

Scientific Sentinels:

What Should Constitute Minimal *Scientific* Evidence
For Identifying Substantial Public Health Problems?

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Summary of Issues

- The Collegium endorses the Precautionary Principle for protecting the public and workplace health; when PP pre-market protections cannot be utilized, what is a **good second best solution**?
- Generic ***philosophic considerations*** for identifying substances of *substantial public health concern*.
- ***Plausible scientific guidelines*** for identifying *carcinogens* as of substantial public health concern.
- An urgent challenge for the future: **developmental toxicants**--
What are appropriate scientific considerations?

Precautionary Principle and the Second Best

- The Collegium endorses the use of the Precautionary Principle for protecting human health and sustainability of the of the environment.
- It urges more **pre-market** testing and approval laws in order to ensure that substances are not likely to present harm or risks of harm to the public or the workforce.

Precautionary Principle and the Second Best

- The moral concerns that animate public health protections, the PP and the Collegium's views-- "First, do no harm"-- can be in tension with non-moral scientific norms under post-market laws that implicitly insist on certain degrees of "good evidence" (left unspecified) needed in science.
- The imperative to protect the public and workplace health argues for doing this as quickly as possible to prevent harm from occurring and prevent experimenting on humans, but typical scientific studies do not permit this.

Precautionary Principle and the Second Best

- Conducting studies and assembling the evidence after exposure takes considerable time, resources and effort, delaying protections for those who have already been exposed or those who are at risk because a toxicant was not detected in pre-market testing (if it was even conducted).
- Any insistence on human studies requires the public or workforce to be at continued risk; requires people to be harmed to show that they can be harmed.

Precautionary Principle and the Second Best

- Many legal systems do not conform to a PP legal strategy. At present the vast majority of substances (e.g., in the U.S.) are subject to post-market laws: they enter commerce without legally required testing; agencies take preventive action only if there is scientific evidence of harm or risk of harm.
 - Also, previously untested products may emerge as problems, e.g., PBDE's, or
 - substances subject to pre-market laws may be missed or mistakes made in assessing their toxicity.

Precautionary Principle and the Second Best

- The tensions between public health protections and scientific conventions concerning sufficiency of evidence are greatly heightened in these circumstances.
- For such circumstances what is an appropriate “second best” strategy to serve the public health?

Generic philosophic considerations for identifying substances of *substantial public health concern*

- How can one resolve in a health-protective manner the tensions between imperatives to protect public health with the extensive, time-consuming and science-intensive procedures that might be needed to document substances of substantial public health concern?
- Make them as quick as possible and not dependent upon human evidence.

Generic philosophic considerations

- I strongly reject a U.S. National Academy of Sciences Committee view that
 - requires epidemiologic evidence for drawing any positive conclusions about potential carcinogenicity; animal evidence and other test information are used only to confirm cancer causation once epidemiological associations have been demonstrated. (NAS, 2006)

Generic philosophic considerations

- Call the science in question the science for a “**substantial**” public health problem **meriting serious attention**.
 - ◆ **Not**: highly certain, fully supported scientific evidence--sufficient for taking public health actions in almost any legal or social venue, e.g., good epidemiological studies supported by good animal studies and a reasonably well understood biological mechanism for the toxic effects.
 - ◆ **Not**: Evidence merely indicating a “possible” toxic effect.
- But the Goldilocks’ science--just right for the issue.

Generic philosophic considerations

- Also, not Bradford Hill's problem:
 - ◆ Lesser evidence for “a drug for early-morning sickness in pregnant women,” and
 - ◆ For changing “from a probably carcinogenic oil to a non-carcinogenic oil in a limited environment and without too much injustice if we are wrong.”
 - ◆ But “very strong evidence [is needed] before we made people burn a fuel in their homes that they do not like or stop smoking the cigarettes and eating the fats and sugar that they do like.” (Hill, 1965)
- He is weighing the certainty of the scientific conclusion against the social costs of action and possible mistakes.

Generic philosophic considerations

- My concern: the scientific decision that occurs before Hill's more comprehensive social decision or before the subtleties of the law are introduced.
- We should seek the kind and quality of evidence that public health-oriented scientific organizations could take positions on that is needed to regard a substance or exposure as of "substantial public health concern."

Generic philosophic considerations

- Such scientific judgments would put the substances in question on an agenda for regulatory action that presumptively should be taken unless there were good reasons to the contrary for taking it.
- Such judgments would resemble *rebuttable legal presumptions* that support required inferences once certain facts have been established. They may be rebutted if there is evidence to the contrary.

Generic philosophic considerations

- Such presumptive scientific evidence plus lists of substances satisfying the criteria would provide
 - ◆ **Alerts** to substantial public health problems in developed and developing countries.
 - ◆ Agencies with **candidate substances** for regulation or product substitution.
 - ◆ **Support for conscientious scientists** who believe they have identified such substances of concern.
 - ◆ Some **support for scientists** who testify in **personal injury cases** when judges fail to recognize the “probabtive” value of a body of scientific evidence.

Generic philosophic considerations

- Ideally, public health scientists would identify the kinds of evidence that would permit scientists and public health agencies to have good scientific reasons to **intervene as early as possible** and to begin to take actions to **reduce risks** to the public.
- Moreover, such evidence would be based upon studies **not requiring human data**, but weight of the scientific evidence data identifying a substance as of substantial public health concern.

