

The Generation and Use of Human Data in the Safety Evaluation of Pesticides, Personal Care Products, Food Ingredients and Pharmaceuticals

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Goals of This Presentation

- What types of human data are generated for different classes of chemicals?
- Why do studies in humans?
- Brief discussion of ethical considerations
- How are these studies used in safety assessment?

What do we mean by human data?

- For purposes of this talk, “human data” is defined as research involving intentional exposures to humans that they would not have experienced had they not participated in the research
- Not epidemiology, not most biomonitoring, not poisoning

Categories of Human Studies

Efficacy

How well does the chemical or product accomplish its intended effect?

Exposure

What is the extent of exposure?

Safety

Studies designed to look at adverse effects or biomarkers

Human Studies-Efficacy

- Clinical trials (Phases 2-3) of pharmaceuticals
- Efficacy tests of personal care products and cosmetics
- Insect repellent use on humans

First Clinical Trial? Dr. James Lind and a Cure for Scurvy

- Dr. Lind conducted a systematic experiment with sailors beginning May 20, 1747
- Twelve sailors with scurvy were divided into six groups
- All received same diet but each group received different supplements
- Cider and citrus fruit supplemented groups showed improvement

Human Studies-Exposure

- Designed to characterize pattern and extent of exposure
- Worker and consumer exposure to pesticides (passive dosimetry or biomonitoring)
- Pharmacokinetics studies of pesticides, pharmaceuticals and food ingredients

Human Safety Studies

- Phases 0-3 Controlled Clinical trials of pharmaceuticals
- Patch testing of personal care products
- Determinations of No Observed Adverse Effect Levels in humans to be used in risk assessments for pesticides, food ingredients and other chemicals

Human Studies of Pharmaceuticals

- Phase 0
 - Exploratory, very small number of patients, obtain preliminary pharmacokinetics and dynamics data
- Phase 1
 - Small groups of healthy volunteers, initial safety assessment
- Phase 2
 - Efficacy and safety assessment, larger groups
- Phase 3
 - Multicenter assessments of large groups of patients

The Tuskegee Study

The Tuskegee study took place between 1932 and 1972 in Tuskegee, Alabama. Penicillin was the standard treatment for syphilis by about 1947, but the men participating in this study were not told about this and continued to go without treatment.



Ethical Considerations Required by Regulation

- Declaration of Helsinki (1964)
- The Belmont Report (1979)
- The Common Rule, 45 CFR 46 (1981)
- EPA “Protection of Subjects in Human Research” (2006)

The Common Rule

- Applies to Federal Agencies and Federally funded research
- Research must meet certain ethical and scientific standards that are described in the rule
- Defines core protections for subjects in human studies
- Research must be overseen by Institutional Review Board (IRB) following procedures described in the rule

The IRB

- IRB review needed for most human studies
- Selected FDA requirements for an IRB (21 CFR 56.107)
 - At least 5 members
 - Sufficient experience to determine whether research is ethical, informed consent is sufficient, appropriate safeguards
 - Different professions should be represented
 - At least one “Community member”

Why are Safety Studies in Humans Useful?

- Humans may be more sensitive
- Some toxicological endpoints cannot be easily studied in animal models
- Default approaches to extrapolation from animal studies may overestimate or underestimate risk

Data Generated from Human Studies are Often More Protective

(Dourson et al, 2001)

- 43 Chemicals in EPA with human and animal data were compared
- For 23% of chemicals with RfDs, EPA's human-based "safe" doses are more than 3-fold lower than animal-based values.
- For 41%, EPA's human-based "safe" doses are more than 3-fold higher than animal-based values

Examples of Endpoints Difficult to Study in Laboratory Animals

- Asthma
- Taste and odor
- Visual disturbances
- Headaches
- Argyria



Food Additive Human Data-Quinine

Changes in Electronystagmography (Zajtchuk et al., 1984)

