Hazard Identification and Classification: Historical Perspective, and Impact

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EUROTOX WORKSHOP 2019
Classification of Carcinogens: What Could Go Wrong?

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Discussion of Cancer Categorization Guidelines
- U.S. EPA as example
- Where these may have failed us
- Where are we now
- Where could we go
Why Do Risk Assessment?

- To provide support for decisions to protect public health and the environment.
  - Complex and controversial
  - Risk assessment summarizes the science
- To deal with lack of data and uncertainties in a rational, scientifically supportable manner
- “... risk assessment should be viewed as a method for evaluating the relative merits of various options for managing risk...” (Science and Decisions 2009)
The 4 Step Process 1983

- Hazard Identification
- Risk Characterization
- Exposure Assessment
- Dose Response Assessment

Risk Management

Risk Communication
Risk Assessment

- Hazard Identification
- Exposure Assessment
- Dose Response Assessment
- Risk Characterization

Risk Management

- Statutory, legal considerations
- Politics
- Social Factors
- Available Technology
- Economics

Risk Management Options

Mode of Action

'83 Risk Assessment Paradigm '19?
NRC (1983) advised US Federal Agencies to publish guidelines for risk assessment

EPA Guidelines and guidance

- Gene Mutation, Cancer, Developmental Toxicity, Mixtures, Exposure (1986)
- Reproductive Effects (1996)
- Neurotoxicity (1998)
- Revised Exposure (1992)
- Revised Cancer Guidelines (2005)
- Microbial Risk Assessment (2012)
Progress in Cancer Risk Assessment

1986
Labels, letters, numbers
Strict rules of evidence (limited, sufficient)
A carcinogen is a carcinogen is a carcinogen
No safe exposure to a carcinogen; linear low dose

Early 2000’s
Narrative categories
More integrated WOE
Consider MOA
Conditions of carcinogenicity
Use MOA in low dose extrapolation

Now?
Do we need carcinogen as a label?
AOP and MOA and WOE
Human relevance of hazard at exposures relevant to humans
Science Evolves

- Effects assessment includes consideration of Hazard Identification and Dose Response Assessment

2005 Cancer Guidelines. What’s Different from 1986?

- Analyze data before invoking default options.
- Mode of action is key in decisions.
- Weight-of-evidence narrative replaces the previous “A-B-C-D-E” classification scheme.
- Two step dose response assessment
  - Model in observed range
  - Extrapolate from point of departure
- Consider linear and non-linear extrapolation
- Address differential risks to children
**Rules and Boxes**

**STRUCTURE OF 1986 GUIDELINES**

1. Animal/Human Tumors
2. Classification A,B,C,D,E

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**WoE Process**

- Hazard Assessment
  - Animal/Human Tumors & Other Key Data

- Hazard Characterization
  - Conditions
  - MoA

- Dose Response
  --BBDR
  --Several Defaults

- Risk Characterization
  Robust qualitative & quantitative description

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**Data Used in Hazard and Dose Response Assessment**

- Human Studies
- Data from other species
  - Standard screening and toxicity studies
  - Toxicokinetic and metabolic studies
  - Mode of action information
- Other relevant information (e.g., chemical and physical properties, SAR, etc.)
Lindane – What constitutes “sufficient?”

Positive response in two well conducted animal studies e.g. NTP bioassay

Analysis of Tumor Data
Animal Data - Long-term Carcinogenicity Studies

- Long-term Carcinogenicity Studies: objective is to determine the potential carcinogenic hazard and dose-response relationships of the test agent.
- NTP bioassay
  - F344 rats, B6C3F1 mice
  - Males and females
  - 90 animals / species / sex / dose
  - Standard histology on all organs
  - Pathology review group
  - EXPENSIVE

Is this one study, two studies, or 4 studies?

Analysis of Tumor Data
Animal Data - Long-term Carcinogenicity Studies

- The high dose is generally selected to provide the maximum ability to detect treatment-related carcinogenic effects, while not compromising the outcome of the study through excessive toxicity, or inducing inappropriate toxicokinetics.
  - MTD

- The purpose of two or more lower doses is to provide some information on the shape of the dose-response curve.
- Vehicle control
  - May serve more than one assay
  - Historical control data are also maintained

Is this well conducted?
Lindane -- What constitutes “sufficient?”

