The Risks of Dioxin: Assessing the EPA Reassessment

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1. Introduction

For at least 15 years several national and international agencies have proposed environmental and occupational policies based upon quantitative estimates of the human health risks of exposure to 2,3.7,8-TCDD and structurally related compounds (referred to as "dioxins" in this paper). Although these estimates all mostly utilize the same data and focus on the same outcome -- cancer -- they have ranged over 5 orders of magnitude. Their variance has largely resulted from assumptions as to mechanisms of action and policy choices on extrapolating human exposures from experimental dosimetry. In 1990 the US EPA commissioned a third risk assessment for the dioxins; this was completed in 1994 and is presently under review. It is the first attempt to incorporate current theories on mechanism and to extend policy concerns to endpoints other than cancer and to species in addition to humans.

All risk assessments for dioxins have been conducted in an intensely political context[1]; if controlling exposures to these chemicals were less controversial, regulatory agencies would long ago have taken courses of action to reduce ongoing sources and to abate existing environmental reservoirs. The problems in reaching consensus on both analysis and action in the case of dioxins may exemplify several problems confronting policymaking in the present post "command and control" era. These problems are: integration of science into policy; use and abuse of risk assessment; alternatives to chemical-based approaches to risk reduction; the crisis of defining goals and managing remediation; valuing noncancer endpoints and nonhuman targets; and prioritization.

The dioxins were never intentional products of the synthetic organic chemical industry. It is estimated that less than 500 kg of dioxins and furans are released per year in the US; overall, from 1940 to 1990, less than 10 metric tons of dioxins and furans were released from chemical products, wastes, and incineration sources[2]. This could be contrasted with mass balance data on lead, in which it is estimated that millions of tons were released from 1925 to 1985 from the use of lead in gasoline alone[3]. Nevertheless, their multiple sources and the persistence of certain compounds in this class have resulted in worldwide contamination of biota and biosphere. PCBs and PBBs, a class of halogenated biphenyls which contain structural analogs to TCDD, were widely used products, useful for heat absorbing and lubricant qualities. Some products contaminated with dioxins were used dispersively (herbicides) and wastes

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containing these chemicals were improperly handled for decades in many countries. However, it is through their generation in incineration and bleaching processes that these contaminants now cause the greatest problems to the environment, to industry, and to governments.

2. History of dioxin risk assessments

The hazards of these contaminant byproducts were evident almost as soon as industry developed to exploit the useful properties of chlorinated benzenes and phenols; the first report of chemical-induced disease (chloracne) was reported in Germany in 1888[4]. Although chemical identification of the dioxins was only published in 1957, their multipotent toxicity was well described in humans and animals by the 1940s. Industrial accidents provided substantial evidence of acute and chronic toxicity in workers, and in 1968 and 1976 (Yusho and Yu-cheng) in others exposed accidentally.

Public concern since the 1970s has been largely exposure-driven. It was primarily the discovery that PCBs, supposedly only used in closed electrical and hydraulic systems, were omnipresent in marine mammals that sparked public concern[5]. Later findings of dioxins in fish, food and human breastmilk[6] sustained public outrage. Like lead, dioxins are now endemic components of the human body burden of xenobiotics.

Governmental responses to dioxins has been slow and inconsistent. For many years, the problem was limited to TCDD and it was assumed that regulation of chlorinated phenols and their derivatives were sufficient to control exposure. However, recognition in the early 1980s that many past waste handling practices had resulted in widespread contamination escalated public concern in such incidents as Times Beach, Love Canal, and Ironbound in the US[1]. The appropriate response to these contaminated sites is as yet undetermined. No formal cleanup standard for dioxins at hazardous waste sites has been promulgated, and the failure to clean up some of these sites has led to conflicts between some environmentalists and those seeking economic development at these sites, often in disadvantaged areas.

Another challenge came with the broader definition of the dioxins as a class of compounds with similar biological properties. In response to a petition filed by the Environmental Defense Fund and the National Wildlife Federation in the US in 1984, the US EPA proposed the concept of toxic equivalency factors, a structure-activity based ranking system for an integrated analysis of exposure and risk. The nature and extent of this TEF system remains controversial[7,8], particularly its expansion to include PCBs because, although much less potent than 2,3,7,8-TCDD, their relatively much greater concentrations in food and biota (often 10^{-3} higher)[6,9] multiplies the problem of an integrated risk management strategy.

The first US risk assessment was elicited by the Times Beach crisis. In 1985 EPA convened an expert panel to provide advice on evaluating risks of TCDD. The resulting document almost exclusively dealt with carcinogenicity and drew upon the only extant data at the time, animal bioassays conducted by Dow Chemical and the National Toxicology Program[10]. Both studies had shown that TCDD was carcinogenic to rats and mice, with varying organ specific tumor yields depending upon species and sex (including reduced incidence of mammary and pituitary tumors). Epidemiologic evidence was largely lacking or inconclusive. Moreover, what was known of the mechanisms of action did not fit existing science-policy models for cancer risk assessment. That is, TCDD does not bind directly to DNA nor does it induce mutations[11,12,13]. These properties have been considered necessary to the science policy

definition of a chemical carcinogen whose risks are appropriately assessed using the low dose linearized multistage model first proposed in 1979 in the US[14]. Despite this, the great potency of TCDD and its ability to induce increased tumor yields absent pretreatment with a mutagen prompted this assessment panel to recommend use of the no-threshold model for human cancer risk assessment. This was clearly a science policy decision; it was consistent with other recommendations to reduce human exposure to the lowest levels possible.

