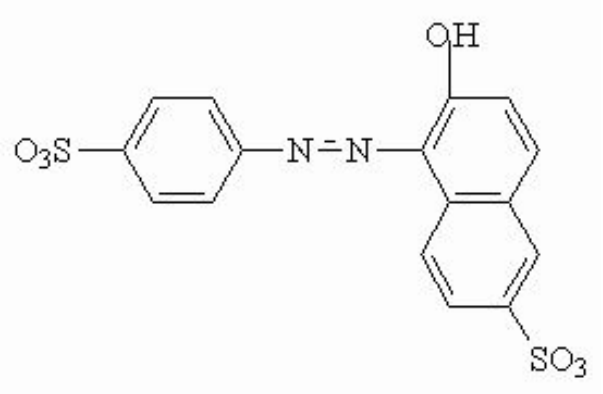
Some figures…

- The total cost of toxicology and exposure testing ranges from $200–300 million for a conventional, food-use pesticide.
- The human health toxicology testing costs $8–16 million and uses 5000–7000 animals.
- Source: Craig et al., RTP, 2019
- Total time for total package up to 10 years.

RISK ASSESSMENT TOOLS AND APPROACHES

TYPES OF DATA: 1. CHEMICAL

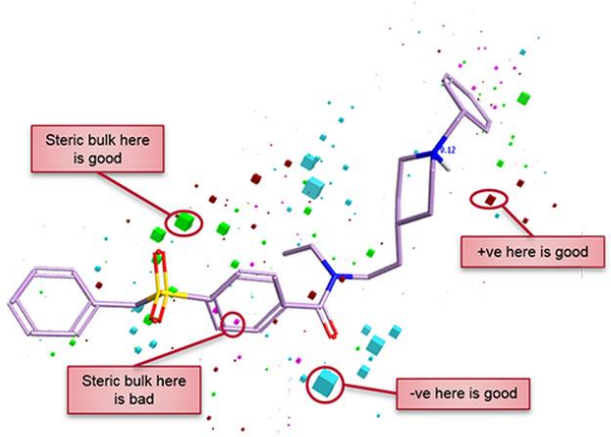
- Identity
  - Name, CAS No., EINECS No., synonyms, molecular and structural formula
  - Single compound or mixture?
  - Isomers
- Physicochemical properties
  - Molecular mass, particle size (nanoparticles!), lipophilicity, appearance, solubility, ionisation constants, etc. and specifications
- Purity
  - chemical purity, impurities (quantities!), contaminants (quantities!)
  - degradation products, commercial product vs test product



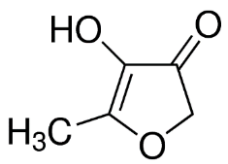
Sunset yellow (E110)

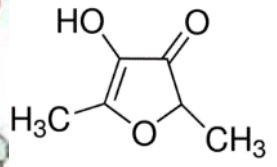
WHAT IF THERE ARE NO DATA: NON-TESTING METHODS

- (Q)SAR (Structure Activity Relationship test)
- Read-across
- Threshold of Toxicological Concern (TTC)



Classification	TTC value in µg/person per day	TTC value in µg/kg bw per day
Potential DNA-reactive mutagens and/or carcinogens	0.15	0.0025
OPs and carbamates	18	0.3
Cramer Class III	90	1.5
Cramer Class II	540	9.0
Cramer Class I	1800	30





TYPES OF DATA: 2. BIOASSAY DATA

- ADME – absorption, distribution, metabolism and excretion (toxicokinetics)
- Acute, sub-acute, and sub chronic in vivo studies
- Gene mutation and chromosome damage studies
- Carcinogenicity
- Fertility, development, parturition and post-natal development
- Special studies

GUIDELINES: OECD

- OECD Guidelines for the Testing of Chemicals
- OECD Principles of GLP
- Mutual Acceptance of Data (MAD) system
  - To avoid conflicting or duplicative safety data requirements
  - Inefficient regulation would have costly implications for the environment, human health, government budgets and industry
- MAD criteria for non-clinical health and safety test study
  - The study must have been conducted according to OECD TGs and principles of GLP;
  - The study must have been conducted in a test facility which has been inspected by a national GLP compliance monitoring programme and;
  - The national GLP compliance monitoring programme must have undergone a successful evaluation by OECD.
- Examples
  - OECD TG 408: Repeated dose 90 day oral toxicity study in rodents
  - OECD TG 443: Extended One-Generation Reproductive Toxicity Study (EOGRTS)
  - OECD TG 489: In Vivo Mammalian Alkaline Comet Assay

