TOXICOLOGICAL RISK ASSESSMENT AS A COMPONENT OF THE ONE HEALTH APPROACH

Alberto Mantovani
alberto.mantovani@iss.it

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Dept. Food Safety, Nutrition and Veterinary Public Health
Istituto Superiore di Sanità, Roma, Italy

ONE Health

"ONE Health" (OH): ***conceptual*** **and** ***operational*** **framework linking environment, animals, food-producing chains, human health**

Not intended to *increase the number of silos*
but to *support cross-fertilization among silos*

a *developing* field: feed-backs and interactions among its components for research and for risk analysis avoiding to "drown into complexity"

Environment is always quoted as OH pillar,
but HOW to interpret Environment within OH?

(Humboldt-Dachroeden S, Mantovani A. *Assessing Environmental Factors within the One Health Approach*. Medicina 2021)

Toxicants and OH

while zoonoses were the "cradle" of OH
Toxicological hazards are now recognized as a component of the OH framework

Let's take it from the standpoint of
Food Safety from Field to Fork (which is *OH approach*

(see The environment-animal-human web: a "One Health" view of toxicological risk analysis, dedicated open-access research topic in *Frontiers in Public Health*, November 2018, ed. C. Frazzoli and A. Mantovani)

- **How the environment modulates risk factors**

- **How the environment is a source of OH risk factors**

Risk assessment (from EFSA Glossary)

A *specialised* field of *applied* science that involves reviewing scientific data and studies in order to evaluate risks (function of probability x severity) associated with certain hazards.
It involves four steps

hazard identification **(*what is it*?) the identification of an agent as capable of causing adverse effects**

hazard characterization **(*how? at what dose levels?*) the nature of the adverse effects and an understanding of the doses involved and related responses.**

exposure assessment ***(how much?)*** **a thorough evaluation of who or what has been exposed to a hazard and a quantification of the amounts involved.**

The above steps are integrated into

Risk Characterization **(*1+2+3*) the likelihood that an agent will cause harm calculated in the light of the nature of the hazard and the extent to which people, animals, plants and/or the environment are exposed**

- the core message is delivered to the *risk managers* (who have to take decisions considering also legal, social economic factors)

- The risk assessors are increasingly requested to integrate in their conclusions also the *analysis of uncertainties* (gaps of knowledge that may influence the outcome of risk assessment)

**(EFSA *Guidance on uncertainty analysis in scientific assessments* 2018 and
EFSA *Guidance on communicating uncertainty in scientific assessments*, 2019)**

Climate changes impact on the dynamics of toxicants

- events driven by climate changes may increase the release of toxicants from "*trapping*" comparts (e.g., *frozen soil*) and their availability for living organisms (*EEA on Mercury, 2018; Kobusińska et al., Chemosphere. 2020*)

- Rising temperatures and humidity increase the vulnerability of edible crops to *microscopic fungi* producing highly toxic metabolites –mycotoxins, including the carcinogenic aflatoxins (increases in crops, feeds and foods noted in temperate Countries since the start of Century: *EFSA 2012, Modelling, predicting and mapping the emergence of aflatoxins in cereals in the EU due to climate change*)

Climate Changes and Toxicants contaminating food chains (cont.)

- Toxins from invading species: the *acutely toxic* ciguatoxin, produced by *unicellular algae* and accumulating in *large predatory fishes* (e.g., tuna): typical of tropical environments, it enters the Mediterranean from the Atlantic (*EFSA Evaluation of ciguatoxins in seafood and the environment in Europe, 2021)*

And toxicants used in agrofarming, such as pesticides

Toxicants from farm to environment: PESTICIDES

Pesticides are a wide and chemically diverse group
unavoidably toxic for target (insecti- herbi- fungicides) AND non-target organisms (incl. humans)
unavoidably leading to residues on treated plants
And exposure of the ecosystems

The safe use of pesticides is regulated on basis of
intended use
parameter-based, realistic worst-case scenarios to asssess environmental exposure
residue formation/persistence

Climate influences the *whole combination* of parameters
agronomic = amount/duration of pesticide use
abiotic (temperature)
biotic (plant microbiome)
Directly modulating the *type* (metabolites) and *amount* of residues in foods/environment