Dose (mg/person)	0	52.5	105
Number of Subjects	4	9	4
Number Responding	0	0	3

Cross-species Peak Plasma/Developmental Toxicity Correlation for Albendazole

Species	Albendazole dose (mg/kg)	Peak Plasma Albendazole sulfoxide (ug/ml)	Developmental toxicity?
Sheep	10	2.5	Yes
Cattle	10	0.57	No
Rabbit	30	8.82	Yes
Rat	10	6.6	Yes
Mouse	30	n.a.	No
Humans	400mg/person (6.6 mg/kg/day)	0.16	No

Food Additives

- Human data important for macronutrients, novel foods and other high consumption ingredients
- Consumption of the ingredient may be at level greater than allowable by the default safety factor approach
- ADI for vitamins, for example, may be less than the RDA

Human Data-Testing of Macronutrients

- Substitutes for fats or carbohydrates may have substantial human exposure
- Laboratory animals can only be fed up to 5% of the diet without nutritional imbalance (5 g/kg)
- 100-fold safety factor results in 50 mg/kg/day ADI from limit dose study
- Insufficient ADI for many macronutrients

Macronutrients

- Approach utilizes human and laboratory animal data (see J. Borzelleca (1996), Reg. Tox. Pharm 23, 15-18)
- Comparative biodisposition study identifies most appropriate laboratory animal for testing
- Repeat dose studies appropriate species
- Repeat dose studies in humans may be conducted
- Reduced safety factor for interspecies sensitivity
- Post-marketing surveillance (active or passive)

Human Studies of Personal Care Products

- Public opinion or legislation (EU) may prohibit animal testing and encourage human or alternative testing of personal care products
- Clinical studies of sensitization and irritation are very common
- Repeat Insult Patch Test (RIPT) is commonly performed
- If no sensitization in 200 subjects, 15/1000 may react in general population
- This response level may be acceptable

Human Studies of Pesticides

- New York state prisoners fed small amounts of the organophosphate, chlorpyrifos (1973)
- Male and female volunteers administered orange juice containing aldicarb (1992)
- Volunteers in California administered methyl isothiocyanate (1994)
- Since the 1996 Food Quality Protection Act, at least 15 safety studies on 10 different pesticides
- Average of 33 human studies per year including exposure and efficacy

Why did FQPA Trigger Human Studies for Pesticides?

- Change in risk assessment approach by requiring cumulative and aggregate exposure assessment
- Cumulative exposure resulted in pesticides with common mechanism of action being assessed jointly
- FQPA safety factor for children
- Result-smaller allowable exposure for many pesticides
- OPs were obvious target of FQPA

Pesticide Studies in Humans



Human Studies Review Board and Protections of Subjects in Human Research on Pesticides

- HSRB established in 2006 by the US EPA in response to ethical concerns regarding human studies of pesticides
- 2006 Regulation prohibits new research involving intentional exposure of children or pregnant women
- Extends the “Common Rule” to other research
- Requires review of protocols of human research
- Reviews of safety studies but also efficacy and exposure studies

EPA Reference Dose (RfD)