INTEGRATION OF DATA

Qualitative

- Qualitative assessment of hazard information
- The United Nations, IARC and ECHA use qualitative classification of animal bioassay results.
- This approach is at the **basis to C&L** (Classification and Labelling of Chemicals).
- This is Hazard Identification (characterisation) and not Risk Assessment

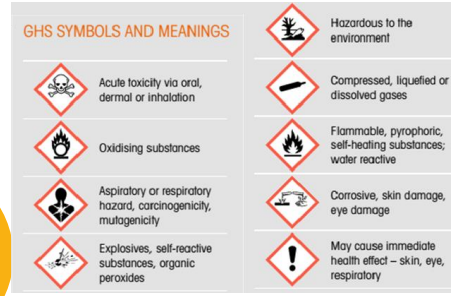
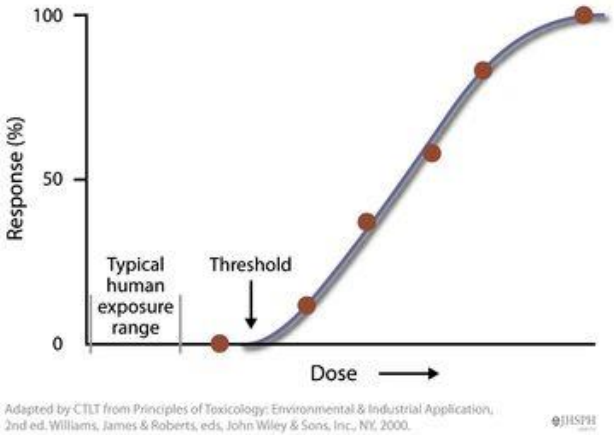


Figure 3.6.1: Hazard categories for carcinogens

CATEGORY 1:	**Known or presumed human carcinogens** The placing of a substance in Category 1 is done on the basis of epidemiological and/or animal data. An individual substance may be further distinguished:
Category 1A:	**Known to have carcinogenic potential for humans; the placing of a substance is largely based on human evidence.**
Category 1B:	**Presumed to have carcinogenic potential for humans; the placing of a substance is largely based on animal evidence.** Based on strength of evidence together with additional considerations, such evidence may be derived from human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen). Alternatively, evidence may be derived from animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case by case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals. **Classification**: Category 1 (A and B) Carcinogen
CATEGORY 2:	**Suspected human carcinogens** The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1. Based on strength of evidence together with additional considerations, such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies. **Classification**: Category 2 Carcinogen

Quantitative

- Involves dose-response assessments
- Need to distinguish threshold approaches versus non-threshold approaches
- Traditionally threshold approaches are applied to non-cancer endpoint
- Non-threshold approaches applied for cancer endpoints.



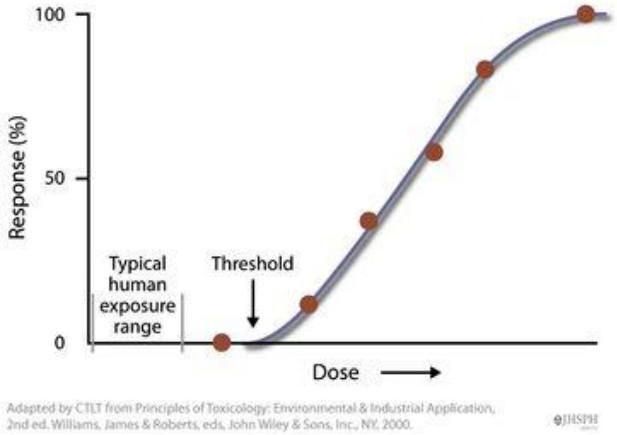
Point of departure:
NOAEL or BMDL

HBGV:
ADI=NOAEL/UF

FROM DOSE-RESPONSE TO HEALTH-BASED GUIDANCE VALUES

ADI – Acceptable Daily Intake

ADI = NOAEL/(UF) or BMDL/(UF)

