Challenges and opportunities of regulatory toxicology in public health: how to report our research to be useful for environmental and regulatory toxicology?

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General challenges & opportunities in regulatory toxicology

Regulatory toxicology faces unprecedented challenges in the 21st century.[1] In addition, due to new developments regulators are able to respond to long-lasting open questions in the field more than ever. This commentary aims to provide a set of considerations to make environmental and clinical human reports more suitable for re-evaluation for toxicity objectives and consecutive policy accommodations.[2]

General regulatory challenges include, but are not limited to:

- Species-specific toxicity,
- Mixture toxicity,
- Low-dose effects,
- Neurotoxicity,
- Endocrine disrupters,
- Nanotoxicology,
- Evaluating molecular mechanisms mediating the toxicity
- Applying simulation and modeling (cheaper and using less animals)

New advances have also been made in laboratory testing that enable regulators to respond to the challenges. For example it is now possible to effectively break down interspecies barriers. Non-animal models including human skin, intestinal and pulmonary barriers are also finding their ways into research-based, industry-driven and regulatory-relevant work.[3]

Public health related challenges & opportunities in regulatory toxicology

First, the applicability of environmental research and reports in environmental and regulatory toxicology is limited by small amounts of relatively poor quality toxicity data from human epidemiological studies.

While experimental designs are under our control, environmental epidemiological data are limited due to their *observational* nature. As a result, using and focusing on experimental models is the official tradition of toxicologists and the use of epidemiological human data are considered mainly supportive.

In addition, regulatory objectives are continuously and substantially growing in both breadth and depth[4], increasing the need for more robust methodologies. As a result, observational epidemiological human studies are considered even less confirmatory.

In addition to advancements in laboratory techniques and basic sciences, human epidemiology data are increasingly more accessible and incorporated into the overall regulatory evaluation of chemicals, --- but still as a side issue! Human epidemiology data as well as alternative testing methods are getting more accepted and validated, a move that should be celebrated! With the help of epidemiology data, it is now possible and perhaps necessary to effectively evaluate additional end points such as lead low level exposure-induced intelligent problems.

As a result, commonly used Acceptable Daily Intake and Reference Dose as statements of scientific fact may hinder the consideration of alternative means to reduce exposure to chemicals that may be harmful.[5] It seems that regulatory objectives are growing more and more conservative leading to no exposure recommendations.

Sources of human epidemiology data

The use of published research such as case reports, case series, case control and cohort studies and randomized control trials in drug development is clearly established. Applicability of observational field studies for toxic exposure, however, is well behind, as they are mainly considered to be supportive. Unique features of epidemiological data regarding human exposure include:

- Data are related to the areas where exposure exists
- They are valuable for hazard identification if their quality is good
- They could provide information regarding susceptible populations

Animal epidemiological data, including outbreaks in wildlife are other important source of data (not discussed here).

How to report public health research to be useful for environmental and regulatory toxicology?

What do regulators need?

Toxicologists need to be able to quantify the relative toxicity of a substance as compared to other toxic agents. Human epidemiological studies are useful for this as they are designed, interpreted and presented to suit this purpose.

It is also worth noting that orthodox reporting of epidemiologic studies could not be sufficient today from another angle, as we are living in a "community right to know" era in which environmentalists' propaganda, anarchistic and chaotic information and even fake news may be perceived as true as official reports on chemical induced health effects at the population level. If the published reports are not toxicological standards and open to interpretation, they can create chaos. Environmental toxicologists used to be the "Lord of the Flies". A scientist who is sitting behind piles of documents including frustrating tables. However, as the established official monopoly does not exist any longer, the need for presentation with more toxicologically-oriented format has increased.

Unique opportunities of epidemiological data

Regulatory standards for chemicals were usually not set based on human effects. They were developed based on a set of animal experiments, applying accepted arbitrary uncertainty factors and practical consideration. It has gradually become clear that lower level exposure to lead, for example, is related to lower IQ in humans. This effect was not detected in animal studies. Similarly, marine biotoxin Domoic acid exposure-induced amnesic shellfish poisoning was not reported from animal studies.

Common misconceptions

Is exposure-based toxicity equal to direct toxicity?

Marine bio-toxins in sea food, lead in drinking water, pollutants in air and fire retardants in costumer products are usually presented as metrics of relative toxicity in humans, in which large environmental data sets are attributed to a single health outcome using [simple] statistical models and [un]verified assumptions. While certain elements of accuracy exist in this approach, caveats are also abundant.

Certain concepts in published epidemiological studies are confusing if not misleading. These studies could have been designed or reported with minor changes to be more suitable for regulators. The following potential mismatches should be watched out for;

(i) Eco-toxicity is not environmental toxicology,

(ii) Environmental health risk assessment is not human health risk assessment, and is not human impact risk assessment,

(iv) Exposure is not the dose,

(v) The concentration of a chemical in media is not equal to the concentration of biomarkers. Chronic or multiple exposures to complex mixtures of chemicals separate exposure - biomarker concentrations.[6]

(vi) The fate of a chemical in environment is different from its fate in our body, and of course

(vii) Epidemiologic association alone is not a toxicological causality, etc. For example, many strong associations of smoking and alleged beneficial effects turned out to be false.