Data from the ’70s
- No tumors in rats NCI
- Mouse NCI (B63F1), maybe liver
- Mouse CF1 males and females, low survival, liver
- Tumors male IRC-JCL, liver
- Male and female dd strain, few survivors, liver
- ORD called it B2/C; OPP called it C

IRIS
- Fought for several months re number of studies and well-conducted
- Today IRIS says no cancer evaluation

Is this a real problem?
- OPP could request more studies under FIFRA
- OW had regulatory boxes under SDWA
  - B2, MCLG = 0
  - C, MCLG = RfD/ safety factor

IARC, Category 2b Vol 20 sup. 7 (1979); Category 1 in Vol 113 (2015)
Benzo[a]pyrene. Is it carcinogenic for humans?
Analyze the available data

Is there too much uncertainty or is critical information lacking?

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There too much uncertainty or is critical information lacking? [Y] [N]

- **Y**: Invoke a default option
- **N**: Conduct risk assessment

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Risk Assessment Science
Use Data Before Invoking Defaults
Hazard Characterization

- Includes dose response assessment and hazard identification
  - IARC does not do dose response assessment
- Considers conditions under which effect is produced
  - Route specific effects
    - e.g. Cr VI, coal tar
  - Effects not relevant to humans
    - e.g. alpha-2-u-globulin, saccharine
  - High dose only effects
    - e.g. chloroform
Under the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996; U.S. EPA, 1999), chloroform is likely to be carcinogenic to humans by all routes of exposure under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues (U.S. EPA, 1998a,b). Chloroform is not likely to be carcinogenic to humans by any route of exposure under exposure conditions that do not cause cytotoxicity and cell regeneration. This weight-of-evidence conclusion is based on: 1) observations in animals exposed by both oral and inhalation pathways which indicate that sustained or repeated cytotoxicity with secondary regenerative hyperplasia precedes, and is probably required for, hepatic and renal neoplasia; 2) there are no epidemiological data specific to chloroform and, at most, equivocal epidemiological data related to drinking water exposures that cannot necessarily be negative, although there are some scattered positive results that generally have limitations such as excessively high dose or with confounding factors. Thus, the weight-of-evidence of the genotoxicity data on chloroform supports a conclusion that chloroform is not strongly mutagenic, and...
Narrative Classification

- **Conclusions**, including a weight-of-evidence descriptor:
  - Carcinogenic to humans
  - Likely to be carcinogenic to humans
  - Suggestive evidence of carcinogenic potential
  - Inadequate information to assess carcinogenic potential
  - Not likely to be carcinogenic to humans

- **Conditions of carcinogenicity:**
  - Route, magnitude, and duration of exposure
  - Susceptible populations and lifestages

- **Summary of key evidence supporting conclusions**

- **Summary of key default options invoked**

- **Summary of potential modes of action**
All “Carcinogens” Are Not Equal

IARC 2A
- Several PAH
- Nitrosoamines (NDMA, MMS, DEN)
- Adriamycin
- Glyphosate
- Red meat
- Hairdresser or Barber

IARC 2B
- Kepone
- Ethylmethanesulphonate
- Riddelline
- Chloroform
- Gasoline
- Coffee

Incomplete information; may be misleading
October 2, 2014

Chemicals Evaluated for Carcinogenic Potential
Office of Pesticide Programs
U.S. Environmental Protection Agency

BACKGROUND

What is this list?
The following list provides an overview of pesticide chemicals evaluated for carcinogenic potential by EPA's Pesticide Program through October 2012. The evaluation of many of these chemicals is an ongoing process. Therefore, the information in this list may be subject to change as new and/or additional data are submitted to EPA. This list will be updated annually.