Ecotoxicological risk assessment for pesticides: a OH-like approach

(*Good modelling practice in the context of mechanistic effect models for risk assessment of plant protection product EFSA 2014*)

Modelling pesticides on ecosystems (both wildlife and man-shaped,) requires *cross-fertilization* among

- Ecological information: selection of relevant species to model for a given community or ecosystem; ecological characteristics relevant to exposure (dwelling, motility, feeding, population lifespan/tutnover);

- Toxicology (sensitivity of taxa, dose-response, lifestage sensitivity, non-lethal effects: reproduction, feeding)

(*Good modelling practice in the context of mechanistic effect models for risk assessment of plant protection product EFSA 2014*)

CONT:

- Data-based abiotic parameters (climate, soil and stream properties) determine the *exposure* to a pesticide, the composition and structure of *communities* and interact with pesticides to determine their effects on species.

- Agronomic parameters: management of the agro-ecosystem (*crops* and their development over time, *tillage and irrigation* practices, structure of the *landscape*).

Dietary risk assessment of pesticide residues: What residues?

(Identification of Toxicologically Relevant Residues. EFSA guidance 2016)

Residues often do not coincide with the parent substance
- a number of different compounds resulting from abiotic or biotic (microbial, plant) transformation, which
- can sum up with the active substance (comparable hazard, but possible different potency)
- or have qualitatively different profile

The azole fungicide Epoxyconazole is both embryotoxic and endocrine disruptor (steroid synthesis inhibitor)
***68 metabolites identified*:**
based on QSAR/read across
The majority can sum-up with parent substance
But others can be more reactive and should be tested

Dietary risk assessment of pesticide residues: What residues?

(Identification of Toxicologically Relevant Residues. EFSA guidance 2016) CONT

The fungicide, Spiroxamine is considered "low toxicity" as parent compound
But *genotoxic concerns are not excluded for 7 (out of 45) metabolites* belonging to three groups
- two metabolites are *significant components of total residue burden* in fruit crops (different metabolism in different crops

Thus, transformation processes
might produce high-concern substances (effect/potency x exposure)
from a low concern parent compound

Dietary risk assessment of pesticide residues

All biotic and abiotic parameters influencing residue formation are liable to be modified by climate changes,

e.g.,

***high temperature and humidity* increase the formation of the *highly toxic (and thyroid-disrupting)* metabolite ETU from widely used dithiocarbamate fungicides (Mancozeb, etc.)**

Then, in dietary risk assessment, never forget the human factors, such as interactions between nutrition and environmental toxicants: in humans the risk of thyroid effects from ETU are definitely higher in iodine-deficient communities (Medda et al., 2017)

Dioxins and dioxin-like PCBs in feed and food (EFSA 2018)

Hazard identification

Dioxins (PCDDs and PCDF): are a wide group (75 PCDDs and 135 PCDFs) of chemicals formed unintentionally in a number of industrial and thermal processes.

***17 of these are relevant* as persistent, fat-soluble, bioaccumulating**

The twelve dioxin-like (DL) PCB belong to wider PCB group (209 congeners): widespread industrial use from 1929 till banning (from 1979). Now, due to persistence and bioaccumulation, still found in foods and feeds (legacy contaminants)

PCDDs, PCDFs and DL-PCBs share the binding to the aryl hydrocarbon receptor (AHR) as molecular initiating event of the toxic effects

