How Poisoning Episodes Inform Our Understanding of Population Effects at Background Exposures

Linda S. Birnbaum[1]

[1]National Health and Environmental Effects Research Laboratory, United States Environmental Protection Agency

Introduction

During the past one hundred years, there have been a number of episodes involving high exposures to 2.3.7.8-TCDD or related compounds. Some of these have been accidental; a few intentional. Some have been occupational, and others environmental. Some have involved relatively large numbers of people, others only one person. Poisonings are distinguished from general population exposures only by the quantity of dioxins involved. Dioxins are ubiquitous environmental pollutants. Dioxins involve not only TCDD and related PCDDs, but also polychlorinated dibenzofurans, biphenyls, and some naphthalenes. In addition, certain brominated compounds are structurally related and cause the same spectrum of responses. A sampling of these high level exposures have been discussed in this session: recent intentional poisonings of Viktor Yuschchenko and of several people in Vienna by pure TCDD; occupational poisoning of laboratory workers by TCDD or TBDD; accidental exposures of large number of people to TCDD in Seveso or to PCBS/PCDFs in Yusho and Yucheng. Many other exposures of occupational workers and of populations surrounding dirty incinerators have been noted. However, the actual number of people who have been exposed to extremely high levels of dioxins is quite small. All of the occupational cohorts with elevated TCDD exposure number less than ~5000 workers.

High Doses

What can we learn from these high-dose exposures about background, or ambient, exposure to the general population? One of the first points to clarify is what we mean by “high”? Clearly, the intentional poisonings in which the first measured blood concentrations were $\geq$100,000 ppt lipid are exceptionally high levels. These unfortunate incidents have clearly shown us that people do not have the same sensitivity to the acute lethal effects of dioxins as guinea pigs or mink or trout. The common physical response seen in all of the highly exposed people, whether the intentional or accidental poisonings, and whether to pure TCDD or to a mixture of other dioxins, is chloracne. In fact, the presence of chloracne is clear and sufficient proof that exposure to dioxin-like compounds have occurred - in other words to TCDD or other compounds which fit the criteria of structural similarity, persistence, common spectrum of responses, and high affinity binding to the Ah, or dioxin, receptor. However, the absence of chloracne does NOT mean the absence of dioxin exposure, but that the necessary levels of exposure have not occurred. There also appear to be susceptible populations, based on age, genetics, etc., which are still to be defined.

Other effects of high exposures seem to be nerve pain and GI effects. Lipid disorders and headaches have also been reported. Some of the acute effects, including severe rashes, may be related to other compounds present during the exposure, such as solvents. Long term effects of high exposure are being investigated in several populations; it is too soon to see whether long term effects will be seen in the Viennese or Ukrainian poisonings.

One of the most important understandings to emerge is that “high dose” is a relative term. In the Seveso situation, while a small number of people were very highly exposed ($\geq$10,000ppt lipid), the median TCDD concentration in the most highly exposed zone A was ~450.[1] If one compares this to the “unexposed” area (non-ABR) in which the TCDD concentration was ~ 15 ppt, this would suggest ~30X higher level. However, the total TEQ in a comparison population at a similar time was ~ 100 ppt TEQ. [2] This would only mean a 4X greater level of total dioxins. Thus, in one case the expectation would be that the people were much higher than the “controls;” in fact, when the actual background is taken into consideration, their exposure is not as high. Could this explain why it has been hard to detect major effects, especially if the studies do not measure the actual body burdens but are ecological in design? The epidemiological studies show associations between elevated exposures to dioxins and cancer, cardiovascular disease, type II diabetes, among others. We can never prove, even in the unfortunate intentional poisonings, that any effects which take years to develop, such as cancer or heart disease, are due to the dioxin poisoning, when 1/3 people get cancer anyway and 1/2 develop heart disease!

Animal Experiments

In order to understand the effects of dioxins, whether at high poisoning doses, or at the low level present in the general population, we need to rely on studies from animals - both experimental investigations as well as observations from wildlife. Dioxins cause a plethora of effects in multiple tissues of both sexes of multiple species throughout the *Vertebrata*. Human cells, tissue, and organs in culture respond similarly, and at similar concentrations, to those of animals. [3] Dioxin is a known rodent (and fish) carcinogen, and the body burden associated with cancer is similar. [4] Effects on the cardiovascular system, known in fish and avian species for many years, are now being seen in experimental mammals.

Children and Adults

One of the important observations from the high population exposures in Seveso and in the rice oil poisonings in Asia, is that children appear to be especially susceptible to the effects of dioxins. Most of the Seveso residents who developed chloracne were children. [5] Follow-up of the Seveso residents has shown that developmental dental aberrations are associated with childhood exposure to TCDD, [6] as predicted from animal studies. The alteration in sex ratio of offspring seems to be associated with exposure to the potential fathers before the age of 18. [7] The association of dioxin exposure and breast cancer may be stronger where the elevated exposure was pre-pubertal. [8] Much of the understanding of the rice oil poisonings come from studies of children who were exposed *in utero*. While the children from the Seveso cohort were directly exposed, the effects seen in Yusho and Yucheng were more obvious and severe: “coca-colored” babies; ectodermaldysplasia; problems at puberty; deficits in IQ; behavioral alterations. Some of the apparent differences between the effects seen in these cohorts and those in Seveso may be due to the timing of the exposure. In addition, the Asian rice oil poisonings involved high concentrations of non-dioxin-like PCBs, as well as TEQ due largely to PCDFs. [9]

Studies looking at associations between exposure to dioxins and effects in the background population have shown some similarities to that observed in the highly exposed cohorts. As mentioned above, alterations in tooth development were seen in the more highly exposed children in Seveso. Similar defects have been observed in children whose mothers are at the high end of the general population. [10] Effects on the immune system, neurodevelopment, and neurobehavior have been demonstrated in the ongoing cohort study in the Netherlands. [11,12,13,14] Many of these types of effects were observed in the children highly exposed prenatally in the rice oil poisonings. [15]

Summary

In adults, we know that chloracne is a high dose effect. This is also true both in experimental and domestic animals. [16] Most other effects observed in people have also been seen in animals. Many of the more subtle effects, such as those on hormones and the immune system, have not clearly been examined in the general population. However, it would be very difficult to detect subtle sub-clinical effects in the general population. While cancer has been associated with dioxin exposure in the occupational and Seveso cohorts, the increased risk - even as high as possibly 1/1000, could never be detected in the general population. The real issue with exposure to background levels of dioxins is the possibility of a shift in the distribution of the population, with more people being at risk for a variety of effects.

(This abstract does not reflect EPA policy)

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