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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 13 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Addressees

SUBJECT: FDA Risk Assessment for Higher Chlorinated Dibenzo-p-dioxins

Attached is a recently prepared risk assessment by the Food and Drug Administration for hexa-, hepta- and octachloro-dibenzo-p-dioxins in chicken eggs.

I believe the analysis presented here is an interesting one and could provide fodder for a future first Friday feed.

Donald G Barnes

Donald G. Barnes, Ph.D.
Senior Science Advisor to the
Assistant Administrator
for Pesticidees
and Toxic Substances

Attachment

Addressees:

Lisa Barrera	A-101
Pat Roberts	A-132
Judy Bellin	WH-565
David Vanormer	TS-769C
Priscilla Holtzclaw	WH-548D
Bob McGaughy	RD-689
✓Al Young	Veterans Adm.
Carl Keller	NIEHS

← If you understand the second paragraph, you know more about EPA than you should!

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date April 29, 1983

From Acting Chief, Contaminants & Natural Toxicants Evaluation Branch (HFF-159)

Subject Levels of Concern for Hexa- (HCDD), Hepta- (HpCDD) and Octachlorodibenzo-p-dioxins (OCDD) in Chicken and Eggs

To Mr. John Taylor
Director, Division of Regulatory Guidance (HFF-310)
Through: Dr. Gary Flamm
Acting, Associate Director for Toxicological Sciences (HFF-100)

As a result of concerns for higher chlorinated dioxin contamination of chickens and eggs the Texas Department of Health has requested "that FDA provide guidance as to health or regulatory significance as well as action guidance" (W. Remle Grove, see attachment # 1). In response to this request, as submitted through DRG, we have reviewed the available information on the toxicity of several dioxin congeners. Based on this review we are suggesting the following levels of concern (LOC) for these substances in chicken and eggs.

	Levels of Concern[a/]
HCDD	300 parts per trillion
HpCDD	500 parts per trillion
OCDD	3 parts per million

a/ Because the amounts of chicken and eggs consumed are similar, a uniform level of concern for the respective contaminants can be applied to each food item.

The rationale, biological and/or toxicological end-points and factors utilized in the development of the above LOC are identified in subsequent pages and attachments. It is important to recognize that the available literature from which these levels were derived is limited.

We emphasize that these levels apply only to the present situation in Texas and do not have general applicability to contamination by the dioxin congeners HCDD, HpCDD and OCDD in food. In this situation the various isomers of each congener will not be dealt with individually but rather as a group (e.g., as congeners). This is so because of a lack of- a) biological and/or toxicological studies on specific isomers, and b) knowledge of the presence of individual isomers involved in the Texas situation. It should also be noted that while the carcinogenicity of these congeners was asssed, where specific studies were available, the potential exposure to them in the Texas incident is considered to be of a relatively

short duration (e.g.,-possibly several weeks up to several months). Therefore, carcinogenic potential was not used as the toxicological determinant in deriving the LOCs for dioxins in chicken and eggs. It is equally important to recognize that other toxic manifestations, such as reproductive and/or teratogenic effects, may result from pulse (single) or short-term (days to weeks) exposures to dioxins such as the HCDD congener. It is the concern for these non-carcinogenic effects which serves as the basis for our evaluation, again since lifetime exposure is not an issue.

Since the tetrachlorodibenzo-p-dioxin (TCDD) congener is the best studied and most toxic member of this class of toxicants, the health assessment performed on the presence of TCDD in freshwater fish from various areas of the Great Lakes (F. Cordle, Reg. Tox. Pharm., 1:379-387, 1981; see attachment # 2) will be used as the basis for the establishment of LOCs for HCDD, HpCDD and OCDD. In that assessment it was determined from a multi-generation reproduction study in rats that the no-effect level for TCDD was 1 nanogram (ng)/kg b.w./day. In keeping with these findings, a concern level of 25 ppt TCDD in fish was recommended by FDA to State officials. The value of 25 ppt TCDD and a fish consumption value of 37 g/day (99th percentile) is used in the present assessment to derive maximum daily intakes for the other dioxins (HCDD, HpCDD and OCDD) based on appropriate safety factors and their biological and/or toxicological potency in relation to TCDD.

In order to evaluate the relative biological/toxicological potency of these toxicants, several different types of studies were assessed. A number of studies have shown that there is a distinct relationship between the ability of the dioxins to elicit several of their toxic and/or biological manifestations and to bind to a cytosolic-receptor. These studies have shown that for the dioxins to produce any appreciable degree of toxicological and/or biological activity the four lateral ring positions must be occupied by chlorine atoms and at least one ring position must be unsubstituted.

The comparative induction of aryl hydrocarbon hydroxylase (AHH) by a number of dioxins, including TCDD, HCDD, HpCDD and OCDD has been studied in rat hepatoma cell cultures by J. Bradlaw and co-workers (Fd. Cosmet. Tox., 18:627-635, 1980). Their studies showed that the relative potency of the most active congeners of HCDD, HpCDD and OCDD were 1/10, 1/200 and 1/25,000 of that of TCDD (relative potency of 1), respectively. In similar studies performed by A. Poland and associates (Mole. Pharm., 9:736-747, 1973) on AHH induction in chicken embryonic livers, the relative biological potency of HCDD was determined to be approximately 1/4.5 when the potency of TCDD was 1, while OCDD was shown to be inactive.

Another type of study which was used to evaluate relative toxicological potency was acute oral toxicity. The following table is a compilation of acute oral LD_{50}s in the guinea-pig for those congeners that have been studied (from J. Huff and co-workers, Enviro. Heal. Perspec., 36:221-240, 1980).