Generic philosophic considerations

- At present the most promising guidelines for carcinogens to pursue are those that emphasize the use of **animal data alone**, or **animal data** together with **mechanistic data** or **mechanistic analogies** to a class of substances that are known or probable carcinogens.
- Unfortunately, animal studies are still time-consuming.
- The public health community should continue to search for less time-consuming kinds of studies.

Scientific guidelines for identifying *carcinogens* as of substantial public health concern

- IARC criteria for identifying substances as “probable human carcinogens” (2A) without requiring human studies:
 - In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental *animals* and *strong evidence* that the carcinogenesis is mediated by a *mechanism* that also operates in humans
- Requiring “strong evidence” that the C. “is mediated by a mechanism that also operates in humans. . .” may be too demanding-- might “scientifically plausible evidence” work?

Scientific guidelines

- NTP criteria for identifying substances as “reasonably anticipated to be human carcinogens” without human data:
 - there is **sufficient evidence** of carcinogenicity from **animal studies**, indicating “an increased incidence of malignant and/or a combination of malignant and benign tumors
 1. in **multiple species** or **at multiple tissue sites**, or
 2. by **multiple routes of exposure**, or
 3. to an **unusual degree** with regard to incidence, site, or type of tumor, or age at onset, or

Scientific guidelines

- NTP criteria (without human data):
 - or, c) there is less than sufficient evidence of carcinogenicity in humans or laboratory animals, . . . [but] the agent, . . . belongs to a **well-defined, structurally related class of substances** whose members are listed . . . as either **known** to be a human carcinogen or **reasonably anticipated to be** a human carcinogen, or there is convincing relevant information that the agent acts through **mechanisms** indicating it would likely cause cancer in humans

Scientific guidelines

- The U.S. EPA's category "Likely to Be Carcinogenic to Humans"
 - An agent that has tested positive in animal experiments in more than one species, sex, strain, site or exposure route, with or without evidence of carcinogenic potential in humans (e.g., Morando's Aspartame studies?);
 - A positive tumor study that raises additional biological concerns beyond that of a statistically significant result, for example, a high degree of malignance or an early age at onset;
 - A rare animal tumor response in a single experiment that is assumed to be relevant to humans; or

Scientific guidelines

- EPA's "Likely to Be Carcinogenic to Humans"
 - or, a positive tumor study that is strengthened by other lines of evidence, [e.g.], either plausible (but not definitively causal) association between human exposure and cancer or
 - evidence that the agent or an important metabolite causes events generally known to be associated with tumor formation (such as DNA reactivity or effects on cell growth control) likely to be related to the tumor response in this case

Scientific guidelines

- Illustration: Ron Melnick's article on epoxides:
 - animal studies by IARC and NTP have identified many epoxides and epoxide-forming chemicals as carcinogenic agents with several . . . **known human** carcinogens (**vinyl chloride, ethylene oxide, benzene, butadiene**) and some . . . **probable** human carcinogens (**vinyl bromide, vinyl fluoride, acrylonitrile, chloroprene, isoprene, glycidol**), but others (**ethylene, styrene**) are not classified in either category.
 - All appear to **act by a common mechanism**, providing good reason for classifying even unclassified substances as probable human carcinogens. (Melnick,2002)

Scientific guidelines

- Illustration: Melnick on epoxides: The body of scientific evidence for mechanistic and other similarities within this class of substances

“raise serious concerns of occupational and environmental cancer risk from exposure to epoxide chemicals. . . reducing occupational and environmental exposures to these chemicals will reduce human cancer risks”
- This class of substances has properties that the science seems to support as of “substantial public health concerns,” provided there are also **appropriate exposures**.

Scientific guidelines

- Two recent NAS committees have proposed similar considerations for identifying substances as of “substantial public health concern” (my term):
 - Strong epi studies but not fully supportive of a causal relationship, or
 - “if there is strong evidence from animal studies or mechanistic evidence, not contradicted by [good?] human or other evidence, then the overall evidence might be categorized as **Equipoise and Above** [more likely than not].”
(IOM VA 2007)

Scientific guidelines

- All new and existing chemicals should be tested, in accordance with practical needs. . . (including human exposures).
 - In order to reduce the use of animal studies agencies should group chemicals “of similar structural class and the in-depth testing of only one or a few representative chemicals; risk assessments of all chemicals in the class would then be based on the resulting data. [In such groupings] “known modes of action [e.g., nicotine agonists] should be emphasized.” (NAS, Toxicity Testing for Environmental Agents, 2006)

Scientific guidelines

- “Ideally, regulations and risk assessment will evolve with testing capabilities and scientific understanding. That issue will increase in importance with greater use of screening approaches that produce indirect evidence (in vitro, gene arrays, and mode-of-action screens) for both cancer and non-cancer endpoints.” (NAS, Toxicity Testing for Environmental Agents, 2006)
- The same should be said for classifying substances as of substantial public health concern.

What are appropriate scientific studies for identifying developmental toxicants as of concern?

- An urgent problem of concern: developmental toxicants, e.g., see the Faroes' Conference statement.
- What might be plausible criteria for identifying toxicants as of substantial developmental toxicants of concern (short of having human epi studies)? Must address for our children!
- Are there criteria for good animal evidence for identifying likely human developmental toxicants?