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CHEMICAL MANUFACTURERS ASSOCIATION

RECEIVE

AUG 28 1986

S. B. HAMILT

August 26, 1986

TO: Dibenzofurans/Dibenzodioxins Program Panel
FROM: C. Stack *C. Stack*
RE: Recent Filings and Documents

For your files the following is enclosed:

- * Panel comments on the EPA Health Assessment Document on Dibenzofurans and cover letters to Drs. Mukerjee and Byrd;
- * Panel comments on EPA's Toxicity Equivalency Factors Scheme and cover letter to Dr. Yosi;
- * The Panel's "Considerations for Assessing Potential Human Risk from Exposures to 2,3,7,8-Tetrachlorodibenzodioxin" sent to all of above;
- * The April 1986 draft of EPA's "Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-p-dioxins and Dibenzofurans (CDDs and DCFs)"

GENP 010810

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CHEMICAL MANUFACTURERS ASSOCIATION

GERALDINE V. COX, Ph.D.
Vice President
Technical Director

August 25, 1986

BY HAND

Terry F. Yosie, Director
Science Advisory Board, A-101-F
Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Mr. Yosie:

The Dibenzofurans and Dibenzodioxins Panel of the Chemical Manufacturers Association (CMA) requests the opportunity to make a five-minute presentation at the Science Advisory Board's (SAB's) Dioxin Toxic Equivalency Methodology Subcommittee meeting on September 8-9, 1986. Dr. James Wilson will make the presentation on behalf of the Panel and will comment on EPA's "Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-p-Dioxins and Dibenzofurans (CDDs and CDFs), the subject of the SAB Subcommittee meeting.

We are submitting with this letter a copy of the Panel's written comments on EPA's Toxic Equivalency Factor (TEF) Scheme for predicting risks from chlorinated dibenzodioxins and dibenzofurans. Dr. Wilson's presentation will briefly summarize these comments.

We are also enclosing with this letter (Attachment I) a copy of a working paper prepared by the CMA Panel entitled "Considerations for Assessing the Potential Human Risk from Exposures to 2,3,7,8-Tetrachlorodibenzodioxin." EPA's Toxic Equivalency Factor Scheme represents an effort by EPA to develop risk values for a number of chlorodibenzodioxins and chlorodibenzofurans in relationship to the toxicity of 2,3,7,8-TCDD. It thus is obviously important that EPA accurately and reliably determine that underlying TCDD value.

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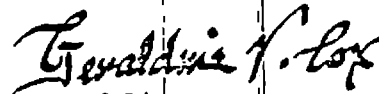
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Terry F. Yosie, Director
August 25, 1986
Page 2

The Panel's working paper discusses the variance between EPA's 1985 risk assessment of TCDD and assessments of other international expert panels. It concludes that EPA overestimates the potency of TCDD by approximately three orders of magnitude. Because the underlying TCDD risk is an integral part of the TEF Scheme, we invite the Subcommittee's attention to this second document.

We are sending copies of these comments directly to all members of the Toxic Equivalency Factor Methodology Subcommittee. If there are any questions, please call Dr. Carol Stack (887-1196) of my staff.

Sincerely yours,



Geraldine V. Cox, Ph.D.
Vice President -
Technical Director

Enclosures

cc w/ encls.: Members of the TEF
Methodology Subcommittee

783623

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Attachment I

COMMENTS OF THE
CHEMICAL MANUFACTURERS ASSOCIATION
DIBENZOFURANS/DIBENZODIOXINS PANEL ON
EPA'S TOXICITY EQUIVALENCY FACTORS (TEF) SCHEME

August 25, 1986

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COMMENTS OF THE
CHEMICAL MANUFACTURERS ASSOCIATION
DIBENZOFURANS/DIBENZODIOXINS PANEL ON
EPA'S TOXICITY EQUIVALENCY FACTORS (TEF) SCHEME

The Chemical Manufacturers Association (CMA) Dibenzo-furans/Dibenzodioxins Panel urges the Scientific Advisory Board to recognize two features of the Toxicity Equivalency Factor (TEF) schemes used by EPA to estimate relative toxicity of different polychlorinated dibenzodioxins and dibenzofurans (PCDDs and PCDFs).

First, none of them is truly valid, nor strongly supported by scientific evidence. The relative activity of different compounds in the dibenzodioxin and dibenzofuran series varies, from species to species and from biological endpoint to biological endpoint, in ways that are not predictable with our present state of knowledge.

Second, the TEF system proposed by Barnes and Bellin, which EPA has used in several regulatory contexts, provides an approximation that can be useful for risk management purposes until more precise information can be developed. At the same time, several downward adjustments to the values attributed to certain congeners by the scheme are necessary to make it more consistent with the available data base.

I. ALL TEF SCHEMES LACK
SCIENTIFIC VALIDITY.

No strong scientific support exists for a TEF scheme for chlorinated dibenzodioxins and dibenzofurans. We focus on the chlorodibenzofurans in this discussion, because they

make up a substantial fraction of the PCDD/PCDF compounds present in hot exit gas streams. However, similar remarks also apply to the chlorodibenzodioxins.

The compound 2,3,7,8-tetrachlorodibenzofuran (TCDF) is closely similar to 2,3,7,8-tetrachlorodibenzodioxin (TCDD) in size and shape, and according to the paradigm currently accepted by many scientists working in this field, should exhibit similar biological activity. This follows from the theory of receptor-modulated toxicity, in which binding to a receptor protein is the first step in the process that eventually leads to the very unusual toxicities exhibited by these compounds. In his cell-culture systems, Dr. William Greenlee of the Chemical Industry Institute of Toxicology indeed found 2,3,7,8-TCDF exhibits the same potency as 2,3,7,8-TCDD.

