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MARILyn-

see paragraph about STS- It needs one or 2 sentences describing the ~~pathology~~ review of pathology-

Bill

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Halperin/Fingerhut

Date: OCT 11 1983

From: Assistant Secretary for Health

Subject: PHS Views on Dioxin

To: PHS Agency Heads
OASH Staff Office Directors

Attached please find an updated copy of the PHS views on dioxin. It reflects all of the scientist's views, and will be updated periodically.

Should you have additional comments, I will be pleased to receive them.

Thank you.

E. N. Brandt

Edward N. Brandt, Jr., M.D.

Attachment

CENTER FOR ENVIRONMENTAL HEALTH

CENTERS FOR DISEASE CONTROL

DETAILED RESPONSES TO SUBCOMMITTEE QUESTIONS ON DIOXIN

For the Record

Introduction

The toxic effects of chemicals and their contaminants are usually determined through animal studies because various doses, exposures, times, etc., can be used to more accurately characterize the chemical toxicologically, and clearly it is unethical to purposely expose humans to such substances. Also, only in animal studies can true dose-response relationships be determined.

Observations in humans are limited to accidental overexposure of individuals or small groups of workers. In these instances, the exact degree of exposure is usually either unknown or not very well delineated. For these reasons, as well as because of long experience with animal research, animal studies are used to predict health effects in humans. With such an approach, there are some uncertainties, since the toxic effects of chemicals sometimes vary in different species. Some of these variations may be caused by

ifferences in metabolism and tissue response and by other factors. Dioxin[1] 2,3,7,8-tetrachlorodibenzodioxin (TCDD)] has been studied in a number of nimal species; certain species are much more susceptible to its lethal and oxic effects than others, and the target organs appear to vary in different pecies.

It is not clear how susceptible humans are to the toxic effects of TCDD. ntil better human evidence exists, animal data must be used to predict human ealth effects.

[1] Dioxin is a name used for at least 75 compounds. Only one of these ompounds, 2,3,7,8-TCDD, is discussed in this document.

uestion 1:

hat is currently known about the acute and chronic human health effects (e.g. eproductive effects, immune system effects, carcinogenic effects, etc.) ssociated with dioxin exposure and what can be inferred about such effects rom animal studies?

Human Health Effects

Most of our information on human health effects has been obtained from orkers who were exposed to dioxin during the production or handling of ,4,5 trichlorophenol and products made from this chemical (Kimbrough 1980) n some plants, exposed workers have primarily developed chloracne but no ystemic illness (May 1973). Other authors have reported weight loss, easy atigability and aching muscles, insomnia, irritability, and loss of libido. he liver may become tender and enlarged and sensory changes, particularly in he lower extremities, have occurred. Total serum lipids may be increased and he prothrombin times may be prolonged (IARC, 1978; Bauer et al., 1961; leiberg et al., 1964; Jensen and Walker, 1972; Oliver, 1975). Porphyria utanea tarda (PCT), an acquired form of porphyria characterized by chronic kin lesions and other symptoms, has also been observed (Jirasek, 1976; and leiberg, 1964; Poland et al., 1971).

number of case control and followup studies addressing the issue of soft issue sarcoma have been conducted in worker populations. As with many pidemiologic studies, one or more of the following deficiencies are found in

ost if not all of these studies: 1) the extent of exposure has not been ocumented sufficiently, 2) sufficient time has not elapsed between the xposure and the study for disease development, 3) a population too small for ne to expect to find cases of soft tissue sarcoma, and 4) possible lack of ontamination of the commercial product with dioxin. The case control studies nclude three Swedish studies, which reported a sixfold increase in risk of oft tissue sarcomas among persons exposed to chlorophenols and phenoxy erbicides (Hardell et al 1979; Hardell et al 1981, Eriksson et al, 1981). reliminary results from a case control study underway in New Zealand have not ndicated an excess risk of soft tissue sarcoma (Smith 1982a, 1982b).

Cohort studies have been conducted among chemical production workers and mong herbicide applicators. In the U.S.A. four followup studies were onducted among workers exposed to 2,4,5-trichlorophenol or 2,4,5-trichloro- henoxyacetic acid (2,4,5-T) (Cook et al, 1980, Ott, 1980, Zack, 1980, Zack nd Suskind, 1980.) Each concluded that there were no excess deaths due to ny cause. However, each of three cohorts had one death due to soft tissue arcoma. Honchar and Halperin (1981) reviewed the four studies and noted that n the four merged cohorts, there were 105 deaths, 3 of which (2.9%) were due o soft tissue sarcoma. On the basis of national death rates for men aged 20 o 80, only 0.07% of deaths would have been expected. Recently, another erson in one of the four cohorts died because of a soft tissue sarcoma (Cook, 981 and Ott, personal communication), bringing the total to four deaths due o soft tissue sarcoma in the four merged U.S. cohorts. Thiess (1982) found n excess in deaths from stomach cancer in a study of West German chemical

workers. May (1982) found no excess deaths in a study of British chemical workers.