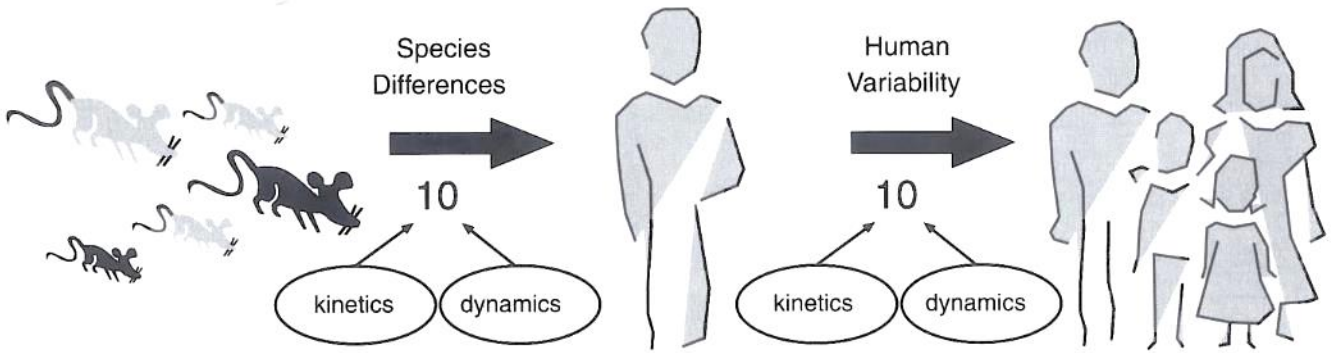


Point of departure: NOAEL or BMDL

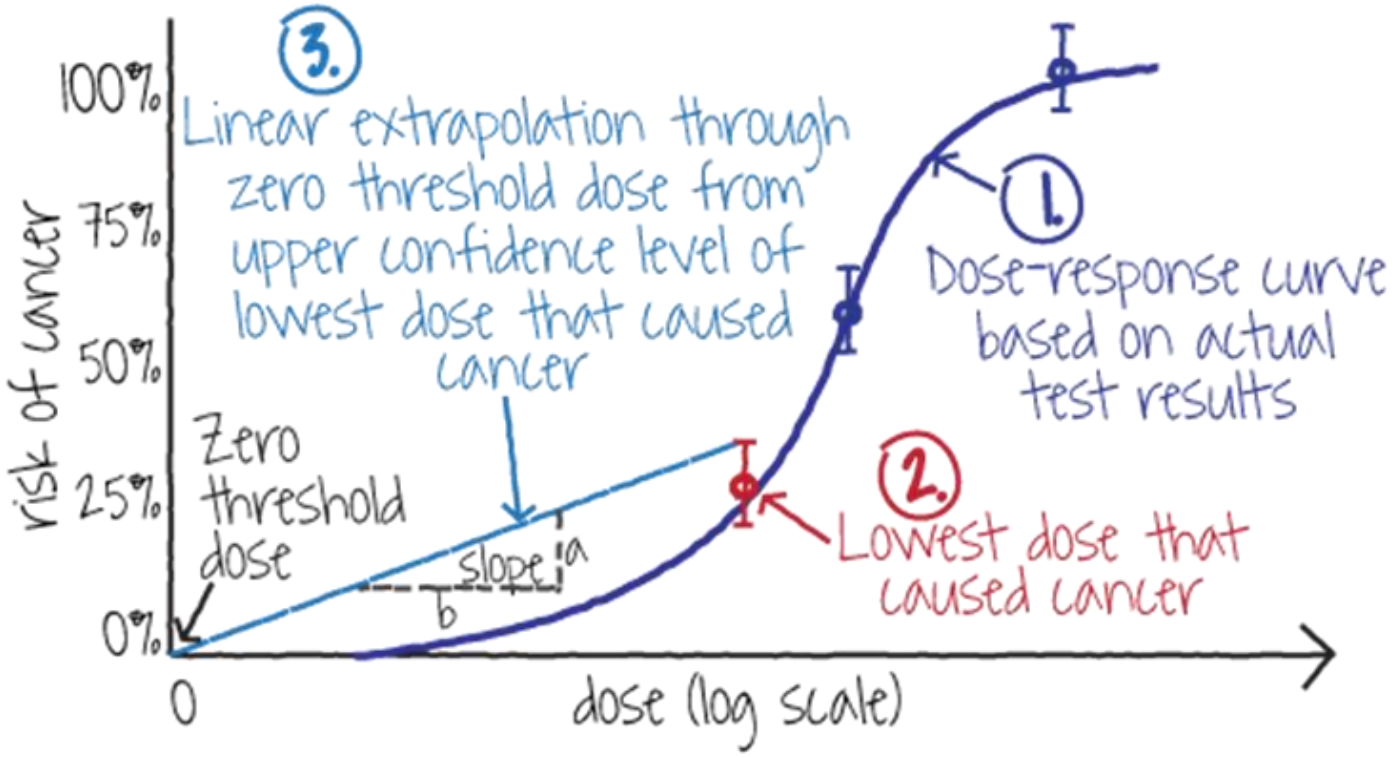
HBGV: ADI=NOAEL/UF

UF is the **uncertainty factor** used to take into account species differences and human variability.