On the other hand, in several systems studied by Safe, et al., TCDF exhibits only one-tenth to three-tenths the activity of TCDD. Birnbaum, et al., also found in the B6C3F1 mouse that 2,3,7,8-TCDF had one-thirtieth the activity of TCDD when the endpoint was hydronephrosis or cleft palate in the fetuses of treated dams. Birnbaum and her co-workers also observed that the relative activities of these two compounds in that mouse strain parallels the relative rates at which they are metabolized and cleared from the body, and that clearance activity was higher in pregnant mice.

Accordingly, at a minimum, the relative activities of different compounds in the dibenzofurans series depend on two factors -- the intrinsic receptor-binding activity and the clearance rates in the organism involved. Other factors not yet identified may also contribute. Greenlee's cell-culture system is capable of little or no metabolic activity, and expresses something nearer to the intrinsic activity than do most other systems yet studied. Conversely, the studies of Birnbaum and her colleagues at NIEHS show the maximal effects of clearance rate on activity.

Safe and his co-workers, as well as many others, have made numerous attempts to derive a self-consistent, regular relationship between the activities of PCDDs and PCDFs so that reliable predictions could be made. These efforts are doomed to failure. EPA should not be encouraged to pursue this line of inquiry.

II. THE EPA TEF SCHEME NONETHELESS HAS
REGULATORY RISK MANAGEMENT UTILITY
AND THUS SHOULD BE AMENDED SLIGHTLY
TO REFLECT AVAILABLE DATA MORE CLOSELY.

CMA recognizes that from time to time circumstances will arise that require risk management decisions to be made on health risks posed by mixtures of PCDDs and PCDFs. Because good data will often not be available on a mixture close in composition to the one at issue, use of a TEF scheme can be justified.

CMA supports use of the Barnes-Bellin TEF scheme for regulatory risk management purposes. Among the several schemes which have been proposed, this one best reflects the complexity of the toxicologic issues and makes use of more of the information available than other schemes. At the same time CMA urges the Science Advisory Board to recommend minor revisions to this EPA scheme so that it will better account for well-known toxicity differences in the tetrachlorodibenzodioxins and tetrachlorodibenzofurans.

The present scheme assigns a single "toxicity equivalent" value for all TCDDs other than the 2,3,7,8-isomer. Existing data indicate, however, that the non-2,3,7,8-tetrachlorodibenzodioxins are not equivalently potent.

It is well known that certain non-2,3,7,8-TCDD isomers, such as the 1,3,7,8-isomer, exhibit activity in several in vitro tests. (Few in vivo results have been reported). The value assigned by Barnes-Bellin for all other TCDDs may be appropriate for these compounds.

However, it is also well known that other members of this series, such as 1,3,6,8-TCDD, exhibit activities orders of magnitude lower than 2,3,7,8-TCDD. In guinea pigs, for instance, the LD₅₀ for 2,3,7,8-TCDD is 0.5 to 2.0 µg/kg, while the LD₅₀ for 1,3,6,8-TCDD is >1.5 x 10 µg/kg, that is greater than 15 grams 1,3,6,8-TCDD per kg body mass. Probably two-thirds of the 22 different TCDDs will be found, like 1,3,6,8-TCDD, to be practically non-toxic.

If all of the nearly non-toxic TCDDs were rare and the more toxic isomers common, a scheme that treated all TCDDs equivalently would have little adverse consequence. However, the 1,3,6,8-/1,3,7,9-TCDD pair together predominate among tetra isomers in environmental sources of mixed PCDDs and PCDFs. At least these two TCDD isomers should be assigned a TEF value of zero.

Similar considerations apply to the tetrachlorodibenzofurans. If these compounds are to be lumped in one category in a TEF scheme, the values assigned should reflect the fact that in most mixtures the non-toxic isomers make up the majority. Similarly, the data now available on pentachlorodibenzofurans should be reviewed to see if the Barnes-Bellin value assigned to this class reflects their activity.

Finally, CMA urges the SAB to recognize that the composition of PCDDs/PCDFs on incinerator-derived particulates to which humans are ultimately exposed differs markedly from the compositions measured in hot gas streams. It is likely that the particulate composition is nearly enough constant that biological effects of this mixture could be measured directly. This would, of course, obviate the need for any indirect TEF estimate of toxicity.



CHEMICAL MANUFACTURERS ASSOCIATION

GERALDINE V. COX, Ph.D.
Vice President
Technical Director

August 22, 1986

BY HAND

Dr. Daniel Byrd, III
Science Advisory Board, A-101-F
Environmental Protection Agency
499 South Capitol St., S.W.
Washington, D.C. 20460

Dear Dr. Byrd:

The Dibenzofurans and Dibenzodioxins Panel of the Chemical Manufacturers Association (CMA) requests the opportunity to make a ten to fifteen minute presentation at the September 2, 1986, meeting of the Halogenated Organics Subcommittee of the Environmental Health Committee of the Science Advisory Board (SAB) to be held in Kansas City. The presentation will be made on behalf of the Panel by Dr. James Wilson.

The Panel has submitted comments to Dr. Debdas Mukerjee of EPA's Office of Environmental Criteria and Assessment on the revised draft Health Assessment Document for Chlorinated Dibenzofurans, which will be the subject of the SAB meeting on September 2. A copy of those comments is attached to this letter. At the SAB meeting, Dr. Wilson intends to summarize briefly CMA's concerns about the draft Health Assessment Document.