Useful information on health effects involving non-occupational environmental exposure is sparse. After an explosion at the ICMESA plant in 1976, children in Seveso, Italy, developed chloracne (Hay, 1976; Reggiani, 1980). Some elevated liver function tests were detected in that population (Reggiani, 1980) and the incidence of abnormal nerve conduction tests was statistically significantly elevated in subjects with chloracne (Fillipini, 1981). A child in Missouri (Carter et al., 1975) who played in dirt in a riding arena contaminated in some areas with 30 ppm (parts/million) TCDD had developed hemorrhagic cystitis. Claims have been made that exposure to 2,4,5-T contaminated with TCDD has resulted in an increased incidence of spontaneous abortions, malformations, cancer and other health problems (Reggiani, 1980). Since the studies reporting such results have severe limitations, additional well designed studies must be conducted before any conclusions can be drawn about these health effects in the general population.

One problem with all of these studies, including reports from workers, is that no exposure data are available. In situations where no systemic health effects were observed, absorption of TCDD may have been minimal or nonexistent. For instance, the highest soil level in Zone A in Seveso close to the factory was 55 ppb [parts/billion (microgram/kilogram)] (ug/kg), but levels on the vegetation ranged from nondetected to 15.8 ppm (mg/kg) (milligram/kilogram). Of the 44 vegetation samples analyzed, 33 had less than 1 ppm TCDD. Most of the vegetation was removed early, moreover people in the area close to the

actory were evacuated 2 weeks after the event and they were warned not to eat egetables out of their gardens. The area where people are living now (Zone ;) has soil levels below 0.15 ppb. For additional information on environ- ıental contamination in different parts of the world, the reader is referred :o Reggiani (1980).

Animal Studies

Animal studies have shown that dioxin is very toxic. The lethality dose of chemicals is conventionally measured by administering single doses of various amounts to rats or other species and determining how many animals die. The lethality dose of dioxin varies widely among species, namely, from).6-2 ug/kg in guinea pigs, and 44 ug/kg in rats, to around 5 mg/kg in ıamsters. Deaths may be delayed from 20 to 30 days or more.

Numerous animal studies have been conducted with dioxin to determine what :he short- and long-term effects and the mechanism of action are. These ;tudies have shown that dioxin causes a multitude of effects and that it may affect different organ systems in different species of animals although the :hymus is affected in all species tested. The mechanism of action of dioxin is not well understood, although some significant findings have been made in ;tudies of mouse epithelial cells (Knutson and Poland 1980). Dioxin seems to)ind a receptor protein and is apparently transported to the nucleus, where i nay affect the expression of enzyme systems which both inactivate and activat ;ome organic compounds into forms which can later interact with deoxyribonucleic acid (DNA). It also appears to induce a whole spectrum of ;nzymes in various tissues. (Poland and Kende 1976, Poland et al 1979)

Perhaps because of this mechanism of action, the toxic effects of dioxin may be delayed. In most small laboratory animals given a lethal single dose of dioxin, the median time to death is 2-3 weeks. For larger domestic animals, dogs, and monkeys, the median time is longer. Many toxic compounds, such as nicotine, cyanide, and botulinum toxin, are rapidly metabolized and excreted. This is not true for dioxin, which in small laboratory animals has a half-life of between 12 and 30 days (Neal 1982). After repeated dosing, dioxin accumulates in the animal's body, where it is stored in adipose tissue, and to some extent, in the liver and other organs. Because of these properties, it has a pronounced chronic toxicity at dosage levels much lower than the doses needed to cause acute effects (Kociba and Schwetz 1982).

It is important to recognize that dioxin affects reproduction in the female but may not in the male animal, (Lamb et al) depresses the cell-mediated immune reponse, is toxic to the liver, and causes cancer in different strains of rats and mice; and is teratogenic in mice and rats (Courtney and Moore 1971). Monkeys and guinea pigs are much more sensitive to the acute toxic effects of dioxin than rats and mice. Lifetime studies, however, have only been conducted in rats and mice.

Kociba et al. (1978) reported a study in which groups of 50 male and 50 female Sprague-Dawley rats (Spartan substrain) were fed diets containing 22, 208, and 2,193 ng/kg (nanogram/kilogram) of dioxin. This is equivalent to daily doses of 0.001, 0.01, and 0.1 ug TCDD/kg bw (microgram TCDD/kilogram body weight). The controls consisted of 86 male and 86 female rats. Numerous

oxicologic effects were observed at 0.1 ug dioxin/kg bw/d (day), including ncreased mortality, decreased body weight gain, depressed hematological arameters, increased urine levels of porphyrins, and morphological changes in iepatic lymphoid, respiratory, and vascular tissues were observed at dosage evels of 0.1 ug/kg and 0.01 ug/kg bw/d. No such effects were seen at daily ioses of 0.001 ug/kg. The rats dosed with 0.1 ug/kg/d TCDD showed statistic-lly significant (P 0.05) increases of carcinoma of the liver, lungs and, iasopharynx.