How should the information provided in this list be used?
Although this list is available to the public, note that the list represents only the potential carcinogenicity hazard for the chemical with no consideration of exposure information. This list is not intended to be used independent of the full risk assessment for the chemical. When EPA completes a risk assessment on a pesticide, a variety of toxicity information, including potential for noncancer effects (e.g., neurotoxicity, developmental and reproductive toxicity, immunotoxicity, etc) and carcinogenicity, are considered in determining whether to register a pesticide and what requirements for use of the pesticide need to be in place to protect human health. The simple fact of being listed here does not imply that the pesticide poses a significant cancer hazard to the public from use.
• Consumer advocates and TV doctor tested supermarket samples of apple juice for total arsenic, reporting that a significant number of them contained arsenic at levels exceeding EPA’s limit for arsenic in drinking water, 10 ppb.
• Our children are drinking potentially dangerous juice and their health may be at risk; FDA should regulate apple juice more stringently.
• Dr. Oz: “There needs to be accountability by regulatory agencies and industry trade groups to parents who are doing their best to raise healthy children . . . as a parent, I would rather be safe than sorry.”
• Apple juice sales decrease sharply
Science and Perception

As Science, Policy

- Cancer associated with lifetime exposure to high drinking water arsenic levels (>150 ppb) but not with lower levels.
- Analytic method for arsenic in juice not the same for \( \text{H}_2\text{O} \)
- FDA limits the permissible level of arsenic in juice (23 ppb); EPA limits arsenic in drinking water (10 ppb) based on 2 l/day for 70 yrs in a 70 kg person
- Juice is tested by apple growers, juice producers, FDA

As in the Media

- There shouldn’t be arsenic in apple juice at all; children are being subjected needlessly to a known health risk.
- FDA isn’t doing its job.
- Consumers trust Dr. Oz & consumer advocates more than juice industry.
- Consumers would “rather be safe than sorry” especially when children’s health is involved
FDA proposed a new limit on As in juice.

- New FDA limit in juice: 23 ppb
- EPA limit in water: 10 ppb
- FDA limit: 23 ppb
- 150 ppb
Why Do these Examples Pose a Problem?

- May result in banning some useful products
  - And substitutes may be more harmful
- Can frighten the public unnecessarily
  - Vaccines and autism
  - Everything causes cancer
  - I don’t trust scientists or science
- Can withdraw attention and resources from more urgent problems
  - BPA vs. Zika vs. ?
**Hazard Classification 1986 Cancer Guidelines**

<table>
<thead>
<tr>
<th>Class</th>
<th>Hazard Type</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Human carcinogen</td>
<td>Sufficient human evidence</td>
</tr>
<tr>
<td>B1</td>
<td>Probable human carcinogen</td>
<td>Limited human evidence</td>
</tr>
<tr>
<td>B2</td>
<td>Probable human carcinogen</td>
<td>Sufficient animal evidence</td>
</tr>
<tr>
<td>C</td>
<td>Possible human carcinogen</td>
<td>Limited animal evidence</td>
</tr>
<tr>
<td>D</td>
<td>Not classifiable</td>
<td>Inadequate human and animal evidence</td>
</tr>
<tr>
<td>E</td>
<td>Evidence of noncarcinogenicity</td>
<td>Sufficient negative evidence</td>
</tr>
</tbody>
</table>

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**Risk = Hazard x Exposure**

There are thousands of chemicals, most without enough data for evaluation.

High throughput in vitro methods (e.g., ToxCast) beginning to bore fruit on potential hazards for many of these chemicals.

High throughput toxicokinetic methods (ToxTK) approximately convert these in vitro results to daily doses needed to produce similar levels in a human (nM/kg).

High throughput exposure forecasting (ExpoCast) can bound mean human exposures for key populations.

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**Breaking Down the Dichotomy**

- **Cancer**
  - Non-Threshold
  - Non-reversible
  - Risk: Value
  - Risk: Factor
  - Risk:
  - Risk: Specific Dose

- **Non-Cancer**
  - Threshold
  - Reversible
  - Safety
  - Safety Value
  - Risk
  - Tolerance
Accepted Manuscript

Chemical carcinogenicity revisited: A unified theory of carcinogenicity based on contemporary knowledge

Douglas C. Wolf, Samuel M. Cohen, Alan R. Boobis, Vicki L. Dellarco, Penelope A. Fenner-Crisp, Angelo Moretto, Timothy P. Peetoo, Rita S. Schoeny, Jennifer G. Seidel, John E. Doe

PII: S0273-2300(19)30021-2
DOI: https://doi.org/10.1016/j.yrtph.2019.01.021

Population model of chemical carcinogenesis. Requires sufficient exposure and maintaining a sustained stress environment.
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US EPA Guidelines for Cancer Risk Assessment

https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment