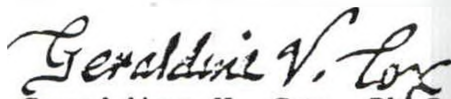
GENP 010819

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Dr. Daniel Byrd, III
August 22, 1986
Page 2

We are sending copies of the CMA Panel comments on the draft Health Assessment Document directly to members of the Halogenated Organics Subcommittee. If there are any questions, please call Dr. Carol Stack (887-1196) of my staff.

Sincerely yours,



Geraldine V. Cox, Ph.D.
Vice President-Technical Director

Enclosure

cc w/enc.: Dr. Debdas Mukerjee
Members of the Halogenated
Organics Subcommittee

783631

GENP 010820



CHEMICAL MANUFACTURERS ASSOCIATION

GERALDINE V. COX, Ph.D.
Vice President
Technical Director

August 22, 1986

VIA FEDERAL EXPRESS

Dr. Debdas Mukerjee
Project Officer for
Polychlorinated Dibenzofurans
Environmental Criteria
and Assessment Office
Environmental Protection Agency
26 W. St. Clair Street
Cincinnati, Ohio 45268

Re: Health Assessment Document for
Polychlorinated Dibenzofurans
(51 Fed. Reg. 26052, July 18, 1986)

Dear Dr. Mukerjee:

The Chemical Manufacturers Association Dibenzofurans and Dibenzodioxins Panel (CMA) appreciates this opportunity to comment on the June 1986 External Review Draft of the "Health Assessment Document for Polychlorinated Dibenzofurans" prepared for the Office of Air Quality Planning Standards.

CMA's comments focus upon the risk assessment in Chapter 8 of the document and the underlying health data upon which this risk assessment is based. We find that the risk assessment overestimates potential risks to chlorinated dibenzofurans by:

- (1) Misinterpreting the toxicology data on which it relies (the Murray three-generation 2,3,7,8-TCDD study) to conclude that 0.001 g/kg/day is a Lowest-Observed-Adverse-Effect Level (LOAEL), when in fact that dose was a No-Observed-Adverse Effect Level (NOAEL); and

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Dr. Debdas Mukerjee
August 22, 1986
Page 2

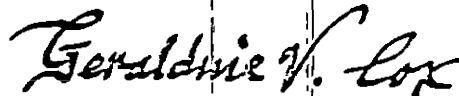
- (2) Underestimating exposures to chlorinated dibenzofurans of persons involved in the Yusho, Japan, incident, thus overestimating potency per unit exposure.

In addition, we find that the document overstates by a factor of approximately 100 the likely dibenzofuran concentration in polychlorinated biphenyls found in the United States. Each of these points are detailed in our Comments (Attachment I).

The draft document does not attempt to determine a unit potency value for potential carcinogenicity of any chlorinated dibenzofurans. CMA agrees development of any such value would be inappropriate given the absence of any long-term studies indicating chlorinated dibenzofurans are carcinogenic. Nonetheless, we are aware that a number of scientists have proposed development of such potency values by analogy to the carcinogenic potency of 2,3,7,8-TCDD. We invite your attention to this document.

We would appreciate your sending copies of our comments to members of the peer review panel that met in late May to discuss the chlorinated dibenzofurans criteria document. If there are any questions, please call Dr. Carol Stack of my staff (202/887-1196).

Sincerely,



Geraldine V. Cox, Ph.D.
Vice President-Technical Director

Enclosures

cc w/encs.: Members of the EPA
Science Advisory Board
Environmental Health Committee
Halogenated Organics Subcommittee

GENP 010822

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Attachment I

COMMENTS OF THE
CHEMICAL MANUFACTURERS ASSOCIATION
ON
EPA'S HEALTH ASSESSMENT DOCUMENT
FOR CHLORINATED DIBENZOFURANS

August 22, 1986

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COMMENTS OF THE
CHEMICAL MANUFACTURERS ASSOCIATION
ON
EPA'S HEALTH ASSESSMENT DOCUMENT
FOR CHLORINATED DIBENZOFURANS

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COMMENTS OF THE
CHEMICAL MANUFACTURERS ASSOCIATION
ON
EPA'S HEALTH ASSESSMENT
DOCUMENT FOR CHLORINATED DIBENZOFURANS

INTRODUCTION

EPA's Health Assessment Document for Chlorinated Dibenzofurans (HAD) concludes with a risk assessment that derives Reference Doses (RfDs) for two chlorinated dibenzofurans -- 2,3,4,7,8-PeCDF and 2,3,7,8-TCDF. These RfDs are derived by analogy to results of a three-generation reproductive study, not of any chlorinated dibenzofuran, but rather of 2,3,7,8-TCDD. EPA also compares the values determined from the TCDD data base to data from the Yusho incident in which humans ingested chlorinated dibenzofurans. The Agency further determines some potential exposure routes, including exposures from polychlorinated biphenyls contaminated with chlorinated dibenzofurans. The CMA Dibenzofurans/Dibenzodioxins Panel finds flaws in each of these three aspects of the HAD.

CMA considers the appropriateness of deriving any Reference Doses for chlorinated dibenzofurans from data on TCDD to be less than optimal. Great uncertainty exists in attempting to estimate risks of one chemical based on data from another chemical. At the same time, we recognize that EPA has often in recent years used a Toxic Equivalency Factor (TEF) scheme in risk management decision-making for estimating the potency of dibenzofurans and dibenzodioxins

other than 2,3,7,8-TCDD given the limited data on these other compounds.