oth et al. (1979) conducted studies in Swiss/H/Riop mice. Three groups of 45 ale mice were given weekly doses (by gavage) of 7.0, 0.7, or 0.007 ug of CDD/kg bw/d for one year, then studied for their entire lifetimes. An equal umber of control mice (45) were given the dioxin vehicle (sunflower oil) each eek. The incidence of liver tumors was significantly increased in the .7-ug-dioxin/kg-bw/d group (48% tumor incidence) compared with that of the ontrol group (18% tumor incidence). The incidence of liver tumors observed n the 7.0-ug-dioxin/kg-bw/d group was 30% greater but was not statistically- ignificantly different from the incidence in the control group; however, hese animals did not survive long enough for tumors to develop. This study uggested that TCDD was carcinogenic at 0.7 ug/kg/d.

The National Toxicology Program (NTP 1982) also conducted carcinogenicity tudies in rats and mice. Oral administration of dioxin was investigated in roups of 50 male and 50 female Osborne-Mendel rats and 50 male B6C3F1 mice 0.01, 0.05, or 0.5 ug/kg/wk), and 50 female B6C3F1 mice (0.04, 0.2, or 2.0 g/kg/wk). Under the conditions of this bioassay, dioxin was carcinogenic for

oth Osborne-Mendel rats and B6C3F1 mice, producing tumors of the liver and hyroid. In addition, the carcinogenicity of dermal applications of an cetone suspension of dioxin applied to the clipped backs of 30 male and 30 emale Swiss-Webster mice 3x/wk (3 times/week) for 99 or 104 wk was nvestigated. Similar groups were treated with one application of 50 ug imethylbenzanthracene (DMBA) in acetone 1 wk before dioxin was administered. emales received 0.005 ug dioxin applications, and males 0.001 ug dioxin. ehicle controls consisted of 45 mice of each sex treated with 0.1 ml acetone x/wk. A significant increase in the incidence of fibrosarcoma of the ntegumentary tissue was observed in female mice given dioxin and those given ioxin following DMBA, when compared with controls. Fibrosarcomas appeared ignificantly earlier in dioxin-dosed males than in vehicle controls, although he increased incidence of such tumors was not statistically significant.

In females the incidence of fibrosarcoma in the integumentary system as 30% (8/27 mice) in the treated group and 5% (2/41 mice) in the controls P=0.007). In the males the incidence of the same tumor type was not ignificantly different, 21% (6/28) among the exposed mice and 7% (3/42) among he controls.

It is nbt yet known whether dioxin is both a promoter and, an initiator f cancer, and, if both, which characteristic predominates. Poland et al. 1982) have recently presented evidence that dioxin promotes tumors in skin of RS/j hairless mice. Pitot et al. (1980) have shown dioxin to be a potent umor promoter in a two-stage model of carcinogenesis in rat liver.

The guinea pig's immune system is extremely sensitive to dioxin. Weekly oses of 40 ng dioxin/kg bw for 8 weeks depressed the delayed hypersensitivit eaction to tuberculin in adult guinea pigs (Vos et al 1973). Studies onducted in rats and mice suggest that although these species are less ensitive than the guinea pig the developing immune system is more susceptibl n young rats and mice, and possibly, in other species. Thus, young animals re particularly susceptible to this effect.

As far as reproduction is concerned, dioxin has been shown to be a eratogen in several strains of mice producing cleft palate and hydronephosis Smith et al 1976). In rats it is more fetotoxic than teratogenic. In a -generation reproduction study in rats, daily doses of 0.01 ug dioxin/kg bw educed litter size, decreased fetal and neonatal survival, and decreased rowth, but daily doses of 0.001 ug/kg had no such effects (Murray et al, 979).

Allen et al. (1979) have reported adverse effects of low concentrations f dioxin on reproduction in nonhuman primates (rhesus monkeys). McNulty 1982) also studied the effect of dioxin in rhesus monkeys. His results upport those of Allen et al. (1979). He observed fetal losses at single oses of 1 ug/kg bw in rhesus monkeys. Thus far, a no-observable-effect leve n reproductive outcomes in the rhesus monkey has not been reported, nor have ny long-term (several years) or multigeneration studies been conducted to etermine chronic health effects in the more sensitive species.

