AGENT ORANGE IN VIETNAM AND HUMAN EFFECTS: WHAT SHOULD WE LOOK FOR? WHAT MIGHT WE EXPECT?

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Introduction

A major legacy of the Vietnam experience has been the lingering questions about the health effects of Agent Orange on the Vietnamese population. Much of this concern centers on the effects of the highly toxic contaminant, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD; "dioxin"). TCDD is a known human carcinogen [1], and has been associated with a plethora of non-cancer effects in epidemiological studies. In addition, it has been shown to cause adverse effects in a wide range of both laboratory and domestic animals, and across the spectrum of vertebrate wildlife. The World Health Organization has established a Tolerable Daily Intake of 1-4 pg/kg/day based on the concordance of multiple effects at low doses in experimental animals [2] .

Discussion

High levels of exposure to people in Vietnam were first measured 30 years ago by Baughman and Messelson who reported breast milks levels as high as 1,850 ppt [3]. Recent studies have shown that in certain villages in Vietnam which had been highly sprayed with Agent Orange during the Vietnam War, blood concentrations of TCDD are still as high as 413 ppt [4]. However, blood and milk data from other areas of Vietnam indicate that current levels in the background population are below those found in Western countries [4-6].

Given the low general levels in the current population, the lack of stored tissue samples (blood, adipose, milk), and the fact that the areas that were sprayed over 30 years ago may not be the areas which have the highest remaining levels of contamination, either in the soil, sediment, or food, or the most contaminated people, what kinds of health studies are most likely to provide information about any lingering health effects of dioxin exposure?

The first requirement is that human body burdens must be measured for any study to be interpretable. Even in the highly sprayed areas, there is tremendous variability in the body burdens of people who live in that area[4-6]. Thus, residence in a contaminated area will not accurately identify who are the more highly exposed members of the population. This is likely due to differential exposure, as well as the potential for differences in human elimination. Because of the persistence of dioxin, it is very difficult to distinguish between past vs on-going exposure. However, our current understanding supports the hypothesis that the body burden is the appropriate dosemetric to use in the association of effects and exposure. If we are going to consider developmental effects, however, our concern will be for the maternal body burden during

development of the offspring. The concentration in breast milk can serve as a good surrogate for fetal exposure[7].

The developing embryo/fetus may be the most sensitive life-stage to dioxin exposure. Offspring of women who have been highly exposed to dioxin and related compounds *in utero*, such as in the Yusho and Yucheng poisoning episodes, have demonstrated effects on skin, hair, teeth and nails, IQ and behavior, disease susceptibility, and male sexual development[8] . Certain of these effects have also been observed in children whose mothers are at the high end of background exposure[9]. In addition, highly exposed populations have been reported to have fewer male offspring. In adult populations, type 2 diabetes has been associated with higher body burdens of dioxin[10]. In more highly exposed populations, increases in cancer overall and lung cancer [1], as well as breast cancer[11] have been reported. Chloracne is a high dose effect whose presence is diagnostic of exposure to dioxin and related compounds, but whose absence does not mean the absence of exposure, or of more subtle effects[12]. A variety of biochemical (e.g., induction of CYP1A1/1A2; effects on growth factors and cytokines) and endocrine responses (e.g., decreases in thyroxine; decreases in LH) have also been reported [13]. Many of the effects associated with exposure to dioxins in epidemiological studies or in the poisoning episodes parallel those seen in experimental animals – wasting, hepatic and dermal toxicity, immunotoxicity, reproductive toxicity, developmental immunotoxicity, reproductive, dental and neurotoxicity, cardiovascular toxicity, endometriosis, etc.[12]

There are a wealth of Vietnamese studies [14] suggesting associations between Agent Orange exposure and a host of adverse effects, ranging from genetic changes to overt birth defects. There is no evidence from either epidemiology or toxicology studies specifically involving dioxin and related compounds that the effects suggested by the Vietnamese effects occur due to dioxins. However, this is not to say that adverse effects may not have resulted, or still be occurring, from the spraying of Agent Orange in Vietnam. But are these, or any, effects associated with exposure to dioxin? In order to address this issue, it is imperative that measures of internal exposure, i.e., body burden, be done. The question then needs to be asked: do you want to look for effects within the range of the background population, or are you looking for effects due to higher exposures? If you want more highly exposed people, such as in the Asian rice oil poisoning studies, Seveso, or the industrial cohorts, then you must first identify who those people are. If you want to look at subtle effects in the general population, and in the case of Vietnam, there may be a potential for a wide range of exposure given that levels in the northern part of the country are lower than in the South, you could conceivably look at the incidence/prevalence of certain effects and then stratify the people by their body burdens. If you want to look at adults, incidence (not mortality) of type 2 diabetes might be a reasonable endpoint to examine. If you have a highly exposed population, it might be reasonable to look for cancer overall, or specifically breast or lung cancer. If there are highly exposed men, it would be interesting to examine the sex ratio of their offspring. If there is information on surgically confirmed endometriosis, an association with dioxin might be examined.

A prospective study looking at birth outcomes and developmental effects might be possible if a longitudinal cohort could be established. (It will be difficult to do a retrospective study unless there is information on the mother's dioxin levels close to the time of pregnancy). This cohort study could be modeled after the studies conducted in the Netherlands, including measures of

dioxin in maternal serum and milk, and in cord blood if possible. Thyroid hormone levels (T4 and TSH specifically) should be measured both in the mother and infant shortly after birth and at several times within the first year, and in the mother at yearly intervals for several additional years. Standard measures at birth should all be taken, and then behavioral, neurological, cognitive tests should be conducted over time. In addition, immune function as indicated by lymphocyte subsets, response to vaccinations, and infectious history (such as respiratory infections, otitis, chickenpox, measles) should be followed. At puberty, male genitalia development and sperm quality should be measured. In the female, breast development should be assessed.

Conclusion

Adequately designed and conducted human studies in Vietnam have the potential to inform not only the Vietnamese of the consequences of Agent Orange spraying, but may have application to other studies of the human effects of dioxins. However, these studies will be extremely expensive to conduct. It is appropriate to ask if this is the best use of limited resources? Is it more important to identify residual hot spots and clean them up?

Acknowledgements

This abstract does not reflect EPA policy.

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