Employment of a TEF scheme is appropriate for some regulatory purposes, but it always must be recognized that the use of such schemes is merely a surrogate and should not be misinterpreted as a conclusion that there is in fact evidence that non-tested chemicals cause the predicted effects. Accordingly, we discuss in these comments the manner in which EPA employs the TCDD data to reach conclusions about chlorinated dibenzofuran potency. As detailed below, we find the Agency has misinterpreted the TCDD data on which it relies and that the effect is to calculate an RfD that is at least ten times too low.

We also comment on the Agency's employment of the human data from the Yusho incident. As our detailed discussion shows, the Agency's incorrect interpretation of these data leads to an overestimate of risk by more than 10 times and further demonstrates the likelihood the RfD derived from the TCDD animal data may be too low.

Finally, we comment on the exaggerated estimate of chlorinated dibenzofuran exposures from potential exposures to polychlorinated biphenyls. The HAD both incorrectly states the contamination level found in U.S. commercial PCB products and inappropriately constructs exposure scenarios that fail to take into account the significant decline in potential PCB exposures that has occurred over the past 15

years since manufacture was voluntarily curtailed and legislatively prohibited.

I. THE DOSE OF 0.001 μ g/kg/DAY IN THE MURRAY THREE-GENERATION TCDD REPRODUCTIVE STUDY WAS A NOAEL, RATHER THAN A LOAEL.

Central to EPA's development of a Reference Dose (RfD) for chlorinated dibenzofurans is its declaration (at p. 8-4) that the three-generation Murray et al. (1979) study found a LOAEL for 2,3,7,8-TCDD of 0.001 μ g/kg/day. To the contrary, 0.001 μ g/kg/day was a NOAEL in this study.

The erroneous interpretation of the Murray TCDD study is based solely on statistical re-evaluation of the data by Nisbet and Paxton (1982) and is contrary to the interpretations of the study rendered by the original authors (Murray et al. 1979), the FIFRA Scientific Advisory Panel (1979), the Ontario Ministry of the Environment Expert Panel on Dioxins (1984), and essentially all experts who have evaluated that study. The overwhelming scientific opinion is that the Murray study defined the dose level of 0.001 μ g TCDD/kg/day to be a NOAEL.

A NOAEL of 0.001 μ g TCDD/kg/day as defined in the Murray multi-generation rat study also agrees with the NOAEL of 0.001 μ g TCDD/kg/day established in the most definitive lifetime study, by Kociba et al. (1978), which subsequently has been used by most regulatory agencies in the derivation of long-term human exposure control limits for TCDD. As

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discussed in Attachment II to today's submission by CMA the same NOAEL has also been demonstrated in a variety of other toxicology studies of 2,3,7,8-TCDD. (See Attachment II, Section II).

Accordingly, if one uses a long-term or lifetime exposure level of 0.001 μg TCDD/kg/day as a NOAEL, application of the 3-fold and 20-fold estimates by EPA of the lesser degrees of toxicity for 2,3,4,7,8-PeCDF and 2,3,7,8-TCDF, would lead to estimation of lifetime NOAELs for 2,3,4,7,8-PeCDF and 2,3,7,8-TCDF in the rat of 0.003 μg PeCDF/kg/day (3 times the TCDD value) and 0.02 μg TCDF/kg/day (20 times), respectively.

The RfD values for human exposure to 2,3,4,7,8-PeCDF and 2,3,7,8-TCDF can thus be established by application of a composite uncertainty factor of 100 to the NOAEL projected for the rat species. This uncertainty factor of 100 is considered scientifically appropriate to represent a factor of 10 for extrapolation from animal to man and another factor of 10 to account for possible interhuman response variability. Thus, the RfD value for 2,3,4,7,8-PeCDF would be 0.03 nanograms/kg/day (30 picograms/kg/day). For 2,3,7,8-TCDF, the RfD value would be 0.2 nanograms/kg/day (200 picograms/kg/day).

The human LOAEL for 2,3,4,7,8-PeCDF of 0.007 μg /kg/day estimated on p. 8-6 of the HAD from Yusho data could also be used to derive short-term and long-term human exposure

control limits. ^{1/} As the LOAEL of 0.007 µg/kg/day was estimated for a 71-day period of exposure in humans, application of an uncertainty factor of 10 will estimate a short-term (71 day) NOAEL RfD for 2,3,4,7,8-PeCDF of 0.0007 µg/kg/day (or 700 pg/kg/day) for humans. To extrapolate from the 71-day short-term RfD to lifetime RfD, application of an additional 10 times uncertainty factor would lead to a lifetime RfD of 70 pg/kg/day for 2,3,4,7,8-PeCDF. This calculated lifetime RfD value of 70 pg/kg/day derived from EPA's human exposure estimates for 2,3,4,7,8-PeCDF is quite similar to the calculated RfD value of 30 pg/kg/day derived from the chronic lifetime animal toxicity data on 2,3,7,8-TCDD, using the 3-fold TEF estimated by EPA for 2,3,4,7,8-PeCDD.

II. HUMAN DATA FROM THE YUSHO INCIDENT
CONFIRM THAT THE REFERENCE DOSES
FOR 2,3,4,7,8-PeCDF AND 2,3,7,8-
TCDF DERIVED FROM ANIMAL DATA ARE
QUITE PROTECTIVE.