Single Oral LD_{50}
(ug/kg b.w.)

Congener	Guinea-pig
2,3,7,8-TCDD	2
1,2,3,4,7,8-HCDD	73
1,2,3,6,7,8-HCDD	70-100
1,2,3,7,8,9-HCDD	60-100
1,2,3,4,6,7,8-HpCDD	> 600

Acute oral toxicity of dioxin congeners has been studied in other species, however, the guinea-pig is being used in this analysis because on an acute basis it is the most sensitive species. An examination of these values reveals that the acute oral LD_{50}s for the three HCDD isomers are very similar. To compare the acute toxicity of HCDD to that of TCDD the lowest reported value of 60 ug/kg b.w. will be used. As in the previous derivation of relative potency, if TCDD is given a value of 1, it follows that the relative potency of HCDD is 1/30 (60 ug/kg-HCDD/2 ug/kg-TCDD) of that of TCDD. Relative potencies for HpCDD and OCDD could not be calculated, because the acute LD_{50} for HpCDD was not specifically identified (> 600 ug/kg b.w.) and no value for OCDD has been reported.

A number of reproductive/teratogenic studies have been performed with TCDD, HCDD and OCDD, while none have been reported for HpCDD. In these studies the lowest no observed effect level (NOEL) for TCDD was shown to be at a dosage of 0.001 ug TCDD/kg b.w./day (3-year rat reproduction study; F. Murray and co-workers, Tox. Appl. Pharm., 50:241-252, 1979). In a teratology study by B. Schwetz et al. (Enviro. Health Perspec., 5:87-99, 1973) the lowest dosage shown not to effect embryonal or fetal development for HCDD was 0.1 ug/kg b.w./day. In this same study OCDD did produce embryotoxicity (subcutaneous edema), but no teratogenic effects at 500 mg/kg b.w./day, however, the next lowest dosage, 100 mg/kg b.w./day, did not cause either teratogenic or embryotoxic effects. In comparing the NOELs for these dioxins a relative potency of 1 is assigned to TCDD. It follows that the relative potency of HCDD is 1/100 and that of OCDD is 1/1 X 10^8 in terms of reproductive toxicity/teratogenicity.

Only one of the congeners of interest, namely HCDD, has been studied in a long-term carcinogenic bioassay (NCI, Technical Report Series No. 198, NTP No. 80-12, 1980). In this study a mixture of two isomers, 1,2,3,6,7,8- and 1,2,3,7,8,9-HCDD, was shown to exhibit a lowest effect level (LEL) for neoplasia in B6C3F1 mice of 0.2 ug/kg b.w./day. This compares to the LEL of 0.01 ug/kg b.w./day which was observed by Kociba and co-workers (Tox. Appl. Pharm., 46:279-303, 1978), in a two-year chronic study in rats. The relative potency for neoplasia of HCDD in comparison to TCDD would,

therefore, be 1/20. It must be emphasized that in this instance the toxic end-point of neoplasia was used solely to derive a relative potency factor for HCDD, not to address the issue of carcinogenicity, per se.

The following table contains a summary of the relative potencies determined for HCDD, HpCDD and OCDD by the methods discussed above.

Relative Biological/Toxicological Potencies*

Dioxin Congener	AHH Induction: Chicken Liver Embryo	AHH Induction: Rat Hepatomas	Acute Oral LD_{50}	Reproductive/ Teratogenic Studies	Carcinogenic Bioassay
TCDD	1	1	1	1	1
HCDD	1/4.5	1/10	1/30	1/100	1/20
HpCDD	NR	1/200	NR	NR	NR
OCDD	NA	1/25,000	NR	$1/1 \times 10^8$	NR

* - 1 is the highest level of activity.
NR - not reported; studies have not been performed.
NA - not active

It is apparent that of the three congeners of interest HCDD demonstrates the greatest activity with HpCDD and OCDD following in order of magnitude. This follows the structure activity relationship for this class of compounds which indicates that those congeners with chlorines in positions 2,3,7 and 8 and with at least one unoccupied ring position will demonstrate the greatest biological/toxicological activity.

Derivation of LOCs

HCDD

The relative potencies of HCDD derived from the various studies cited above range between 1/4.5 and 1/100. Since the incident in question involves an acute or short-term exposure the risk of a pulse (single) exposure during pregnancy would be of most concern. Therefore, while not ignoring the trend suggested by the smaller relative potency factors for HCDD, more weight is given to the larger factor determined on the basis of the teratogenic study performed with HCDD. It was, therefore, decided that a more appropriate relative potency for HCDD is 50. This was then used to derive the LOC for HCDD according to the following calculation -

25 ppt* X 50 X (36.8 g/53.9 g)** = 853 ppt (rounded to 850 ppt)

*- The 25 ppt used in this calculation is the health advisory level which was issued for the TCDD contamination of fish from the Great Lakes. As it was stated previously it is the Great Lakes health advisory which is used as the basis for the derivation of the levels of concern for the higher chlorinated dioxins in the present assessment.

**- ratio of food factors; 36.8 g/day - 99th percentile intake for fish; 53.9 g/day - total intake for eggs (28.5 g) and chicken (25.4 g) consumed by children 2 to 5 years of age (supplied by Dr. F. Cordle, HFF-108, 4/14/83, see attachment #3).

This level of 850 ppt, however, applies to the adult and not to children. The latter are of greater concern in this case because they are likely to consume more eggs and chicken per kg of body weight than adult. Therefore, the 850 ppt level is divided by a factor of 3 to account for this increased exposure of children to give a value of 283 ppt which is rounded off to give a LOC of 300 ppt for HCDD.