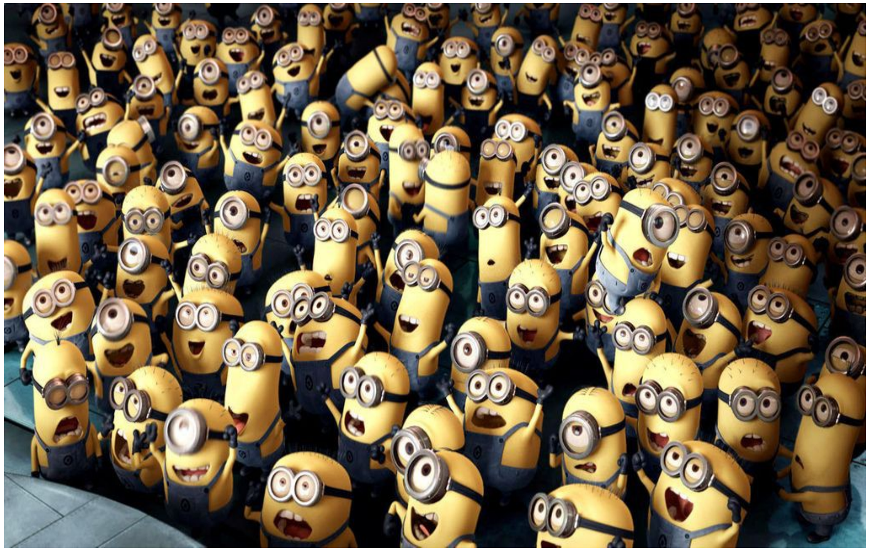
Stepwise Risk Assessment of OH contaminants

Hazard characterization

PCDDs, PCDFs and DL-PCB may occur together in the organisms (body burden, especially in liver and lipid fraction of tissues) and have the same mechanism:
therefore, combined effect of a mixture
where each component contributes in function of *both* the potency (binding to AhR: *toxicity equivalency factor, based on the most potent compound, TCDD*) and of the amount in the mixture

100 Minions might make more damage than

1 Hulk



Exposure assessment

Human and animal exposure are related to the proximity to sources of emissions (e.g., steel factories) and/or to wind-driven emission fall-out

Human exposure is related to the consumption of foods that are *both* rich sources of dioxins and are highly consumed
- Foods of animal origin (accumulation in food chain) and
- lipid content

-***Fatty fishes*** **(from eel to salmon; especially the big ones, because of greater bioaccumulation)**

-**Milk and especially *butter and cheese* (more fat, less water)**

- *Livestock meat* (more exposed to environment than pig)

Stepwise Risk Assessment of OH contaminants

Hazard characterization **(cont.)**

inappropriate and sustained activation of AHR**, a receptor involved in the response of the cell to external stimuli,** ***including hormones***

A ***number of effects*** **in animals and humans, depending also on the "*****hormone status*****" of the organism (*****sex, age*****: generally higher susceptibility during development)**

Tumour promotion, liver toxicity, immune depression, reduced fertility, teeth and bone development etc. = need to identify the effect(s) that occur at ***lower dose levels*** **(*****critical/leading effect*****)**

Impaired semen quality, following pre- and postnatal exposure

(rodent and human studies)

Tolerable Weekly Intake of 2 pg TEQ/kg body weight/week

(why week and not day? approach for bioaccumulating substances)

Exposure assessment

In humans *age classes*:

Children (especially toddlers, 1-3 years) eat *more* than adults (relative to body weight)

and eat foods with *different* frequency (more milk, less shellfish..)

Internal exposure

All *well absorbed, slowly metabolized and excreted*

most show *long half-lives (several years)*

(half life: time an internal dose reduces by 50%)

- long half-life + continuous intake of small residues = body burden

- Adiposity matters! Half-life and body burden related to BMI

- Body burden mainly in *liver and adipose tissue*, but equilibrium with the lipid fraction of blood =

Blood can be used for biomonitoring of populations

Stepwise Risk Assessment of OH contaminants

Risk characterization in the European Union

Comparing the Tolerable Weekly Intake with the different exposure estimates in the EU states
which depend on
The levels found in foods (hence environmental levels)
And the consumption of different foods (*variable* dietary styles in EU) including information on high consumers (95th percentile of target foods)

The higher estimates could exceed by more than 4-fold the TWI
Indicating
A concern for health risks (especially for next generation(s))
And the need to reduce emissions

The biology of living organisms that produce foods

Dioxins much higher in livers from sheep than cattle (EFSA, 2011)
- fall down on pastures from airborme particulates and adhere to the organic fraction of soil
- Sheep grazing behaviour leads to a much higher soil (hence dioxin) ingestion than cattle

The background lipid content of muscle tissue predicts bioaccumulation
In *farmed* fish PCDD/Fs and DL-PCBs are accumulated to a greater extent in "*oily*" species (such as salmon and trout) than in *leaner* species such as carp and seabream
(literature reviewed in EFSA 2018)