To attempt to confirm the accuracy of the Reference Dose developed from the 2,3,7,8-TCDD three-generation study, the criteria document compares the animal-derived value to a determination of the LOAEL for 2,3,4,7,8-PeCDF in the

^{1/} We note in Section II of these comments, however, that this value is not appropriate reflection of the Yusho data of human effect levels.

Western Japan poisoning incident. In so doing, however, EPA incorrectly assesses that incident. As detailed below, the human data suggest a lifetime RfD for total PCDFs in the Yusho episode of 500 picograms/kg/day, thus corroborating the appropriateness of RfD values of at least 30 and 200 pg/kg/day for 2,3,4,7,8-PeCDF and 2,3,7,8-TCDF, as derived from the animal data discussed above.

A. Detailed Data Exist on Human Exposures to and Effects of PCDFs in the Yusho Incident.

Persons in southern Japan ("Yusho" - 1968) and Taiwan ("Yu-Chen" - 1976) ingested cooking oil that had been become contaminated with heat-transfer fluids during processing. Originally thought to result from the chlorobiphenyls present in the oil, Yusho symptoms have now been shown by Japanese investigators to be largely due to PCDFs present at ppm levels in the oil. (Masuda, et al., 1985; Chen et al., 1985; Miyata, et al., 1985; Kashimoto, et al., 1985; Kunita, et al., 1985.)

More than 1,000 patients with the Yusho syndrome had been identified in Japan by 1971; a larger number were affected in Taiwan. People intoxicated in both incidents exhibited a complex of symptoms very similar to what has been called "chloracne" when seen in industrial situations in the United States and Europe. (Kimbrough 1983; Kuratsune, et al., 1972.)

To estimate the amount ingested by persons with Yusho symptoms, Kuratsune, et al., surveyed 146 users of the contaminated oil, which was produced February 5, 1968, and was distributed in 16.5 kg cans. They estimated the level of consumption of contaminated oil from cooking and eating habits. The population was divided into three dose groups: those who consumed: (1) less than 720 ml, (2) between 720 and 1,440 ml, and (3) more than 1,440 ml, of the contaminated oil. Ten of 80 in the low-dose group were without symptoms; all 66 in the mid- and high-dose groups exhibited either "light" or "severe" symptoms. Thirty-one of 80 in the low-dose group (38.8%), 31 of 45 in the mid-dose group (68.9%), and 18 of 21 in the high dose group (85.7%), exhibited "severe" symptoms. From these data and knowledge of the concentration of PCDFs in the oil that was ingested, an approximate ED₅₀ value for grade III Yusho (clinical chloracne) can be estimated. 2/

The concentration of PCDFs in the contaminated oil has been studied by Buser, et al., (1978), Miyata, et al., (1985), Morita, et al., (1972). Each group used comparable

2/ By Kuratsune's terminology, "light" symptoms correspond to clinical grades I and II Yusho symptoms, while "severe" corresponds to clinical grades III and IV. Grade III corresponds approximately to chloracne as it would have been diagnosed by physicians seeing workers exposed to TCDD in 2,3,5-trichlorophenol production accidents.

techniques -- medium-to-high resolution gas chromatography with mass spectrometric detection, and their results are comparable. All reported concentrations of total PCDFs in the range of 1.9 to 7.4 mg/kg oil. The high report of Miyata, et al., comes from a sample described as "5 February 1968 production"; this matches the date on which the oil consumed by patients surveyed by Kuratsune, et al., was reported to have been produced and shipped. Samples described as having been produced on February 9 and 10, 1968, were estimated to contain 1.9 and 2.3 mg/kg PCDFs, respectively. The sample examined by Morita, et al., was described as having been produced February 12, 1968. Buser, et al., gave no description of the origin of the sample they examined. Because of the coincidence of production dates, and the evident decline in PCDF concentration with time over the period from February 5 to February 9-12, 7.4 mg PCDF/kg rice oil is a reasonable estimate of the concentration of these agents in the oil ingested by the survey population.

B. EPA Misinterprets the Yusho Data.

As a means of checking the reliability of the RFD determined from animal data, EPA employs the Yusho data. In so doing, however, it fails to employ the relevant data correctly.

EPA's calculation is based on the following factors:

- (1) minimum quantity to cause a grade III response of 121 ml;
- (2) a mean latency period of 71 days;
- (3) PCDF concentration in the oil of 3.85 ppm; and
- (4) a concentration of 2,3,4,7,8-PeCDF of 8.4% of total PCDFs in the oil.

Based on these factors, EPA concludes the LOAEL for 2,3,4,7,8-PeCDF was 0.007 $\mu\text{g/kg/day}$, thus leading it to conclude that the LOAEL it derived from the animal studies of 0.003 $\mu\text{g/kg/day}$ is reasonable. EPA's calculations contain several errors.

First, no source is given for the value of 121 ml that is cited as "the minimim quantity ... that led to an observed effect" As detailed above, in the studies reported by Kuratsune, et al. (1972), only estimates of the amount of oil ingested were given, and the lowest range cited was "less than 720 ml." Over the period of ten or so days during which the contaminated rice-bran oil was produced, the concentration varied by at least a factor of three. Data from the Yusho reports show that oil processed February 5, 1968 had about 7.4 ppm of total PCDFs and that this had fallen to about 2 ppm by February 10. If it were not possible to relate the amount of oil ingested to the effects seen, use of the mean value would be acceptable. However, since good data are available on a population known to have ingested oil produced on a particular date, oil for

which an analysis is available, the concentration given for this known oil should be used.