Some health effects have been observed in humans which also occur in xperimental animals, including chloracne, liver toxicity, including porphyri

utanea tarda (PCT), an increase in serum lipids, and abonormal liver function
ests. However, it is not clear whether other effects observed in animals
ccur in humans. Recently a possible association between exposure to dioxin
nd phenoxy herbicides and related products and an increase in mesenchymal
umors has been reported in humans, but further studies are needed to confirm
his possibility. Similar tumors were noted in mice that had been exposed
ermally to dioxin (Coggon and Acheson 1982). A number of epidemiology
tudies and health assessments in humans have given negative results.
owever, these negative studies cannot be deemed conclusive because of the
roblems associated with epidemiologic studies after low-level exposure.
hese problems are accentuated because of the difficulties in measuring
xposure to dioxin through tissue levels, and it is difficult to study immune
unction in people because extensive baseline data for the general population
o not exist and because small differences in immune function would be
ifficult to prove. Another example is that effects on reproduction after
ow-level exposure in the general population are difficult to detect, since
ther confounding variables such as alcohol consumption, smoking, use of
ecreational drugs, and malnutrition, outweigh the effects of dioxin. This
ould be so, simply because exposure to chemicals such as alcohol is much mor
revalent and occurs at higher dosage levels in the general population.

Because of these limitations as far as the general population is
oncerned, worker populations have been studied more extensively--since they
sually have higher exposures. However, the number of workers exposed to
ioxin during production processes is relatively small (several thousand in

all industralized nations) and may not be large enough to show small changes. They are predominantly adult males, and the literature gives no information about the doses of dioxin these workers actually received, nor are the report clear on how thoroughly these workers were examined. Furthermore, women and children, who make up a large portion of the general population, are not really represented in this group. The lack of definitive human data dictates that animal data must be used to predict possible human health effects. However, some animal species are much more sensitive to the toxic effects of dioxin than others. In rats in a 2-year feeding study, a daily dietary dose of 1 ng/kg bw/d has been reported as a no-observable or detectable effect level. On the other hand, if monkeys are given a single dose of 1 ug/kg bw, they cease to reproduce normally (McNulty, 1982). Although the epidemiological data seem to suggest that humans are less sensitive than monkeys, we do not know exactly how sensitive or resistant humans are. Moreover, since the human population is heterogeneous some subpopulations may be much more susceptible than others.

In the absence of useful human data, prudent public health policy dictates an assumption that humans could suffer effects similar to those observed in animals and that preventive public health policy must be based on available animal data.

Question 2:

What dioxin health effects research is currently underway and what will it tell us about the nature and extent of human health problems associated with dioxin?

In addition to animal studies, a number of human studies are underway. These studies address four problem areas:

1. The questions Vietnam Veterans have raised about the possible adverse health effects of their exposure to Agent Orange, an herbicide mixture that contained dioxin.

2. The question of whether exposure to phenoxy herbicides contaminated with dioxins and perhaps with other chlorinated phenols results in an increased incidence of malignant mesenchymal tumors.

3. The question of whether the health of people who live or have lived in areas contaminated with "above background" levels of dioxin (e.g. Times Beach) has been or will be affected by such exposures.

4. The question of what is the morbidity and mortality experience of dioxin-exposed workers with chloracne.

These studies are conducted or funded by the U.S. Air Force, the Veteran
dministration, and The Department of Health and Human Services (Centers for
isease Control/Center for Environmental Health/National Institute of
ccupational Safety and Health, and National Institutes for Health/National
nstitute of Environmental Health Sciences). In addition, the Environmental
rotection Agency is engaged with the Veterans Administration in an effort to
onitor dioxin adipose tissue levels in a limited number of human tissue
amples collected in the 1970's.

At this time, we cannot predict what these studies will tell us. One
roblem with all of these studies is that the actual dose of dioxin the
ndividual received cannot be determined. Therefore, theoretically, it would
e possible to mix people who absorbed varying amounts of dioxin with people
ho did not absorb any. This misclassification could then produce erroneous
esults. The only population group in which measurement of dioxin tissue or
lood levels could prevent such misclassification and would at the same time
ive us information about a dose an individual receives from contaminated soil
s the exposed Missouri population. In the case of the Vietnam veterans, such
easurements would be meaningless, since the last exposure would have occurrec
ore than 13 years ago and since the general population is exposed to minute
mounts of dioxin from various sources.

Studying the population at Times Beach, Missouri, still does not give us
nformation about low-level, lifetime exposure to dioxin. Since it would be
nethical to administer dioxin to humans, we must rely on animal studies to

ake predictions about the toxic effects of dioxin. Similarly, it would not e useful to look for acute subclinical health effects of dioxin in a opulation that had its last exposure many years ago, such as some of the roduction workers. In such a population, the analysis of morbidity and ortality data would be more fruitful.

CDC is conducting studies of the health effects of occupational exposure o dioxin. Since 1979, CDC has been investigating the possible link between ioxin exposure and health effects in workers occupationally exposed to ioxin-contaminated products. In 1979, CDC began work on a registry of U.S. roduction workers who were potentially exposed to dioxin during the synthesis r formulation of substances contaminated with dioxin. The substances include uch commonly used products as trichlorophenol; 2,4,5,-T, the herbicide which as one component of Agent Orange; and pentachlorophenol, a wood preservative.