HpCDD

The amount of data available on HpCDD is quite meager. If the relative potency value of 1/200 is used, a LOC is derived which is unduly high, particularly in light of the information on the structure-activity relationship of the dioxins. The two hepta isomers have chlorine atoms at carbon positions 2,3,7, and 8, one unoccupied carbon position, and only differ from the most toxic hexa-isomers by the presence of one additional chlorine atom. Therefore, it is felt that a LOC of 500 ppt would be more appropriate.

OCDD

After evaluating the available information on the toxicological and/or biological potency of OCDD it was determined that the most reliable data was that from the reproductive/teratology study reported by Schwetz et al. (1973). In that study the NOEL for OCDD was 100 mg/kg b.w./day Using this value together with a 1000 fold safety factor and accounting for the lower body weight of 2 to 5 year old child, a tentative LOC of concern equivalent to 30 ppm was determined, as shown below:

LOC = 100 mg/kg b.w./day (NOEL) ÷ 1000 (S.F.)
= 0.1 mg/kg b.w./day x 16 kg b.w. (child)
= 1.6 mg/day ÷ 53.9 g/day (total consumption of chicken and eggs by child)
= 29.68 ppm or 30 ppm

While the value is based on "in vivo" experimentation, it appears to be unrealistically high for a congener which belongs to a class of toxicants, e.g., dioxins, for which so much concern has been expressed. Furthermore, it should be stressed that this value is derived from a single study using

only one animal species, e.g., the rat. If we consider the "in vitro" data on AHH enzyme induction, it is seen that OCDD has only a minute fraction of the activity reported for TCDD. Nevertheless, there is some concern over the possibility that exposure to OCDD at the level suggested by the tentative LOC of 30 ppm may result in some degree of enzyme induction activity in humans. Therefore, the application of a further safety factor of at least 10 is considered appropriate. Thus, a LOC of 3 ppm is recommended for OCDD in chicken and eggs.

Since the amounts of chicken and eggs consumed are similar, a uniform LOC for the respective congeners can be applied to each food item. Again it must be emphasized that these levels apply only to the present situation in Texas and have no application to other incidents. It should also be reiterated that while the induction of neoplasia was used to derive one of the comparative relative potency factors for HCDD the issue of carcinogenicity was not utilized directly in this evaluation because of the limited, short-term exposure of this situation. Finally, although structure-activity information was considered in deriving the LOCs for the higher chlorinated dioxins it is recognized that additional data on such relationships is required to refine the significance of such parameters in the toxicological assessments of these toxicants.

Michael Bolger 4/29/83
Michael Bolger, Ph.D.

Garfield N. Biddle 4/29/83
Garfield N. Biddle, Ph.D.

Attachments

cc:
HFF-100
HFF-150 (Blumenthal)
HFF-152 (Jackson/Edwards)
HFF-159 (Shibko)

HFF-159:GNBiddle:MBolger:clw:4/29/83:472-5706:2095A

15. 83-261-360 IN PROCESS
12 SUBS - SCRAPINGS
FROM EQUIPMENT

16. 83-292-061
1 SUB - SHEEP WOOL FROM SHEEP
MEAL SCREEN
RECEIVED FROM H.T.C. RENDERING,
SAN ANGELO, TEXAS

17. 83-261-062
1 SUB - MEAT & BONE MEAL
95% SHEEP MEAL

18. 83-292-063
1 SUB - POULTRY MEAL

19. 83-292-064
1 SUB - POULTRY MEAL

20. 83-292-065
1 SUB - MEAT & BONE MEAL

21. 83-292-066
1 SUB - POULTRY MEAL

22. 83-292-067
1 SUB - MEAT & BONE MEAL

23. 83-292-068
1 SUB - MEAT & BONE MEAL

24. 83-292-069
1 SUB - DIRT, DEBRIS, FROM
INSIDE HEARTH OF OLD
INCENERATOR

SHIPPED TO CINCINNATI LABORATORY:

25. 83-261-359
23 SUBS - LUBRICANTS, DEODORANTS,
INSECTICIDES, BOILER
COMPOUNDS, VARIOUS
LIQUIDS AND POWDERS.

UPON RECEIPT OF C/R'S, I WILL DESCRIBE SUBS THAT RELATE TO EACH SAMPLE.

IN REGARDS TO 83-261-350, SUB #1 MEAT & BONE MEAL, SUB #2 ANIMAL FAT, COLLECTED FROM LOADS RECEIVED FROM TEXAS BY PRODUCTS COMPANY, SAN ANTONIO. IT BELIEVED THAT BOTH COMPANIES ARE UNDER THE SAME OWNER. THIS WILL BE DEVELOPED 4/11/83, AS TO COMMON SUPPLIERS, PROCESSING, ETC.

NOTE THAT 83-261-350, COLLECTED ON 4/4/83 WAS RECEIVED FROM TEXAS BY-PRODUCTS COMPANY, SAN ANTONIO, TEXAS. SUB #1 MEAT & BONE MEAL WAS COLLECTED FROM THE TRANSPORT TRUCK, AND ANALYSIS REVEALED 25.5 PPM. OUR SAMPLE 83-260-356, MEAT & BONE MEAL, COLLECTED ON 3/16/83 REVEALED 16.0 PPM PCP'S. THIS SAMPLE WAS COLLECTED FROM A STORAGE BIN, AND IS NOW BELIEVED TO BE A PORTION RECEIVED FROM TEXAS BY-PRODUCTS.

TEXAS RENDERING IS OWNED BY HUBERT L. LINENBERGER, AND ALSO FUNCTIONS AS THE PRESIDENT. LINENBERGER ALSO OWNS 75% OF THE STOCK OF TEXAS BY-PRODUCTS, SAN ANTONIO, AS WELL AS OWNING A MAJOR INTEREST IN TEX-HENS, INC., NIXON, TEXAS.

TEXAS RENDERING RECEIVED APPROX. 3-4 LOADS OF MEAT & BONE MEAL PER WEEK FROM TEXAS BY-PRODUCTS, ESTIMATED AT APPROX. 150,000 LBS. OR MORE. IT WAS REPORTED THAT THIS MEAT & BONE MEAL IS VERY HIGH IN FAT CONTENT AND IS RUN THROUGH THE EQUIPMENT AT TEXAS RENDERING TO EXTRACT ADDITIONAL FAT. IT IS ALSO REPORTED THAT PRODUCT SAMPLED UNDER 83-261-350, SUB #2, ANIMAL FAT FROM TEXAS BY-PRODUCTS IS ACTUALLY STREET GREASE, AND IS NOT ANIMAL FAT PROCESSED BY TEXAS BY-PRODUCTS. ALL ANIMAL FAT PROCESSED BY TEXAS BY-PRODUCTS, SAN ANTONIO, REPORTEDLY GOES TO JACOB-SIERNS, HOUSTON, TEXAS.

WHILE TEXAS RENDERING RECEIVES MEAT & BONE MEAL AND STREET GREASE FROM TEXAS BY-PRODUCTS, SAN ANTONIO, TEXAS RENDERING DOES NOT SHIP PRODUCTS TO THEM. ALSO IT WAS REPORTED, THESE FIRMS DO NOT HAVE COMMON SUPPLIERS. ALSO NO PRODUCTS ARE SHIPPED FROM TEXAS RENDERING TO TEX-HENS, INC., NIXON, TEXAS.

A GENERAL PROCESSING FLOW AT TEXAS RENDERING IS AS FOLLOWS:

AS PRODUCT IS RECEIVED, MEAT & BONE MEAL, DEAD ANIMALS, SCRAPS, ETC., IT IS DUMPED INTO A PIT WHERE IT IS AUGERED TO TO AN INDUSTRIAL GRINDER, AUGERS OVER MAGNETIC PLATE (REMOVE METAL) TO MEAT STORAGE VAT, TO ONE OF 5 MEAT COOKERS. THE COOKERS ARE CHARGED WITH APPROX. 6,000 LBS. OF PRODUCT AND APPROX. 2,000 LBS. OF ANIMAL FAT IS ADDED (USUALLY PROCESSED THE NIGHT BEFORE). AFTER COOKING AT APPROX. 315 DEGREES F. THE PRODUCT EXITS AND SCREENED WITH THE FAT GOING TO ONE OF 3/20,000 LB. WORKING VATS. THE FAT IN THESE VATS IS USED TO INJECT INTO THE COOKING VATS AS STATED ABOVE.

AS FAT IS NEEDED FROM THESE WORKING VATS, IT DRAINS TO A FLAT DRYING VAT TO DRY OFF WATER. FROM HERE, IT IS PUMPED TO EITHER OF 3/30,000 LB. STORAGE VATS.

AS THE MEAT EXITS THE COOKER, IT GOES TO THE PRESSES WHERE MORE FAT IS EXTRACTED (FAT GOES TO THE WORKING VATS). THE MEAT THEN PASSES THE SCREENER, WHERE LARGE PIECES OF BONE, HAIR, ETC., ARE REMOVED. THE MEAT THEN GOES TO THE HAMMER MILL, THEN THE MEAL TO EITHER OF 8/60,000 LBS. STORAGE BINS AS FINISHED MEAL. THE BONES, ETC., REMOVED BY THE SCREENER, GOES BACK TO THE ORIGINAL AUGER AT THE STARTING POINT OF THE PROCESS.

DISCUSSIONS WERE HELD ON MONDAY, 4/11/83, BY HOUSTON STATION WITH OFFICIALS OF THE TEXAS DEPT. OF AGRICULTURE AND TEXAS DEPT. OF HEALTH AND OUR SAMPLE RESULTS KNOWN AT THE PRESENT TIME WERE DISUCSSED. THE INTRASTATE SHELL EGGS WERE DISCUSSED WITH TEXAS DEPT. OF HEALTH, HOWEVER, THEY DO NOT HAVE THE CAPABILITIES OF ANALYZING FOR PCP'S TO DETERMINE THE CURRENT STATUS OF EGGS FROM SMITH FARMS AND POSSIBLY OTHERS. IF FDA CAN PROVIDE CURRENT ASSAYS, THEY ARE WILLING TO ACT, HOWEVER, REQUESTED THAT FDA PROVIDE GUIDANCE AS TO HEALTH OR REGULATORY SIGNIFANCE AS WELL AS ACTION GUIDANCE.

*

[illegible] THE TEXAS DEPT. OF AGRICULTURE IS QUITE CONCERNED AND IS CURRENTLY ANALYZING SAMPLES SUBMITTED BY THE FIRM OF FINISHED PRODUCT, HOWEVER, THEY ALSO REQUESTED GUIDANCE.

FROM THE HIGH LEVELS OF PCP'S FOUND IN MEAT & BONE MEAL FROM TEXAS BY-PRODUCTS, SAN ANTONIO, IT APPEARS THAT THIS COULD BE A CONTINUOUS SOURCE OF CONTAMINATED PRODUCTS. AN INVESTIGATION OF THIS FIRM IS CURRENTLY BEING DISCUSSED.

Attachent #2

REGULATORY TOXICOLOGY AND PHARMACOLOGY 1, 379–387 (1981)

The Use of Epidemiology in the Regulation of Dioxins in the Food Supply[1]

FRANK CORDLE

Epidemiology and Clinical Toxicology, Bureau of Foods, Food and Drug Administration, Washington, D. C. 20204

Received November 1981

Residues of tetrachlorodibenzo-*p*-dioxins (TCDD) were detected recently in several species of freshwater fish from various areas of the Great Lakes. Concern for the potential human health risk associated with the consumption of these fish prompted the Food and Drug Administration to assess epidemiological and toxicological TCDD data in order to determine the need for regulatory action. In the assessment, pertinent animal and human data and data for the TCDD residues in the freshwater fish, for the amounts of the different fish species consumed and for the number of individuals who consumed the fish, were evaluated. The various methods of evaluation used to reach a regulatory decision are described.

INTRODUCTION

Although epidemiology may have first been used by Hippocrates, the definition or meaning has undergone some significant changes since then. First described as the study of epidemics and, later, as the study of the determinants of differences in disease distributions in human populations, epidemiology today, especially in regulatory agencies, refers essentially to the activities of the epidemiologist. In a regulatory agency such as the Food and Drug Administration (FDA) the role of the epidemiologist is to assimilate, digest, and synthesize the best available data from survey, clinical, and laboratory experiences, either firsthand or from the scientific literature; these human and animal data are then combined and interpreted in order to address a basic question: Does the evidence of adverse human health effects from exposure to the various chemical substances that fall under FDA regulatory authority present a risk to public health safety that is sufficient for FDA to initiate or make a change in regulatory action? The importance of the contri-

[1] Presented at the international symposium Human Health Aspects to Accidental Chemical Exposure of Dioxins—Strategy for Environmental Reclamation and Community Protection, organized by the International Academy of Environmental Safety (IAES) and the International Society of Ecotoxicology and Environmental Safety (SECOTOX) jointly with the Instituto Superiore di Sanita, Rome, and the Gesellschaft fur Strahlen- und Umwelt Forshung MbH, Munich.

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bution of epidemiology in the regulatory public health arena seems obvious. Without adequate assessment of factors that appear to increase the risk of disease in humans from chemical substances in the food supply, food may be destroyed, the public may be unnecessarily inconvenienced or inadequately protected, and the costs may be enormous. In short, epidemiological efforts are directed toward the prediction of such risk at the community, state, or national level.

It is quite likely that the majority of humans are exposed to a large number of chemical substances in small amounts over an extended period of time rather than to large doses such as those described in the mercury episode in Minamata or in the PCB exposure in Japan. The importance of the possible cumulative effects from these small doses versus the importance of the effects from a single large dose or from relatively large doses over a short period of time is the subject of considerable scientific debate.

Much of the information concerning the toxicity of various chemical substances has been obtained from experiments in animals. In general, safety testing depends upon the fact that as the exposure dose is decreased, toxic effects also decrease, and a dose is finally established at which "no observed effects" are seen. Such dose-response relations are central to toxicity studies in animals and should be of equal concern in the evaluation of human exposure to a variety of environmental and other insults. However, dose-response relations in humans must be established or identified with a great deal of care and caution. Outcome may vary greatly in significance: At one extreme is death and at the other are changes in physiological or psychological function. The weight that should be given to each relation in formulating regulatory policy may vary greatly.

The lack of good examples of dose-response relation, even in the area of occupational exposure, is remarkable. Where dramatic incidents of exposure to environmental contamination have occurred through ingestion of contaminated food, efforts to establish an acceptable dose-response relation in humans have met with little success.

However, epidemiological study should not be limited to outbreaks of disease that are obviously caused by high exposures to toxic chemicals: it should be equally concerned with the effects of lower, more prolonged, and sometimes insidious exposures.

EPIDEMIOLOGICAL METHODS

In the traditional manner, epidemiologists deal with epidemics by interpreting patterns of disease, testing hypotheses, and assessing the risks and benefits of various options. Their methods involve the use of two categories of epidemiology often referred to as analytical and descriptive epidemiology. The analytical epidemiological methods generally involve either a case-control, retrospective approach or a cohort, prospective approach.

In analytical epidemiology, the goal of epidemiological activity is to identify and, if possible, to quantify the association between a causal exposure or characteristic and a disease under circumstances that permit the best possible discrimination between cause and alternative hypotheses. Chance will always affect the alternatives; thus the feasibility of such a study is limited by factors such as sample size,

Since a precise hypothesis permits the use of a well-thought-out and properly planned study design, it is better to use the cohort approach to measure relative and attributable risk, for example, than to try to detect trends from descriptive data. Nevertheless, sample size considerations, cost, and time constraints often restrict the kind of epidemiological study undertaken, even though the cohort approach might be preferred for a given problem.

Case-control studies of disease, i.e., studies looking at the past history of exposure, are often more feasible than cohort studies because they can be conducted in a relatively short time and are easily repeatable, and because a large number of cases can be studied economically. They do have some special liabilities, however, in terms of validity, since such studies depend entirely on the comparability of cases and controls and on the specific methods used to measure the exposure. Although frequently used, the methods for estimating relative risk or risk ratio from case-control studies also present some special problems of inference.

Cohort studies, i.e., studies looking forward in time, are especially costly because of the time involved in the prospective follow-up. They do, however, provide an opportunity to compute a more reasonable relative and attributable risk, and specious relationships resulting from bias in data collection are less likely to occur.

Descriptive epidemiological methods can be used by a regulatory agency such as FDA to determine trends in disease and magnitudes of exposed populations largely from data that are readily available, e.g., mortality data, data from National Cancer Institute (NCI) surveys, census data, and food consumption data. The goal of these studies is to identify any unexpected changes in incidents or mortality through surveillance of the available data for time trends and through probes of specific data collected during research activities or gathered in support of regulatory decisions.

Epidemiological studies also provide information that is used to identify and quantify differences in species responsiveness to environmental agents in a variety of other ways. One use, for example, pertains to the difficulty associated with comparing data derived from studies of highly inbred animal strains to data of a genetically heterogeneous human population. In this case, epidemiological methodologies provide the means for stratification of study data according to sex, age, race, and other variables that characterize human populations. Certain problems may also be minimized when epidemiological considerations are employed in risk assessments that are based on comparisons involving data of humans and data of animal models. These include problems associated with limited sample sizes, migration in and out of the exposure area, and toxicity due to causes other than that associated with exposure to the etiologic agent under study.

EPIDEMIOLOGICAL AND TOXICOLOGICAL ASSESSMENT OF TCDD EXPOSURE

Recent concern for the potential human health risk associated with exposure to residues of the tetrachlorodibenzo-*p*-dioxins (TCDD) in several species of freshwater fish from various areas of the Great Lakes has resulted in an epidemiological and toxicological assessment of the problem that utilizes currently available data from a variety of data sets. For a regulatory decision to be made, several elements

were needed. These included data for the TCDD residues in the freshwater fish, for the amounts of the various fish species consumed and for the number of individuals who consumed the fish, and assessments of pertinent animal data and previous human exposure to TCDD.

Animal Data

A number of toxicological studies with TCDD have been conducted to assess the potential for acute toxicity and teratogenesis. Kociba *et al.* (1976) reported the results of a subchronic study using rats that were given 1.0, 0.1, 0.01, 0.001, or 0 μg TCDD/kg body wt/day for 5 days/week for 13 weeks. Doses of 1.0 μg TCDD/kg/day caused some mortality, inactivity, decreased body weights and food consumption, pathomorphologic changes in the liver, lymphoid depletion of the thymus, increased urinary excretion of porphyrins, and minimal alterations of some hematopoietic components. Doses of 0.1 μg TCDD/kg/day caused decreased body weights and food consumption and slight degrees of liver degeneration and lymphoid depletion. These data indicate that no discernible ill effects occurred in rats given 0.01 or 0.001 μg TCDD/kg/day for 5 days/week for 13 weeks.

In a 2-year chronic study in rats Kociba *et al.* (1978) reported that the ingestion of 0.1 μg TCDD/kg/day caused an increased incidence of hepatocellular carcinomas and squamous cell carcinomas of the lung, hard palate/nasal turbinates, or tongue, whereas a reduced incidence of tumors of the pituitary, uterus, mammary glands, pancreas, and adrenal glands was noted. Other indications of toxicity at this dose level included increased mortality, decreased weight gain, slight depression of erythroid parameters, and increased urinary excretion of porphyrins. Gross and histopathologic changes were noted in the hepatic lymphoid, respiratory, and vascular tissues. The primary hepatic ultrastructural change at this high dose level was proliferation of the rough endoplasmic reticulum. Terminal liver and fat samples from rats given this high dose level contained 24,000 and 8100 parts per trillion (ppt) TCDD, respectively. Rats given 0.01 μg TCDD/kg/day for 2 years showed less severe toxicological effects than those given the highest dose level. These included liver lesions (including hepatocellular nodules) and lung lesions (including focal alveolar hyperplasia). Terminal liver and fat samples from rats given this dose level contained 5100 and 1700 ppt TCDD, respectively. Ingestion of 0.001 μg TCDD/kg/day (22 ppt in the diet) caused no effects of any toxicological significance. Terminal liver and fat samples from rats given this low dose level each contained 540 ppt TCDD.

In a 3-year reproduction study in rats given dose levels of 0, 0.001, 0.01, or 0.1 μg TCDD/kg/day, Murray *et al.* (1979) reported no significant toxic effects in the f_0-generation rats of either sex during the 90 days of TCDD ingestion prior to mating. However, significant decreases in fertility and neonatal survival were observed in the f_0-generation rats receiving 0.1 μg TCDD/kg/day. At 0.01 μg TCDD/kg/day, fertility was significantly decreased in the f_1 and f_2 generations, but not in the f_3 generation, and decreases in litter size at birth, gestational survival, and neonatal survival and growth were also noted. Among the rats receiving 0.001 μg TCDD/kg/day, no effect on fertility, litter size at birth, or postnatal body weight was observed in any generation. No consistent effect on neonatal survival was observed at a dose level of 0.001 μg TCDD/kg/day.

Allen *et al.* (1977) reported results of a subchronic study in which female rhesus monkeys consumed a diet containing 500 ppt TCDD for periods as long as 9 months. It was calculated that these monkeys ingested a total of 2–3 μg TCDD/kg body wt over the course of the 9-month study. Clinically, these monkeys showed changes similar to those described by McConnell *et al.* (1978) as well as some hematologic depression and hemorrhages in various tissues. Hypertrophy, hyperplasia, and/or metaplasia were noted in the epithelium of the bile ducts, salivary glands, bronchi, pancreatic ducts, sebaceous glands, skin, gastric linings, and urinary tracts of these monkeys given diets containing 500 ppt TCDD.

Human Experience

Although 22 incidents of human exposure to TCDD in connection with the manufacture of chlorinated phenols have been reported worldwide since 1949 (Holmstedt, 1980), there remains a scarcity of reliable information concerning the results of these exposures.