Second, in using these data from the Yusho episode, the LOAEL value can be considered an approximation of the dose level that gave low incidence of the effects seen in studies of the population. Use of a single extreme value, as EPA has done, however, is improper. It incorrectly mixes risk management judgments into the risk assessment. When proper dose-response information can be extracted from the available data, as is the case here, it should be used to calculate a population mean dose for the effect.

Third, the work of Birnbaum (1985) and others has shown that the effects of compounds in the chlorinated dibenzofuran class are additive. In a series of experiments, effects seen were directly proportional to the sum of the products of concentration of each compound times its relative activity in producing that effect in the animal being tested. Thus it is entirely incorrect to ignore the contributions to Yusho symptoms of compounds such as 1,2,3,7,8-penta, 2,3,4,6,8-penta, and 1,2,4,6,7,8-hexa chlorodibenzofurans. Individually, their contributions may be less than that of the 2,3,4,7,8 congener, but their total contributions may well exceed those of the latter. As no data are available to estimate reliably the relative activities of these compounds in whole animals, no attempt should

be made to estimate the relative contribution of a single compound to the activity of this mixture. 3/

We discuss next appropriate use of the Yusho data to determine acceptable daily intakes for total chlorinated dibenzofurans involved in the Yusho episode. We encourage EPA to review this assessment closely.

- C. Properly Interpreted, the Yusho Data Show an Acceptable Lifetime Average Daily Dose of 500 Pico-grams Total PCDFs/Kilogram/Day.

Combining the Yusho analytical, consumption and effects data demonstrates the following Effective Doses (EDs):

- (1) From the low-dose group: 4/

$$\begin{aligned} \text{ED}_{39} &< (0.72 \text{ l}) (0.91 \text{ kg oil/l}) (7.4 \text{ mg} \\ &\quad \text{PCDF/kg oil}) / 60 \text{ kg body weight} \\ &= 81 \text{ } \mu\text{g/kg.} \end{aligned}$$

$$\text{ED}_{39} < 81 \text{ } \mu\text{g/kg.}$$

3/ In addition, it is known that the rate at which a compound is metabolized and thus deactivated affects its activity in the whole animal. In a situation such as Yusho, where a large number of very similar compounds are present, the activity of individual compounds cannot be assessed because enzymes that would deactivate them if present alone may preferentially react with more reactive compounds also present. Because easily-metabolized compounds are present in the body along with the more toxic, activity of the less easily metabolized 2,3,4,7,8-pentachlorodibenzofuran may be greater than it would appear to be when tested alone.

4/ We assume that the rice-bran oil of Yusho has the same specific gravity as cottonseed and corn oils (0.91 kg/l) and that the mean body weight of the Yusho population studied by Kuratsune, et al., was 60 kg.

(2) From the mid-dose group:

$$81 < ED_{69} < (1.44 \text{ l})(0.91 \text{ kg/l}) \\ (7.4 \text{ mg/kg oil/60 kg}) = 162 \text{ } \mu\text{g/kg.}$$

$$81 \text{ } \mu\text{g/kg} < ED_{69} < 162 \text{ } \mu\text{g/kg}$$

(3) From the high-dose group:

$$ED_{86} > 162 \text{ } \mu\text{g/kg.}$$

From analyses of these data by a normal probit method, an estimate of the ED_{50} value for grade III Yusho can be made:

$$46 < ED_{50} < 105 \text{ } \mu\text{g/kg. } \underline{5/}$$

It would be desirable to relate the activity of this mixture to that of some single standard, such as 2,3,7,8-TCDD. However, that is problematic in this case, for three reasons.

First, no isomer-specific quantitative analysis of Yusho oil has been published. The results of Buser, et al., suggest that more than 30 tetra-, penta-, and hexachlorodibenzofurans were present in the oil.

Second, the relative activities of these different congeners are unknown, even in in vitro systems.

Finally, such a congener assessment would require determining the contribution of chlorobiphenyls and -quaterphenyls to the activity since these were present in

5/ An ED_{01} estimate can also be made: 2.6 to 10 $\mu\text{g/kg}$. However, we have more confidence in the ED_{50} value, as it is almost independent of the form of the dose-response curve assumed.

the oil at more than one hundred times greater concentration, and Birnbaum, et al. (1985), as previously noted, have shown that some compounds from these classes contribute to effects from PCDFs in an additive manner. It is reasonable to conclude that at least some of the PCDFs present in the Yusho oil would be more active than this aggregate dose-response estimate suggests, but it is unlikely that any would be more than ten times more so. Using the estimated low ED₅₀ value from the above analysis (46 µg/kg) as a point of departure for standard-setting, we thus incorporate, as detailed below, an extra order of magnitude for this uncertainty.

Employing the ED₅₀ value of 46 µg/kg, short-term and lifetime health advisory levels can be developed from the Yusho data. Each is explained below.

Single Dose Health Advisory (SDHA)

The above estimates of Effective Doses in the Yusho incident were made from exposures that occurred over a period of about 50 days. This period approximates the estimated half-life for these compounds in the body (King, et al., 1983). Because of poorer absorption and more rapid excretion at higher dose rates, a single dose of twice that accumulated at Yusho would have approximately the same effect.