After the CDC registry is completed, our first research task will be to ompare the causes of death in these workers with the causes of death in the .S. population. We expect to include about 6,000 workers in this study. As f July 1, 1983, 5,000 have been included in the registry. Enrollment will b ompleted by December of 1983. We plan to have all information relating to he status of these workers collected and analyzed by March 1985--well before he final results of CDC's Agent Orange Epidemiology Study will be available.

CDC is exploring other uses of the worker registry, including use in tudies of certain illnesses and problems with reproduction among exposed

persons. Decisions to proceed with these kinds of studies depend on scientific feasibility and the availability of resources.

Since most of the workers included in the CDC registry were exposed during the period 1940-1970, we will--to the extent that there are diseases with long latency periods--be able to find them. However, we plan to continu to evaluate the health status of these persons at 5-year intervals.

Workers have been exposed to dioxin in facilities in other countries, an production personnel in these facilities constitute a valuable study group. The National Institute of Environmental Health Sciences (NIEHS) awarded a contract to the International Agency for Research on Cancer (IARC) to establish and maintain an international registry of persons exposed to phenox acid herbicides and contaminants. That registry is similar to CDC's. In December 1982, Dr. Patricia Honchar, on detail from CDC/NIOSH to IARC, completed the feasibility assessment for this project. Cohorts from more tha 20 production facilities throughout Europe and Australia and New Zealand were evaluated to determine their suitability for epidemiologic study. Now that the feasibility study has been completed, a joint IARC/NIEHS meeting has been scheduled for mid-October 1983 to bring together potential collaborators to decide whether to continue the project and to define an action plan.

In addition to the above studies, CDC continues to examine reported association between dioxins and disease in occupationally exposed workers. I 977, cases of soft tissue sarcoma were reported among Swedish lumberjacks wh

had been exposed to phenoxy acid herbicides. This clinical observation led researchers in Sweden to conduct two separate epidemiologic case-control studies which showed increased risk of soft tissue sarcoma. Later, results o four small, independent studies in the U.S.A. showed no association between soft tissue sarcoma and work exposure to dioxin. When data from the four U.S studies (which include three deaths from soft tissue sarcoma) were combined, however, the same association noted in the Swedish studies was found. Later four additional persons who worked at 2,4,5-T production facilities in the U.S.A. were reported to have soft tissue sarcomas. At CDC, work is underway to gather the work histories and pathologic specimens for all seven cases. CDC will evaluate the histories of exposure, and the Armed Forces Institute o Pathology will review the specimens and the pathologists' findings. The goal is to gain an understanding of any common characteristics which may exist among the sarcoma cases and to focus medical expertise on the question of the legitimacy of grouping different types of sarcomas.

We believe that information suggesting an association between soft tissu sarcoma in humans and exposure to dioxin-contaminated products is accumulating. International studies that fail to confirm an association between soft tissue sarcoma in humans and exposure to dioxin-contaminated products suffer from the deficiencies previously described on page 3. The controversy over this association is ongoing within the scientific community. For these reasons, careful epidemiologic analyses are needed. The question o an association of sarcomas and exposure to phenoxy acids and chlorophenols is being addressed in the CDC Dioxin Registry mortality study and will be addressed by the IARC study. In addition, other studies, such as case

:ontrol studies, are being proposed and conducted. Epidemiologic studies lik
:hese will further delineate any association.

A number of case-control studies have either been proposed or started.

1. A National Cancer Institute (NCI) study will concentrate on soft tissue sarcomas in Kansas and determine whether a higher incidence of these tumors can be related to occupational exposure.

2. NCI is funding a grant for studying the relationship between cancer incidence and phenoxy herbicide exposure in 13 counties in Washington State.

3. The Armed Forces Institute of Pathology, and the U.S. Veterans Administration will also conduct a case-control study of soft tissue sarcomas. Since these tumors are rare, most pathologists do not see man and have difficulty in diagnosing them. Hans Enzinger, of the Air Force Institute of Pathology, is an expert in the diagnosis of these tumors an has a large collection from around the country. These tumors will form basis of the study.

4. CDC has proposed an additional study using the NCI's Surveillance Epidemiology End Results (SEER) network.

Other pertinent ongoing or proposed studies are listed below.

1. CDC has been conducting an investigation, with support from the Veterans Administration and the Department of Defense, to determine whether Vietnam veterans have a higher risk of fathering children with birth defects. Data collection is to be completed by the end of 1983, and the preliminary analysis is to be done shortly afterwards.

2. CDC has developed a proposal for the Veterans Administration to conduct large epidemiology study in Vietnam Veterans.

3. The Veterans Administration is conducting a mortality study on personnel who served in the military during the Vietnam war.