Table 1. Suggested toxicological requirements of published reports in public health.[1 2 3 4 5 6 7 8 9 10 11 12 13]

	Epidemiological component(s)	***Additional toxicological component(s)***
Introduction	Provide epidemiological background and association	Provide toxicological rationale
	Use the appropriate epidemiological terminology	Use the appropriate and up-to-date toxicological terminology e.g. use Reference Dose rather than Acceptable Daily Intake
Conceptual model	Present a conceptual association model from the causes to the effects	Present a conceptual mechanistic model for the mode[s] of action for the effect prior to conducting the study
Objective	Detect a valid association	Describe a valid causal relationship
Null hypothesis	Null hypothesis is exposure and effect-related	Potential pathway[s] are included in the null hypothesis
	Ad hoc statistical adjustments are common	Ad hoc additions to "save" hypotheses from apparent contradiction weaken the degree of reliability.
Exposure assessment	Usually concentration comes from one medium	Dose; integration of xenobiotic concentration from all media are used to define the external dose
	Usually exposure is duration of exposure and repetitive exposure-independent	Route of exposure; certain routes of exposure could be more important (aluminum absorption from olfactory nerve) e.g. direct and systemic toxicity are different
	Confounding factors and limitations (epidemiologic and statistical) are given	Include duration of exposure (time-dependent)
	In majority of toxicological issues, distribution of exposure among population is not normal (positively skewed* data)	Include bioaccumulation
		Consider sensitive populations (subjects with chronic diseases, fetus, nursing children, etc.)
		Justify the selection of the biomarker* (blood, urine, hair and nail)
		Distribution of effects among the population (and skewed* data)
		Estimation of both peak plasma level and concentration at steady state level for the duration of exposure could be useful
Assumptions	For the statistical model	Adjustments* including assumptions, variabilities and modifying factors for the toxicological model
Adequately control / adjust	Epidemiologically modifying factors	Toxicology modifying factors including physical, chemical, and biological, etc.
Fate of xenobiotic	Modeling in environment (weight of particulate matters, wind speed, etc.). In this comportment, just the parental agent but not metabolites are considered.	Modeling in both environment and human body (toxicokinetic - toxicodynamic (TDTK)) models for both the toxic agent as well as its metabolites
Statistics	Clearly describe the selection of the statistical model, validating approach and sensitivity analysis.	Clearly describe selection of the toxicology metrics/methods, sensitivity, specificity, positive and negative prediction values, preseason, reliability and validity
	Provide size, effect size; strength, direction, [over] power, P-value	Clarify dose – response curves
		Association could be with or without point of departure
		Association could be monotonic or non-monotonic
		Provide information usable for threshold concentration, if any Report all findings (significant and non-significant) Describe the range of exposure
Point of comparisons	Usually central tendencies (mean and median) for the concentration in media	Central and variation tendencies (mean and median) as well as distribution tendencies (95 percentile and maximum) in both media and biomarker are important. --- Treat the concentration of biomarker and media differently
		Any apparent exceptions and failures to account for some data must be plausibly explained.
Synergism	Statistical	Statistical and kinetic
Interpretation	Association could be [in]adequate	Associations are inadequate, causality should be rationalized

Adjustments Assumptions and modifying factors are made arbitrary based on and in order of magnitude, which may be too [less] conservative.

Biomarker Selection of the biomarker of choice should be done prior to the study.

External dose External dose is dominantly considered to be equal to the internal dose in the body.

Skewed data Distribution of environmental toxicology data are usually positively skewed, as a result, frequency of cases with very high [or low] values are low undermining the validity.

An approach to assess causation and its application to regulatory toxicology is rather too vague than formulaic, and professional judgment is hard to trace to its scientific basis.[7] Hypothesis-based weight of evidence needs much more clarification.

From another angle, certain questions have remained. What if an association with the values above the regulatory limit is reported in a study? Should we consider it as *causal*? Or what if an association is found with the values below the regulatory limit? Shall we ignore it? Both of which turned out to be wrong in many cases. For example, research from the past few decades has shown that xenobiotics below acceptable limits could cause harm, an effect that is decelerated at higher concentrations. This is a difficult concept for non-toxicologists to accept!

How to report epidemiological data to suit regulators?

First, as much as it is important to consider the measured or unmeasured confounders, it is important to be aware of the underlying mechanism of action. Theorizing a causal relationship should be done prior to conducting the study with sound mechanism(s) of action. Ad hoc additions to "save" hypotheses from apparent contradiction weaken the degree of reliability.

Pure statistical association following regrouping the data should be looked at with caution. Currently, health professionals are more familiar with epidemiological requirements of human observational studies as they are trained so. Also, they frequently apply these requirements to infections, etc., which seem to be enough. A list of potential differences and recommendations from literature and personal experience are presented below [certain concepts could be controversial and any feedback would be highly appreciated]. Factors that modify toxicity may include, but are not limited to, exposure conditions including pH, temperature, humidity, hydrophobicity, lipid content, age, sex, race, ethnicity, body size, exposure durations, smoking, life style, underlying diseases, and genetic and metabolic biotransformation variation.

Certain combination of chemicals or common mode of toxic action (via Critical Body Residue differences), and metabolic degradation are other determinants and should also be considered.

Conflict of interest; None. This short communication is not peer reviewed.

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