In a recent report of the mortality experience of a cohort of workers exposed to TCDD in Nitro, West Virginia, in 1949, Zack and Suskind (1980) described some of the signs and symptoms observed in the exposed population shortly after the accident occurred. Employees who worked in the area of 2,4,5-trichlorophenol (TCP) production or were involved in the cleanup began to develop symptoms immediately following exposure to the material, which was discharged from the autoclave. Symptoms included eye and respiratory tract irritation, headache, dizziness and nausea, and a severe irritant reaction of the exposed skin. After these initial symptoms subsided, chloracne and other symptoms became evident. A total of 12 more severely affected workers were examined on three occasions during the period 1949–1953. Another 26 persons with chloracne that was apparently unrelated to the accident were also examined in 1953.

The clinical symptoms included acneform lesions; severe pains in muscles of upper and lower extremities, shoulders, and thorax on exertion; fatigue; nervousness and irritability; decrease in libido; dyspnea; vertigo; and intolerance to cold. All of the cases showed evidence of chloracne. For the six workers examined during 1949 and 1950, another examination was carried out in 1953, and at that time six additional workers involved in the accident were also examined. The findings in this later examination indicated a general regression of both the cutaneous and noncutaneous symptoms which had been present earlier. No specific levels of exposure could be determined.

In other reports of industrial exposure to TCDD from Great Britain, the Netherlands, West Germany, and Czechoslovakia, chloracne was the most common and prominent sign observed following exposure. In some reports liver function tests indicated liver damage, whereas in other reports they did not. Two major problems encountered in all of these studies were the lack of a clear identification of those exposed, other than their subsequent development of chloracne, and the absence of any measures for the levels of exposure that might have taken place.

Pazderova-Vejlupková *et al.* (1981) reported results of a 10-year follow-up study of workers exposed to TCDD between 1965 and 1968 during the production of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). In this study group of 55 individuals

(originally 80 of the 400 persons engaged in the production became ill), the first indications of illness were feelings of sickness, fatigue, weakness in the lower extremities, and the formation of chloracne. Subsequent examinations indicated that about 20% had mild hepatic lesions.

During the 10-year follow-up study of these exposed individuals, most of the patients did not experience all of the symptoms and signs of intoxication, and some patients showed the same symptoms and signs as others, but in different combinations. It is assumed that in this type of intoxication all the systems and organs mentioned in the study were simultaneously affected, although some were affected only slightly. This assumption is supported by several facts. Fluorescence of liver tissues in ultraviolet light, which is a sign of pathological porphyrin metabolism, was present in all cases of necropsy and biopsy, i.e., in persons for whom long-term monitoring of porphyrin excretion in urine was carried out and in whom δ-aminolevulinic acid values were constantly within normal limits. Probably a slight subclinical lesion was present in each of these patients. Further evidence was furnished in repeated neurological examinations. Polyneuropathy of the lower extremities was manifest in some patients only in the third or fourth year of illness. There is definite clinical and electromyographic evidence that the results of the first examinations conducted when the illness commenced showed that the patients were entirely normal.

Additional study results have been reported recently by Zack and Suskind (1980), Ott *et al.* (1980), and Cook *et al.* (1980), describing the mortality of employees engaged in the manufacture of 2,4,5,-T. In two of these studies cohorts of employees were assembled on the basis of their exposure to TCDD, which was indicated by the presence of chloracne; the third cohort consisted of individuals employed over the same time period. Unfortunately, each of these three cohorts comprised a limited number of individuals; e.g., the chloracne groups contained 121 and 49 individuals and the employee group contained 204.

In each of these studies there does not appear to be an apparent excess in total mortality rate or in deaths from malignant neoplasms. It must be pointed out, however, that each of these studies does have limitations both in the size of the population studied and in other methodological areas, such as exposure levels.

For a more detailed description of these studies as well as the Seveso incident, the reader is referred to the original papers and to Holmstedt (1980), Reggiani (1980), and Pocchiari *et al.* (1979).

Human Exposure to TCDD Residues in Fish

Although there are no epidemiological studies which have firmly established an association between cancer in humans and TCDD exposure, and although comparisons of human exposure data and animal studies appear to indicate that humans may be less sensitive than animals to TCDD exposure, prudence dictates that human exposure to TCDD be kept to a minimum. With this public health objective in mind, FDA recently completed an assessment of the problem of TCDD residues in some species of freshwater fish in the Great Lakes for the purpose of determining whether consumption of such fish provided a potential public health problem.

Results of the analyses of fish samples collected by Canada and the United States

TABLE 1

HUMAN CONSUMPTION OF DIOXIN BASED ON FISH CONSUMPTION DATA

Hypothetical dioxin residue level in fish consumed (ppt[a])	Total daily intake (ng[b])			Total daily intake/body wt (pg[c]/kg)		
	From all selected species		From pike, 99th percentile	From all selected species		From pike, 99th percentile
	90th percentile	99th percentile		90th percentile	99th percentile	
100	1.57	3.683	8.4	22	50	120
50	0.77	1.84	4.2	11	26	60
25	0.38	0.92	2.1	5.5	13	30

[a] ppt = parts per trillion.
[b] 1 microgram (μg) = 1000 nanograms (ng).
[c] 1 ng = 1000 picograms (pg).

indicated that TCDD levels as high as 30 ppt with an average value of 25 ppt were present in the edible portion of salmonoid fish (salmon, trout) from Lake Ontario. Lower levels of TCDD were reported to be present in the edible portions of commercial species (bullhead, perch, catfish, sucker, etc.) from Lake Ontario, although up to 40 ppt TCDD were found in eel and smelt from the lake. Less than 10 ppt TCDD was seen in samples from Lake Erie, and limited data for fish from the other Great Lakes were similar to those obtained from Lake Erie fish, except that higher levels of TCDD were present in fish from Saginaw Bay, Michigan.