4. The Veterans Administration has also proposed a study of twins, only one of whom served in Vietnam.

5. The U.S. Air Force is conducting a study of personnel who conducted spraying in Vietnam--the "Ranch Hand Study." Some results of this study should become available during 1983. A mortality study of this group with only a very limited number of death certificates, was negative.

6. CDC is conducting preliminary studies in selected Missouri populations which have been exposed to dioxin-contaminated soil. Some information from these studies should become available by the end of 1983.

Question 3:

What additional research on the health effects of dioxin is needed and why?

Animal research has established that dioxin is very toxic, that it is fetotoxic, and carcinogenic and that it impairs the cell-mediated immune response. Dioxin serves no useful purpose but, instead, is an impurity in certain chlorinated commercial products. A number of areas in the United States have become contaminated with dioxin. Most of this dioxin is in soil. Dioxin in soil is somewhat less available than free dioxin. Although some studies on uptake from soil are available, we need further studies on the uptake and bioavailability of dioxin from different soils, either for humans or animals. (Note: Recently completed but not yet reported animal studies by the National Toxicology Program on bioavailability of dioxin in contaminated soils, indicate high levels of dioxin are bioavailable in two different types of soil.).

To provide answers to the question of whether human health has been affected by dioxin exposure we must do additional human epidemiology studies. The most useful studies would be those of the highest exposure to the largest number of people for the longest time. If those studies showed no effect, it would be reasonable to assume that nothing could be gained from studying individuals with lower and shorter exposures. If health effects are identified in these studies, investigators could look for them in less exposed populations.

For the health effects data to be most useful, investigators should determine dioxin body burdens in the study population.

For this reason, the ratio between dioxin levels in blood and adipose tissue should be determined. The methods for dioxin analysis in blood and adipose tissue need to be standardized, and appropriate quality controls and quality assurances needs to be established. For screening purposes, we hope that it will be possible to determine dioxin levels in blood. It is much easier and less traumatic to collect blood specimens than to obtain surgically removed fatty tissue.

<u>The following information relates to the Subcommittee's questions regarding CDC's determination of the 1-ppb level of dioxin in soil.</u>

In a risk assessment based on available animal data and on an evaluation of how individuals can be exposed to soil and contaminants in soil, the CDC estimated that 1 ppb of dioxin in a residential area would represent a risk for human exposure to dioxin. This assessment was based on a number of "best judgment" assumptions for which definitive evidence is not available. Some of these assumptions deal with the extrapolation from animal data to humans and with judgments concerning the mode and degree of exposure.

This concentration was calculated by considering how much dirt a toddler (child age 1-3 years) might eat, how much dirt might be picked up by the skin during such activities as gardening, and how much dust might be inhaled. It was also considered that

toddlers would only eat dirt for a few years and that gardening would not be done on a daily basis, particularly in the winter. It was assumed that if the dioxin was bound to soil, absorption of dioxin from skin might be 1-10%; from the intestinal tract, 30%; and from the lungs, 50%. At 1 ppb dioxin in the soil (if the dioxin was bound to soil), if a toddler ate 1 gram of dirt, got one gram of soil on his or her skin, and inhaled dust from the area, his or her total daily dose would be between 311-400 picograms. If 10 grams of dirt were ingested and 10 grams of dirt made contact with the skin, the dose of dioxin would be 3,000-4,000 picograms.

Therefore, on a body weight basis, for a 10-kg (about 22 lbs.) toddler, the doses that could be received might be between 31-400 picogram/kg bw/d for 3-to 4-year period (ages 1 1/2 - 5 years). During this time, the dose per unit of body weight would gradually decrease, since the child gains weight while hand-mouth activities decrease. The dose for adults would be less on a g bw basis.

The no observable effect level in rats is 1,000 picograms per kg bw; with a safety factor of 100, the daily allowable dose would be 10 picogram/kg bw for humans for a lifetime. Additional safety factors should be added because of the effects on reproduction in monkeys at dosage levels of 1,800 picograms/kg, because dioxin causes cancer in rodents, and because species vary in sensitivity. Exposure would not be for 24 hours a day every day, and although dioxin is extremely persistent in soil, soil levels would gradually

diminish. If an adult received a daily dose of 4,000 picograms, his or her dose on a kg bw basis would be $\frac{4,000}{70}$ or about 57 picograms/kg/d. If he or she received 400 picograms, the dose would be 5.7 picograms/kg/d. These dosage levels are below the no-observable effect level in rats; however, they do not allow a sufficient safety factor, nor do they take into account the variation in sensitivity between species.

Levels below 1 ppb in soil may be found in many areas of the United States and may represent background levels. Some of the sources of these dioxins are combustion and general pollution due to use of chlorinated phenol products since about 1945. Not much information is available, however, on dioxin background levels in the environment.

The level of 1 ppb is not to be construed as a "safe" level; however it is a level of concern developed for one specific residential site. Levels of concern must be developed for each site and depending upon the various circumstances, will likely be different in differing sites.