Because human data are used as the basis here for determining a single dose health advisory (SDHA) guideline, an

uncertainty factor of 1,000 applied to the ED_{50} would be a quite conservative approach. One factor of ten is applied because the base dose is not a NOAEL; a second factor of ten is applied to take into account conservatively the distribution of susceptibilities in the population; and a third factor of ten to allow for uncertainties in the activity of the various PCDFs present in the Yusho oil, as mentioned above. Thus:

$$\begin{aligned}SDHA &= 2 \times ED_{50}/1000 = (2)(46)/1000 = 0.09 \text{ } \mu\text{g total} \\&\quad \text{PCDF/kg body weight} \\&= 9 \times 10^{-5} \text{ mg total PCDF/kg, or 90 ng} \\&\quad \text{PCDF total/kg}\end{aligned}$$

Short-Term Health Advisory (STHA)

For cumulative exposure over a 10 to 100 day period, one one-thousandth of the low ED_{50} dose at Yusho can be considered to be protective of human health for determination of a short-term health advisory (STHA) guideline. Thus:

$$\begin{aligned}STHA &= ED_{50}/1000 = 0.046 \text{ } \mu\text{g total PCDF/kg body weight.} \\&= 4.6 \times 10^{-5} \text{ mg total PCDF/kg, or 46 ng} \\&\quad \text{total PCDF/kg}\end{aligned}$$

Long-Term (Lifetime) Health Advisory (LADD)

A lifetime health advisory or lifetime acceptable daily dose (LADD) should be estimated taking possible accumulation of chlorinated dibenzofurans into account. That is, the intake required to reach serum concentrations equal to those

implied by the STHA dose should be estimated. However, analysis of Yusho data shows that such an analysis would require more data on human pharmacodynamics than is now available. Absent these data, use of an additional conservative uncertainty factor of 100 applied to the STHA is appropriate. Here, that is appropriately represented by $LADD = STHA/100$. Thus: 6/

$$\begin{aligned} LADD &= 0.046 \text{ } \mu\text{g total PCDF/kg body weight/100} \\ &= 4.6 \times 10^{-7} \text{ mg total PCDF/kg/day,} \\ &\text{or 460 total PCDF pg/kg/day.} \end{aligned}$$

6/ In 1973 FDA estimated the mean oil intake of all Yusho patients to be 15 grams/day for 50 days, or 750 grams. The mean PCDF concentration is not known, but we know it to be greater than about 2 ppm (the minimum concentration reported). Thus the mean intake of PCDFs was $> (2 \times 10^{-6})(750 \text{ g}) = >1.5 \times 10^{-3} \text{ g} = >1.5 \text{ mg}$. FDA assumes a mean body weight of 50 kg, and further assume that one-tenth the mean dose could be taken as a tolerable dose of PCBs. (This logic was used to derive a tolerance level for PCBs.)

Following similar logic, we could define a tolerable dose for PCDFs to be $>1.5 \times 10^{-3} \text{ g}/50/10 = 3 \times 10^{-6} \text{ gm PCDF/kg} = 3 \text{ } \mu\text{g/kg}$. FDA reasoned that a total accumulation of less than the dose so calculated would cause no effect. This quantity was divided by 675 days (22 months) to obtain an acceptable average daily intake (AADI). Applying a similar procedure here, one would obtain an LADD of $4 \times 10^{-9} \text{ gm PCDF/kg/day} = 4 \text{ ng/kg/day}$.

Our lower value differs from FDA's in three respects: we started with a higher "effect" dose ($46 \mu\text{g/kg}$ vs. $30 \mu\text{g/kg}$) and included a much more conservative uncertainty factor to arrive at a tolerable accumulated dose ($0.046 \mu\text{g/kg}$ vs. $3 \mu\text{g/kg}$), but allowed a shorter time to reach equilibrium body burden. On balance, we believe an LADD of 500 pg/kg/day to be quite protective of human health.

This LADD of 460 picograms/kg/day derived from the Yusho data for total polychlorinated dibenzofurans is higher than the LADDs derived both by analogy to the TCDD animal data (30 and 200 picograms/kg/day for 2,3,4,7,8 and 2,3,7,8, respectively, see page 4 above) and by calculations based on what EPA says is the LOAEL in the Yusho incident (70 picograms/kg/day for 2,3,4,7,8, see page 4 above). It thus supports the clear adequacy of 30 to 70 and 200 picograms/kg/day RFD values derived for 2,3,4,7,8-PeCDF and 2,3,7,8-TCDF from animal data.

III. THE CONCENTRATION OF CHLORINATED
DIBENZOFURANS IN, AND POTENTIAL
EXPOSURES TO, PCBS ARE OVERESTIMATED.

Section 4 of the HAD also requires comment, especially in light of the misuse of some of the exposure information set forth in other sections of the report, most notably Section 6.3. The Section 4 discussion of chlorinated dibenzofuran (PCDF) contamination of polychlorinated biphenyls (PCBs) is not relevant to the situation in the United States. American PCB products have consistently been shown to contain extremely low levels of PCDFs, compared to normal foreign materials, let alone the thermally stressed materials involved in the Yusho and Yu-Cheng episodes. Numerous exaggerations and misleading statements need to be eliminated from the HAD.

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The errors on this issue begin in the HAD Chapter 4 discussion of potential exposures of PCDFs. On page 4-11, the statement that less than ppt levels of PCDFs were detected in Aroclor 1016 is misleading. The correct statement would be that no PCDFs were detected in Aroclor 1016, at a detection limit of X ppt. The next sentence is also erroneous, in that Bowes, et al., did not have in 1975 the analytical capability to detect 2,3,7,8-TCDF or 2,3,4,7,8-PeCDF in PCB formulations. At that time, as acknowledged on page 3-6, there were neither columns available to separate 2,3,7,8-TCDF from coeluting isomers nor standards to determine the retention time of potential interferents.