Data on fish consumption from the National Marine Fisheries Service (NMFS) were extracted for the eight Great Lakes states, Illinois, Indiana, Michigan, Minnesota, New York, Ohio, Pennsylvania, and Wisconsin. These data were collected in a national sample of households, consisting of approximately 25,000 individuals. From the data presented, individuals who consumed the species of interest, i.e., the species currently being analyzed for dioxin residues were identified in the total sample, and the mean fish consumption, in grams per day, was computed. The 90th and 99th percentiles were also computed. On the basis of the proportion of individuals in the sample population consuming the species of interest, 17,057,791 individuals in the eight Great Lakes states would be expected to consume these same species. It must be pointed out that the number of consumers in the total population can be considered only an estimate because of the lack of information on potential sampling error as well as other factors. These data indicated that the 99th percentile for daily consumption for all consumers of the selected species was 36.8 g; the 90th percentile for daily consumption was 15.7 g. For a single species of fish such as pike, which appeared to be consumed in larger amounts than all the species combined, the 99th percentile of consumption was 83.95 g. Table 1, which is based on these fish consumption data, shows the daily human consumption for a range of hypothetical dioxin residue levels.

Thus, the four elements of the model for a scientific regulatory assessment, i.e., animal data, human data, consumption data, and residue data, were available. In this instance the human data concerning TCDD exposure contributed little to the regulatory decision because of the uncertainty of the exposure data as well as the

uncertainty of the outcome of the exposure. It was necessary, therefore, to rely on extrapolation from animal to human. In this case the rodent data from the 2-year chronic feeding study (Kociba *et al.*, 1978) were used for the extrapolation.

Results of that study showed that

(a) at 0.001 μg/kg body wt/day, no adverse effects were noted in rats exposed for their lifetimes to the dioxin;

(b) at 0.01 μg/kg body wt/day, hyperplasia of the liver and lung was observed to occur, thus indicating an observable effect related to enzyme induction and liver cell response to the compound;

(c) at 0.1 μg/kg body wt/day, an increase in liver carcinomas was observed.

The animal-to-human extrapolation of the no-effect level for TCDD exposure from the rodent data indicated an intake of 1 ng/kg body wt/day or a total daily intake of 70 ng as the no-effect level. If fish containing average TCDD residue levels of 25 ppt were consumed in the amount of the 99th percentile, i.e., 36.8 g/day, the total daily intake of TCDD would be 0.92 ng or 13 pg/kg body wt/day or less than 1/70th of the no-effect level, less than 1/700th of the lowest-effect level, and less than 1/7000th of the carcinogenic level. The safety margin at the 90th percentile of consumption is even greater.

As a result of this assessment, a public health advisory was sent to the health officers in each of the Great Lakes states, encouraging a continued monitoring of TCDD residues in fish, especially in certain local areas where TCDD levels might be higher than the average, and where local fish consumption might also be higher than that for the Great Lakes area as a whole.

This example in regulatory decision making illustrates FDA's role in protecting public health by ensuring a safe and nutritious food supply. This responsibility is exercised by individuals who call upon science, law, and the regulatory process to accommodate the demands of safety, contamination, food requirements, Congress, consumers, and the courts. Although the regulatory process has often been criticized, on the whole it has provided effective public health protection for the millions who consume food in the United States.

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From F. Conlle HFF
April 14, 1983

FOOD INTAKE FOR DIOXIN, PCP LEVELS OF CONCERN

	18-45yrs bw.71.2	2-5yrs bw.16.3
Total red meat and poultry	212g	109.6g
Total red meat	108g	
Beef	134g	65.6g
Veal	20g	
Beef + veal	136g	
Lamb + mutton	17g	
Beef liver	20g	
Pork	67g	36.3g
Pork (45-64 years)	75g	
Pork liver	8g	6.7
Poultry (total)	53g	
Poultry (total; 45-64 years)	56g	
Chicken	44g	25.4g
Chicken (45-64 years)	47g	
Chicken liver	13g	4.4g
Turkey	33g	
Duck	17g	
Eggs	47g	28.5g
Eggs(45-64 years)	58g	
Milk fat	24g	23.4g
Milk fat(13-17 years)	31g	
Non-fat milk	48g	
Non-fat milk (13-17 years)	74g	

Samples collected from Smith Farms (26 operating farms) on 1/17/83

Eggs - Farm #34	0.20ppm (PCP)	Feed - 0.03ppm (PCP
Eggs - K&M Farm	0.15ppm (PCP)	Feed - 0.07ppm (PCP)
Eggs - Farm #40	0.13ppm (PCP)	Feed - Trace (PCP)
Eggs - Henders Farm	0.26ppm (PCP)	Feed - Trace (PCP)

Food consumption by days and meals:

	18-45 years	2-5 years
Beef	134g X 5 meals=670g	65.6g X 5 meals=328g
Pork	75g X 5 meals=375g	36.3g X 5 meals=182g
Chicken	44g X 4 meals=176g	25.4g X 4 meals=102g
Eggs	47g X 7 meals=329g	28.5g X 7 meals=200g
Milk fat	24g X 7 meals=168g	23.4g X 7 meals=174g
Other	30g X 7 meals=210g	10.0g X 7 meals=70.0g
	1928g	1056g
	1928g/7=275.4g/day	1056g/7=151g/day