REFERENCES

Allen JR, Barsotti DA, Lambreckt LK, Van Miller JP. Reproductive effects of halogenated aromatic hydrocarbons on non-human primates. Ann. NY. Acad. Sci. 1979;320:419-25.

Bauer H, Schulz KH, Spiegelberg U. Berufliche vergiftungen bei der herstellung von chlorphenol-verbindungen. Arch. Gewerbepathol. Gewerbehyg. 1961;18:538-55.

Bleiberg J, Wallen M, Brodkin R, Applebaum IL. Industrially acquired porphyria. Arch. Dermatol. 1964;89:793-7.

Carter CD, Kimbrough RD, Liddle JA, Cline RE, Zack MM Jr, Barthel WF, Koehler RE, Phillips PE. Tetrachlorodibenzodioxin: An accidental poisoning episode in horse arenas. Science 1975;188:738-40.

Coggon D, Acheson ED. Do phenoxy herbicides cause cancer in man? Lancet 1982;7:1057-1059.

Cook R, Townsend J, Ott NG, and Silverstein G. Mortaility experiences of employees exposed to 2,3,7,8-tetrachlorodibenxo-p-dioxin (TCDD). J. Occup. Med. 1980;22:530-532.

Cook RR. Dioxin, chloracne, and soft tissue sarcoma. Lancet 1981;618:3-14.

Courtney KD, and Moore JA. Teratology studies with 2,4,5-trichlorophenoxyacetic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol. Appl. Pharmacol. 1971;20:396-403.

Eriksson M, Berg N, Hardell L, Moller T, and Axelson O. Soft tissue sarcomas and exposure to chemical substances, a case-referrent study. Br. J. Ind. Med 1981;38:27-33.

Fillipini G, Bordo B, Crenna P, Massetto N, Musicco M, Boeri R. Relationship between clinical and electrophysiological findings and indicators of heavy exposure to 2,3,7,8 tetrachlorodibenzodioxin. Scand. J. Work Environ. Healt 1981;7:257-62.

Hardell LK, and Sandstrom A. Case-control study: Soft-tissue sarcomas and exposure to phenoxyacetic acids or chorophenols. Br. J. Cancer 1979;39:711-717.

Hardell L, Erikson M, Lenner P, Lundgren E. Malignant lymphoma and exposure to chemicals, especially organic solvents chlorophenols and phenoxy acids: A case control study. Br. J. Cancer 1981;43,(2):169-76.

Hay A. Toxic cloud over Seveso. Nature 1976;262:636-8.

Honchar P, and Halperin W. 2,4,5-trichlorophenol and soft tissue sarcoma; Lancet 1981;(1):269.

IARC. Chlorinated dibenzodioxins. In: Monographs on the evaluation of the carcinogenic risk of chemicals to man. Lyon, France:WHO,1978;15:41-102.

Jensen NE, Walker AE. Chloracne: Three cases. Proc. R. Soc. Med. 1972;65:687-8.

Jirasek L, Kalensky J, Kubec K, Pazderova J, Lukas E. Chlorakne, porphyria cutanea tarda und andere intoxikationen durch herbizide. Hautarzt 1976;27:328-33.

Kimbrough RD. Halogenated biphenyls, terphenyls, napthalenes dibenzodioxins and related products. Top. Environ. Health Amsterdam, New York:Elsevier North Holland, 1980;4:406.

Knutson JC, and Poland A. Keratinization of mouse teratoma cell line X8 produced by 2,3,7,8-tetrachlorodibenzo-p-dioxin: an in vitro model of toxicity. Cell 1980;22:27-36.

Kociba RJ, Keyes DG, Beyer JE, Carreson RM, Wade EE, Dittenber DA, Kalmins RP, Krauson LF, Park DN, Barnard SD, Hummel RA, Humiston CG. Results of a two year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in rats. Toxicol. Appl. Pharmacol. 1978;46:279-303.

Kociba RJ, Schwetz BA. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Drug Metabolism Reviews 1982;13(3):387-406.

Lamb JC, Moore JA, Marks TA. Evaluation of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) toxicity in C57BL/6 mice: Reproduction and fertility in treated male mice and evaluation of congenital malformations in their offspring. Natl. Toxicol. Program, Research Triangle Institute, Research Triangle Park, NC. Report No. NTP-80-44, 57pp.

May G. Chloracne from the accidental production of tetrachlorodibenzodioxin. Br. J. Ind. Med. 1973;30:276-83.

May G. Tetrachlorodibenzodioxin: a survey of subjects ten years after exposure. Br. J. Ind. Med. 1982;39:128-135.

McConnell EE, Moore JA, Haseman JK, Harris MW. The comparative toxicity of chlorinated dibenzo-p-dioxins in mice and guinea pigs. Toxicol. Appl. Pharmacol.;1978b;44:335-356.