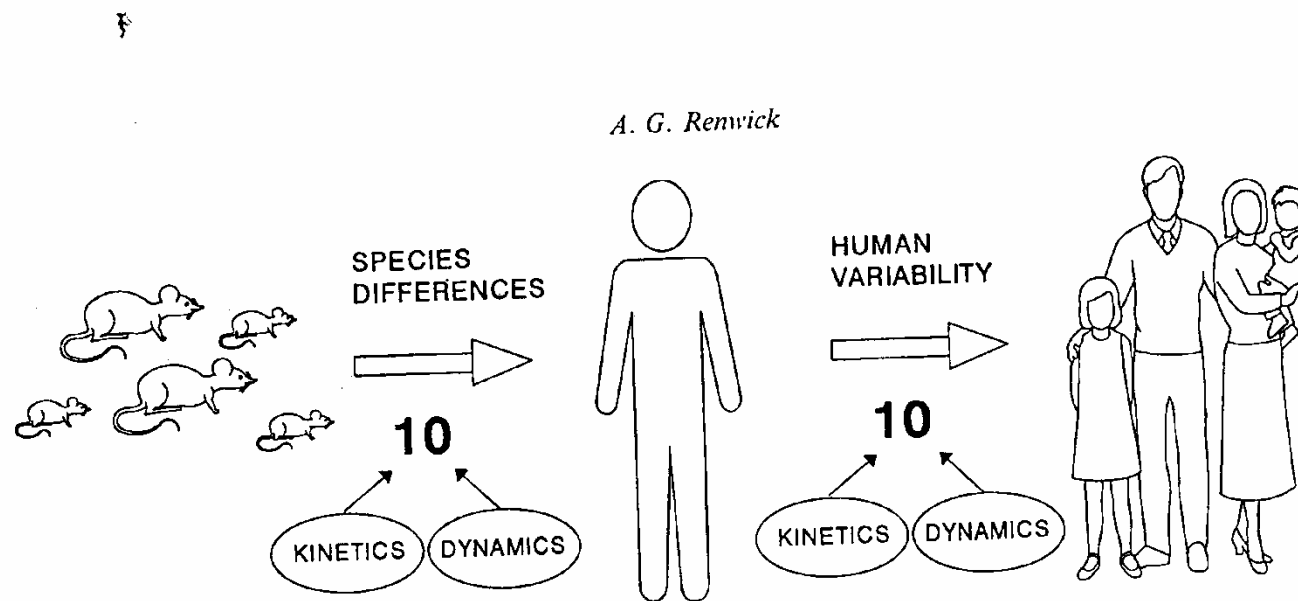
...an estimate (with uncertainty spanning perhaps an **order of magnitude**) of

a daily exposure to the human population
(including **sensitive subgroups**)

that is **likely to be without** an appreciable
risk of deleterious effects during a lifetime.

Default Method for Determining RfD or ADI

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Uncertainty or safety factors are used to extrapolate from a group of test animals to an average human and from average humans to potentially sensitive sub-populations

Figure 1. The use of uncertainty or safety factors.

Chemical Specific Adjustment Factors

- Proposed by the International Programme on Chemical Safety at World Health Organization in 1994 as an alternative to default uncertainty factors in the setting of ADIs
- Based upon Renwick (1993)
- Both the interspecies and intraspecies uncertainty factors are divided into toxicokinetics and toxicodynamics components

Chemical Specific Adjustment Factors

	Kinetics	Dynamics
<i>Interspecies</i>	4.0	2.5
<i>Intraspecies</i>	3.2	3.2

CSAF for Lindane

- Lindane is an organochlorine molecule that has been used for several decades in agriculture, as a veterinary drug and a pediculicide (lice control agent) in humans
- Lindane has a large toxicological data base including several human studies
- Pharmacokinetic and pharmacodynamics studies in humans and laboratory animals

Application of CSAF to Lindane

For intraspecies toxicokinetics WHO recommends addressing the following questions:

1. Are data on interindividual toxicokinetics differences available?
2. Did studies use adequate methods?
3. Has the active moiety been identified?
4. Does toxicity depend on AUC or C_{max}?
5. Is PBPK model required to describe target organ dosimetry?
6. Were doses appropriate to expected human exposure?
7. Were number of subjects adequate to describe variability?

CSAF for Lindane (Intraspecies Toxicokinetics)

Mean	Variability (SD or range)	No. of subjects	Ref.
24.6%	2.5%	6	Feldman and Maibach, 1974
9.3%	1.5%	6	Feldman and Maibach, 1974
0.41 ng/l	0.26-0.69 ng/ml	8	Ginsberg and Lowry, 1983
1.1 ng/ml	0.81-1.33 ng/ml	4	Ginsberg and Lowry, 1983
14.1 ng/ml h	8.0 ng/ml h	4	Dick, Blain and Williams, 1997

CSAF for Lindane

Component	Toxico-kinetics	Toxico-dynamics	Total
Interspecies	2	2.5	5
Intraspecies	2	3.2	6.4
			32

Experts Contributing to Lindane CSAF

- John Doull MD, PhD
University of Kansas
- Robert Krieger PhD
University of California Riverside
- John Ross PhD
Infoscientific.com
- Mark Goldberg PhD
GlobalTox
- Earle Nestmann PhD
CANTOX

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Thank You