The role of farming "environment"

Organic farmed poultry may have *more dioxin residues* than conventional poultry =
more contact with soil and environment
(*Dervilly-Pinel et al., Food Chem, 2017*)

Aquaculture feeds made of fish meal and fish oil are the main vehicle for transfer of environmental pollutants to farmed fish
(*reproduce* the predation chain "*big fish eats small fish*" which leads to biomagnifiction in the ecosystem)
The (now increasingly widespread) use of vegetable ingredients in feeds can drastically reduce the accumulation of dioxins and DL-PCB (and other main contaminants) in fish, besides increasing the sustainability of aquaculture
(Mantovani, Ferrari & Frazzoli 2015, Int J Nutr Food Sci)

E.g., Cadmium, from fertilizers to traditional recipes

Cadmium (Cd) is an important environmental contaminant. Main hazard: chronic kidney toxicity (*EFSA 2009*)

Mineral phosphorus fertilizers are a main source of Cd into soils, ready for *uptake by edible plants* (e.g., wheat) especially in *acidic soils* (*Bracher et al., Environ Pollut. 2021*) and indirectly for water bodies

Vegetable foods (*bread, potato*) are main contributors to the dietary intake of Cd (non-dietary is *tobacco smoke*); molluscs play also a role (approx. 3% of total, *EFSA 2009*)

The "brown meat" of crustacean head is a rich source of Cd. Appreciated in some food cultures (incl. seashore Southern Italy) where it provides a hotspot of Cd intake (*Ariano et al J Food Prot, 2015; Zhao et al. Biol Trace Elem Res 2020*)

Tips for Discussion: environmental drivers and assessment of toxicants

Climate changes

Call for *updating data sets and models used for exposure assessment*

Persistent contaminants: *Increased availability* for organisms and food chains

Contaminants produced by living organisms (mycotoxins, biotoxins): increased *presence and diffusion*

Pesticides:
***Increased use* in agriculture of hazardous substances if safer alternatives are *unavailable* for crop protection**

Parameters for ecotoxicological and residue risk assessment may need updates in order to *afford adequate protection*

Circular Economy

Recycled materials, their use and fate, are a new scenario

Interest in the circular economy and therefore in recycling has increased considerably.

***However* recycled products and materials may contain hazardous substances that indicate the need for a OH-based risk assessment (environment, food chains, aggregate human exposure).**
Toxicants of concern: flame retardants, lead, cadmium, phthalates, polycyclic aromatic hydrocarbons, etc.
materials at risks: plastics, rubber, polystyrene, e-waste, etc.

***Exploiting* advantages of recycling (more energy-efficient and CO2-efficient production)**
calls for OH-based exposure scenarios from recycled materials.
(*Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) of the European Commission "Statement on emerging health and environmental issues" 2018*)

Tips for Discussion: environmental drivers and assessment of toxicants

Search for more sustainable food sources

Sustained livestock production may be problematic in terms of emissions (green-house gass, nitrogen) and consumption of soil and water (*Gonzales et al., Food Res Int 2020*)

The expectations toward new animal protein sources should always consider:
***How much and why* these may carry *recognized* contaminants?**
Do they carry *new* contaminants ?

In the case of insects, assessed as novel foods by the EFSA NDA Panel (2021)
The consumer intake of recognized contaminants (such as toxic metals) dependes on the quality assurance plan of farming (feed and "fodder")
New issues are high non-protein nitrogens, allergens and possibly some species-specific toxins
Know the biology of the new protein sources!

Philippus Aureolus Theophrastus Bombastus von Hohenheim
Paracelsus (Einsiedeln, CH, 1493 – Salzburg, AT, 1541

Paracelsus

Shaper of the *embryo* of experimental toxicology

Precursor of *One Health* because his theories lie on the cross-talk between
the *macrocosmos* that stays "in high place" (the influxes of the sky above and around creatures) and
the *microscomos* that stays "in low place" (the dynamic physiology of the organism)

Precursor of *Risk Assessment*, as science applied to action because

"What sense would it make or what would it benefit a physician if he *discovered the origin* of the diseases
but *could not cure or alleviate* them?"

THANK YOU

Thanks a lot for patient listening!