McConnell EE, Moore JA, Dalgard DW. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Rhesus monkeys (Macaca mulatta) following a single oral dose. Toxicol. Appl. Pharmacol.;1978b;43:175-187.

cNulty WP. Rhesus macaques: Pertinence for studies on the toxicity of hlorinated hydrocarbon environmental pollutants. In: Chiarelli AB, arruccini RS, eds. Advanced Views in Primate Biology. Berlin: pringer-Verlag, 1982.

urray FJ, Smith FA, Nitschke KD, Humiston CG, Kociba RJ, Schwetz BA. Three eneration reproduction study of rats given 2,3,7,8-tetrachloro- ibenzo-p-dioxin (TCDD) in the diet. Toxicol. Appl. Pharmacol. 979;50:241-252.

ational Toxicology Program. Carcinogenesis bioassay of 2,3,7,8 etrachlorodibenzo-p-dioxin (CAS No. 1 1746-01-6) in Swiss-Webster mice dermal study). Natl. Toxicol. Program Tech. Rep. Ser. 1982a;Issue 201, 113 p.

ational Toxicology Program. Carcinogenesis bioassay of 2,3,7,8 etrachlorodibenzo-p-dioxin (CAS No. 1 1746-01-6) in Osborne-Mendel rats and 6C3F1 mice (gavage study). Natl. Toxicol. Program Tech. Rep. Ser. 982b;Issue 209, 195 pp.

eal RA, Olson Jr, Gasiewics TA, Geiger LE. The toxicokinetics of ,3,7,8-tetrachlorodibenzo-p-dioxin in mammalian systems. Drug Metabolism eviews 1982;13:355-385.

liver RM. Toxic effects of 2,3,7,8 tetrachlorodibenzo 1,4 dioxin in aboratory workers. Br. J. Ind. Med. 1975;32:49-53.

)tt M, Holder B, Olson R. A mortality analysis of employees engaged in the ımnufacture of 2,4,5-trichlorophenoxyacetic acid. J. Occup. Med. 1980;22:47-50.

'itof HC, Goldworthy T, Poland A. Promotion by 2,3,7,8-tetrachlorodibenzo-p-dioxin of hepatocarcinogenesis from diethylnitrosamine. Cancer Res. 1980;40:3616-20.

'oland A, and Kende A. 2,3,7,8-tetrachlorodibenxo-p-dioxin: environmental contaminant and molecular probe. Fed. Proc. 1976;35:2404-2411.

'oland A, Glover E, Kende AS. Stereospecific high affinity binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin by hepatic cytosol. J. Biol. Chem. 976a;251:4926-4946.

'oland A, Greenlee WF, Kende AS. Studies on the mechanism of action of the hlorinated dibenxo-p-dioxins and related compounds. Ann. N.Y. Acad. Sci. 979;320:214-230.

oland A, Palen D, Glover E. Tumor promotion by TCDD in skin of HRS/j airless mice. Nature 1982;300:271-3.

oland AP, Smith D, Hetter G, Possick P. A health survey of workers in a ,4-D and 2,4,5-T plant. Arch. Environ. Health 1971;22:316-27.

eggiani G. Localized contamination with TCDD-Seveso, Missouri and other reas. Topics in Environ. Health 1980;4:303-371.

Reggiani G. Acute human exposure to TCDD in Seveso, Italy. J. Toxicol. and Environ. Health 1980;6:27-43.

Smith, AH, Fisher DO, Pearce N, Teague CA. Do agricultural chemicals cause soft tissue sarcoma? Initial findings of a case control study in New Zealand. Community Health Studies 1982a;6:114-119.

Smith AH, Fisher DO, Giles HJ, Pearce N. The New Zealand soft tissue sarcoma case control study: interview findings concerning phenoxyacetic acid exposure. Poster session, 3rd International Symposium on Chlorinated Dioxins and Related Compounds, October 12-14. Salzburg, Austria. 1982b

Smith FA, Schwetz BA, Nitschke KD. Teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in CF-1 mice. Toxicol. Appl. Pharmacol. 1976;38:517-23.

Thiess AM, Frentzel-Beyme R, Link R. Mortality study of persons exposed to dioxin in a trichlorophenol-process accident that occurred in the BASF AG on November 17, 1953. Am. J. Ind. Med. 1982;3:179-189.

Toth K, Samfai-Kelle S, Sugar J, Bruce J. Carcinogenicity testing of the herbicide 2,4,5-trichlorophenoxyethanol containing dioxin and of pure dioxin in Swiss mice. Nature 1979;278:538-549.

Dos JG, Moore JA, Zinkl JG. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the immune system of laboratory animals. Environ. Health Perspect 1973;5:149-62.

Zack J. Suskind R. The mortality experience of workers exposed to tetrachlorodibenzodioxin in a trichlorophenol-process accident. J. Occup. Med. 1980;22:11-14.