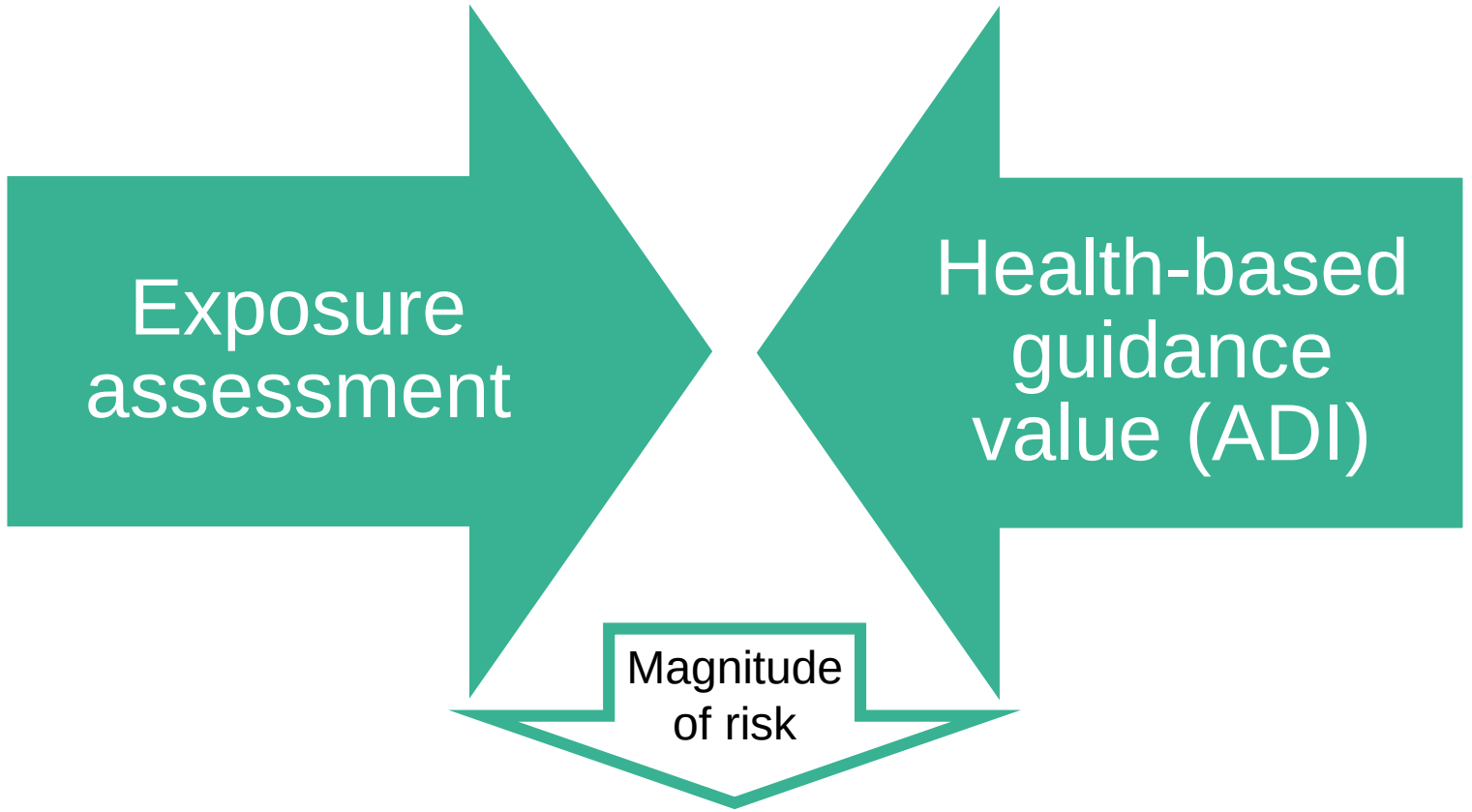
- **The UF is typically 10 x 10 = 100**



INTEGRATION OF DATA: GENOTOXIC CARCINOGENS



THE FINAL STEP: RISK CHARACTERISATION



Communication to risk managers

MAIN SOURCES AND TYPES OF DATA RECEIVED BY EFSA

In vivo biological studies	• ADME studies • Following OECD TG and GLP criteria
In vivo toxicological studies	• Sub-chronic, chronic, repro-dev studies • Following OECD TG and GLP criteria • Traditional Tox parameters
In vitro studies	• Mainly for genotoxicity and metabolism • Following OECD TG and GLP criteria

- **Traditional chemical risk assessment relies mainly on animal bioassays**
- **The future: NGRA - AOPs, NAMS, IATAs**

감사합니다 Natick

Grazie Danke Ευχαριστίες Dalu Obrigado

Thank You Köszönöm

Tack

Спасибо Dank Gracias

谢谢 Merci Seé

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International Association for Food Protection WEBINAR

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