Despite this document, EPA took no regulatory actions except for requiring testing for dioxins in several chemicals and waste streams. In 1988, EPA reopened the dioxin risk assessment, under pressure from the paper industry, which was under public scrutiny following discovery that chlorine based Kraft bleaching of wood pulp could generate dioxins and furans. This realization has resulted in a significant broadening of the issues, as discussed below, to the issue of the industrial use of chlorine. It has been suggested that there is a positive correlation between chlorine concentration and PCDD/PCDF emissions[2].

The overt question of the second EPA risk assessment was to explore if sufficient new information existed to cause reconsideration of the 1985 conclusion. After review of both epidemiological information (some data were available from cohorts occupationally and accidentally exposed in the US, Europe, and Japan) and mechanistic research, the panel concluded with somewhat stronger qualitative conclusions as to dioxin's carcinogenicity and reaffirmation of the applicability of the no-threshold model for risk assessment at low dose[1]. No new animal bioassay information was available[10].

Yet this was not enough in the US. Germany and Scandinavia, among other countries took actions on a broad basis to restrict the production of chlorinated byproducts, including dioxins from industrial processes and incineration[15]. In the US yet another risk assessment was undertaken in 1990. This latest process has now concluded, reaching several important conclusions, some of them supportive of earlier statements and some of them contributing new elements to the science policy debate. The 1994 risk assessment confirmed earlier conclusions as to the likely nature of dioxin as a human carcinogen. Whether this judgement will be changed to classify dioxin as a "known" human carcinogen is unclear, given the difficulty in clarifying exposures and the relatively small cohorts available for analysis. However, for the first time, equal weight was given to noncancer risks to development, reproduction, and immune function. Moreover, effects on nonhuman organisms were reviewed in depth with field data ("eco-epidemiology") cited as evidence. Second, the broad class of dioxins and furans resembling TCDD were expanded by the addition of coplanar PCBs. Third, the extent of existing levels of contamination and human exposures was extensively discussed, and it was suggested that for some portion of the US population, exposures to these compounds, primarily through food, was already at levels within the range considered to be toxic to reproduction and development (Birnbaum, 1994). Fourth, the mechanism of action of dioxins was identified as receptor mediated alterations in gene expression, and this mechanism was proposed to be an appropriate basis for using linearized mathematical models to estimate low dose cancer risk[16,17].

3. Lessons from dioxin: science and policy

This extended process of assessment and reassessment has done little to enhance public confidence in policymaking in the US. Actions taken by industry to reduce ongoing sources of dioxins may or may not reduce human and wildlife exposures in the absence of

regulatory action. Because of the importance given to risk assessment as an instrument of policymaking in the US, it is important to evaluate what the dioxin issue reveals.

1. *The dioxin assessment demonstrates that risk assessment methods will not in themselves lead to more efficient or less controversial policymaking.* The stated purpose of risk assessment in the early 1980s and in current regulatory reform legislation in the US, was to enhance the role of science in decisionmaking and to thereby reduce controversy and increase the efficiency of regulatory controls by identifying high priority problems and calibrating regulations accurately in order to maximize the net benefits of such interventions. The dioxin risk assessments have been highly influenced by political controversy and they have yet to demonstrate net benefits for public health or the environment (Webster and Commoner, 1994). In contrast, regulations to restrict or ban production and uses of PCBs and lead in the US, taken in the absence of formal risk assessments, have demonstrably reduced environmental levels of these compounds and human exposures[18,19].

2. *risk assessment as a tool of policy provides no guidance on how to reach resolution.* Recent scientific advisory groups have recommended an iterative approach to risk assessment[14]. However, far from focussing debate or resolving issues for policymakers, the successive dioxin risk assessments have become larger in scope and reach. From the initial focus on TCDD and hexaCDDs in 1985, the range of chemicals now in discussion includes PBBS, PCBs, dibenzofurans, and other structural analogs. Some have suggested that the real issue is chlorine, or persistent chlorinated compounds[20].

3. *Mechanism based approaches to risk assessment do not assist in making difficult policy decisions.* Application of new information on dioxin mechanism has provided no new methods for risk assessment. Rather, the argument appears to be whether or not receptor-based mechanisms are likely to produce linear dose:response relationships at low dose[12,16,21]. The hormone-like nature of the dioxins, and their ability to interfere with endogenous hormones such as estradiol, glucocorticoids, thyroxine, retinol, insulin, and growth factors[13,22], has opened a debate on the significance of xenobiotic hormone-like agents in the environment, which may be extended to include nonpersistent compounds such as the nonylphenols, as well as the dioxins[23].

4. *Whatever assessment of dioxin risk is adopted, little is known of the relative importance of various sources and pathways of exposure for human populations or wildlife.* The dioxin debate has been so long focussed on characterizing risk that very little data exists on sources[2]. EPA admits that about 60% of current dioxin inputs cannot be identified with confidence. Very few would argue that the dioxins are devoid of risk, and most would adopt as prudent policy the goal of reducing controllable sources that contribute to human exposure and environmental contamination. The relative role of past discharges and releases, including industrial accidents, may outweigh these present inputs. If this is the case, it may be difficult to increase the rate of reductions in biota beyond that observed for other persistent pollutants such as lead, PCBs, and DDT. Success in reducing human body burdens of these three toxicants suggests that controlling current inputs and identifying significant environmental sinks are both important to reducing collective exposures and risks.

4. **References**

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