HEALTH CONSEQUENCES OF DIOXIN EXPOSURE

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Abstract
TCDD is often called the most toxic man-made chemical because of its potency to cause health effects in a wide variety of vertebrates. Structurally related persistent compounds, known as "dioxins", have the same plethora of responses. Dioxins have effects in multiple tissues and organs at various life stages, including developmental, reproductive, cardiovascular, hepatic, dermal, and endocrine toxicities, among others. TCDD is also a human carcinogen.

Introduction
Since chloracne was first reported over 100 years ago, and TCDD ("dioxin") was identified 50 years ago, concern has grown about the consequences of human exposure. Several unfortunate poisoning incidents have helped inform the consequences of high levels of exposure to dioxin and related compounds; however, there is ongoing debate about the results of lower levels of exposure which have occurred in several populations, and continue in parts of the general population. Much of our understanding of the human effects of dioxins comes not only from studies in experimental animals, but from effects which have been observed in multiple species of wildlife. Key reviews are given as references[1-7].

Results and Discussion
TCDD is the prototype for a family of chemicals which have a common mechanism of action, induce a common spectrum of responses, and are both environmentally and biologically persistent. The common mechanism, which involves persistent binding to a highly conserved cellular receptor, the "Ah receptor", is necessary but not sufficient for all of the effects of dioxins. This initiating pathway occurs in people, as well as all other vertebrates examined. Human cells and organs in culture respond similarly to those of animals. For certain responses, human tissues appear less responsive than certain rodent cells; for other effects, humans are equally or more sensitive.

Dioxins alter metabolism, growth factors, hormones, proliferation and differentiation, and apoptosis. They have been shown to cause a plethora of effects, ranging from changes in molecular biology and biochemistry through changes at the levels of cells, tissues, organs, and the entire organism. While not all responses are common to all species, there are many effects which are seen in a majority of organisms in which they have been investigated. The concept of dioxin as an environmental hormone, along with the fundamental role of the Ah receptor in normal biology, lends credence to the key role of context and complexity in the pattern of responses observed.

The understanding that dioxin exposure is ubiquitous, although levels may vary, is extremely important in the interpretation of human studies. There is no one with zero exposure to dioxin-like compounds. It is also essential to compare exposure on the basis of total dioxin equivalency, TEQ, not look only at TCDD in isolation as we now know that the difference between many of the TCDD-exposed cohorts and the TEQ in the background comparison population is often very small.

Chloracne is one of the few dioxin responses for which there is unequivocal consensus that it is a result of exposure to dioxins. However, it is a high dose effect and may reflect biological susceptibility. There is also general consensus that dioxin has the potential to be a human carcinogen, but whether there are unique sites of tumors and what body burden is associated with the response is not definitively known. Cardiovascular disease, type 2 diabetes, endometriosis, and endocrine disruption have all been reported in multiple studies. In concert with the results of animal studies, developmental effects may be of greatest concern as effects on skin, teeth, bones, nervous system,

reproductive system, and the immune system have been seen in multiple populations. Diverse populations have been investigated for TEQ effects which seem relatively generalizable across ethnic and cultural boundaries.

Conclusions

While dioxins are extremely persistent, levels are decreasing in people in response to the effectiveness of the regulatory agendas world wide which have led to a decrease in dioxin emissions into the environment. Back extrapolation to predict human body burdens in the past are complicated as the half-lives of these compounds are dependent upon dose, body composition, and possibly age. Since most human exposure is a result of microcontamination of the food supply, ecological measures of exposure are inaccurate in establishing differential body burdens. Thus, the most informative data on human health requires prospective studies with ongoing measures of internal exposure to total TEQ, not just TCDD. Continued analysis of existing cohorts with ongoing follow-up will help to resolve issues of dioxin effects in people, only if internal dose is measured and appropriate studies and endpoints are examined in truly more highly exposed populations.

Disclaimer: This abstract does not reflect Agency policy.

References

1. Birnbaum LS *Environ Health Perspec* 1994; 102(9):157
2. IOM *Veterans and Agent Orange - Update 2004*, 2005; Washington, DC, National Academies Press. (www.nap.edu)
3. IARC *Evaluation of Carcinogenic Risks to Humans: Polychlorinated Dibenzo-p-dioxins and Polychlorinated Dibenzofurans*, 1997; 69. World Health Organization.
4. NAS *Health Risks from Dioxin and Related Compounds - Evaluation of the EPA Reassessment*, 2006; Washington, DC, National Academies Press http://www.nap.edu/catalog/11688.html
5. Schecter A, Gasiewicz T 2003, *Dioxins and Health, 2nd Ed*, John Wiley and Sons. Hoboken, NJ, 2003 952 pp., ISBN: 0-471-43355-1
6. US EPA, *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo*-p-*Dioxin (TCDD) and Related Compounds National Academy Sciences (NAS) Review Draft*, 2004; http://www.epa.gov/ncea/pdfs/dioxin/nas-review/
7. Van Leeuween FSR, Younes MM *Food Additives Contam.* 2000; 17:223-369.