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## APPENDIX FOUR

### REVIEW OF EPIDEMIOLOGIC DATA ON HUMANS EXPOSED TO DIOXIN-CONTAMINATED SUBSTANCES

Agent Orange is composed of equal parts of esters of two phenoxy herbicides, 2,4-D and 2,4,5-T. During the production of the 2,4,5-T there was unintended generation of small amounts of a contaminant, 2,3,7,8-TCDD. The production was a two step process of making 2,4,5-trichlorophenol and then using this substance to make 2,4,5-T.

The interest in the CDC study is exposure to Agent Orange contaminated with 2,3,7,8-TCDD in amounts up to about 50 ppm, with an average level of contamination of 2 ppm. In evaluating studies of exposed populations reported in the literature to determine whether they have relevance to exposures of the veterans to Agent Orange, the following exposure situations are of interest. The published reports were examined to learn whether the literature contains data to permit judgments about how much exposure to Agent Orange would be necessary to cause harmful medical effects after an individual has been exposed.

1. Chemical workers who made dioxin-contaminated 2,4,5-trichlorophenol and 2,4,5-T and/or who were exposed following industrial accidents.
2. Herbicide sprayers who sprayed 2,4,5-T in forests, fields, and rights of way and foresters exposed to pentachlorophenol.
3. Citizens exposed in the contamination of a large area in Seveso, Italy following an industrial explosion.
4. Citizens of Missouri, U.S.A. following exposure to soil contaminated with waste oils containing 2,3,7,8-TCDD.
5. Three British laboratory scientists who suffered health effects after they had synthesized 2,3,7,8-TCDD.
6. Instances of application of substances to humans which produce chloracne.

#### 1. Chemical workers:

Chemical workers who made the substances contaminated with 2,3,7,8 TCDD are generally considered to have had much heavier exposures than would have been experienced by most veterans because of the daily opportunity for exposure and because some workers worked for many years. These substances include 2,4,5-trichlorophenol and 2,4,5-T. Severe medical disorders of the peripheral nervous system, liver and skin occurred following some industrial explosions, and some of the disorders have persisted for many years. It is generally assumed that the workers experienced heavy exposure, but there are no published data providing detailed assessments of the exposures. Since all explosions occurred in trichlorophenol reactors, the specific substances to which the workers were exposed were the reactants of the 2,4,5-trichlorophenol process, including the contaminating 2,3,7,8-TCDD. The actual amounts of

2,3,7,8-TCDD present are not known and would have been dependent on the particular stage and conditions under which the explosion occurred.

In recent years epidemiologic medical and mortality studies have been conducted of chemical workers exposed during the industrial explosions and also during daily job duties. The major limitations of the studies have been small size and limited information about exposures of the individuals in the study. The results have suggested that the medical problems experienced following the explosions do persist in some workers. Unfortunately, no data are present to address the question whether persons with low levels of exposure are at increased risk of medical problems. Several current studies improve upon the earlier design limitations of small size and inadequate exposure assessment. The National Institute for Occupational Safety and Health (NIOSH) has gathered detailed exposure information for 7,000 U.S. chemical workers which is being applied in a large mortality study and two large medical studies of chemical workers.

## 2. Herbicide Sprayers and Pentachlorophenol Workers:

The definition of "exposure" is unclear in studies of herbicide sprayers. Sprayers use numerous types of herbicides and, generally, the particular types and amounts sprayed by each individual are not known. A number of case control studies have evaluated the possible association of soft tissue sarcoma, lymphoma, nasal and colon cancer with exposures to phenoxy herbicides and chlorophenols by interviewing subjects regarding prior exposures. These studies defined exposed sprayers as those who worked more than 1 day. In these situations an individual was considered "exposed" even if the phenoxy herbicide, such as 2,4-D or MCPA, contained no 2,3,7,8-TCDD. Additionally, no distinction in exposure was made for individuals working with pentachlorophenol, which might not contain 2,3,7,8-TCDD, but could contain substantial amounts of more highly chlorinated and less toxic isomers of dioxin.

## 3 & 4 Citizens of Seveso and Missouri:

Studies of citizens of Seveso have had major design problems and have included no measurements of levels of exposure, making it impossible to assess a relationship between medical problems and levels of exposure to the spewed contents of the trichlorophenol reactor. Cases of chloracne did occur following the Seveso explosion, especially among children. Recent studies of citizens in Missouri, U.S.A., who were exposed to soil contaminated with 2,3,7,8-TCDD in waste oils have noted no cases of chloracne, but have found indications of possible immune effects.

## 4. British laboratory workers:

Three British laboratory workers who synthesized 2,3,7,8-TCDD experienced medical problems similar to the chemical workers exposed in industrial accidents, including chloracne and neurologic problems. However, there is no information on the levels of their exposures.

## 5. Application of chloracnogens to human skin:

No published studies have examined the relationship between level of exposure and the appearance of chloracne in humans. NIOSH may be able to contribute information on this question when the evaluation of hundreds of medical records of chemical workers has been completed and the results interpreted in light of individual exposures.

Consequently, anecdotal situations of application of chloracnogens to humans are of interest. At best these are very rough estimates because of the variability encountered among individuals. In the mid-1960's, sixty volunteer persons were treated on the forearm or mid-back region with between 0.2 and 8 ug dioxin and the application repeated two weeks later. No one developed chloracne, yielding the conclusion that humans can tolerate exposure to 16 ug dioxin without developing chloracne. (The study design was based on prior animal studies which showed that rabbits developed mild chloracne from application of 0.5 ug dioxin inside the rabbit ear. Application of 1-2 ug caused a more pronounced effect, and 4-8 ug, a severe effect). Subsequently, the researcher applied 7,500 ug in one square inch to the back area of ten volunteers, of whom 8 developed chloracne which lasted 4-7 months. No other medical information was described. Therefore, limited information suggests that the human threshold for chloracne lies between 16 and 7,500 ug of dioxin applied in a small area of the back.

### Conclusions:

Knowledge of the actual exposure experienced by study participants is the weakest characteristic of all published studies of human exposure to dioxin-contaminated substances. Several current but not yet completed studies have good exposure estimates. The published studies do not provide definitions of exposure which are useful in evaluating how much exposure to Agent Orange would be necessary to cause harmful health outcomes for the veterans.

### Bibliography

The information presented here can be explored in greater detail through the use of the following publications, which review and cite other valuable references.

- (1) Tucker, R., Young, A., and Gray, A., (eds.). Human and Environmental Risk of Chlorinated Dioxins. Plenum Pres, New York, 1983.
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