On page 4-12, the statement that the composition of Kanechlor 400 resembled that of Aroclor 1248 is also erroneous and misleading, especially since the statement implies that the Aroclor product contained the same level of contaminants as "Yusho" fluid. In fact, the fluid responsible for the Yusho incident did not even resemble Kanechlor 400, having been thermally stressed and exposed to oxygen, as later acknowledged expressly in the same paragraph.

On page 4-12, the HAD attributes a 2,3,7,8-TCDF concentration of 1.25 ppm to a thermally stressed heat exchange fluid, but notes in the next sentence that at least one other isomer coeluted under the conditions used. Nonetheless, the 1.25 ppm value is used in Section 6.3 to calculate exposure to PCDFs from any exposure to PCBs.

All of pages 4-13 is a compilation of "suspected", "probablies" and "may haves". This section of the HAD thus exaggerates the contribution of PCB exposure to potential effects of PCDFs.

The calculations in Section 6.3 of the HAD, purporting to estimate maximum exposure levels associated with PCB exposure, are not realistic estimations, even assuming the desirability of developing a worst-case scenario.

First, the dietary intake value, stated to represent present intake is taken from an eight-year-old paper. The quoted paper relies on data obtained before the voluntary cessation of PCB manufacture in the United States, and thus bears little relation to current potential exposures. More recent EPA and FDA evaluations clearly reflect the fact that PCB levels in fish from the Great Lakes are decreasing.

A more serious error, and substantial exaggeration, is the use of 2,3,7,8-TCDF concentration in PCBs of 1.25 ppm. This value is not representative of 2,3,7,8-TCDF concentrations in American PCB products and in fact represents the reported concentration in a severely heat-stressed and oxygen-exposed Japanese product, used under conditions known to maximize PCDF concentrations in PCBs. (See Rappe, C., et al., 1985). Nor is it correct to maintain that this material is "similar to Aroclor 1248".

Japanese PCB products have consistently been shown to contain higher concentrations of PCDFs, even ignoring the

issue of heat stress. The same author who reported the value of 1.25 ppm in the heat-stressed Japanese product has also reported levels of PCDFs in truly representative American PCB products. (Rappe, C. et al., 1985). The 2,3,7,8-TCDF concentrations in Aroclor 1254 and Aroclor 1260 were reported as 19 and 13 ppb respectively. Although these data are presented in Table 4-8 of the HAD, they are later ignored in the exposure assessments. Accordingly, the HAD exaggerates potential PCDF exposures due to PCBs by a factor of almost 100 by using data not representing PCBs that could be the source of exposure to the American public. Using more realistic values for 2,3,7,8-TCDF in American PCB products reduces the value for stored 2,3,7,8-TCDF to about 0.002 ng/day, if one assumes no excretion, another exaggerated assumption.

The same factor of 100 should be applied to all of the other calculated exposure levels in Section 6.3 of the HAD. The entire section thus needs to be rewritten to reflect representative exposures, even in developing worst case scenarios so popular in EPA risk assessments.

The mention of exposure based on pentachlorophenol ingestion on page 6-19 is also misleading given the fact that the rest of the paragraph is a discussion of exposure to 2,3,7,8-TCDF resulting from exposure to PCBs. In the next paragraph, PCDD exposure is discussed, if only to conclude that "no firm conclusions could be reached." The rest of

the paragraph is pure speculation, typified by the doublet "might possibly."

The second paragraph on page 6-20 contains further examples of unwarranted speculation. Although generation of PCDFs as by-products of the incomplete combustion of PCBs in fire-related situations has been demonstrated in the laboratory and is substantiated by measured levels of PCDFs in building fires, the other exposure scenarios in the paragraph are not realistic and certainly do not support the statement that "exposures should be investigated." The use of PCBs in casting waxes, carbonless copy papers, and heat transfer systems was voluntarily curtailed by 1972 and was expressly banned under TSCA in 1979. Such exposure scenarios are thus very unlikely. 7/

In sum, a consistent pattern exists in Chapters 4 and 6 of the HAD of over-estimation of the contribution of PCDF contamination of PCBs to potential human exposures. A complete rewrite of these sections of the report is necessary to reflect accurately both the actual concentrations of

7/ In addition, there is an apparent misunderstanding of the chemistry and physical properties of PCDFs. The HAD evidences apparent surprise at the fact the PCDFs were not extracted by water from latex nipples, "unlike pentachlorophenol." Pentachlorophenol is a polar material with a measurable solubility in water, while PCDFs are insoluble in water -- thus it should clearly not be surprising that water is not a good extractant for PCDFs.

PCDFs in commercial U.S. PCBs and the limited current potential for human exposures to PCBs. Unless such changes are made in the HAD, it will inaccurately express unwarranted cause for concern about PCDF/PCB exposures.

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Attachment II

CONSIDERATIONS FOR ASSESSING
POTENTIAL HUMAN RISK FROM EXPOSURES
TO 2,3,7,8-TETRACHLORODIBENZODIOXIN

A Working Paper of the
Dibenzofurans/Dibenzodioxins
Panel of the Chemical Manufacturers Association

August 22, 1986

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CONSIDERATIONS FOR ASSESSING
POTENTIAL HUMAN RISK FROM EXPOSURES
TO 2,3,7,8-TETRACHLORODIBENZODIOXIN

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CONSIDERATIONS FOR ASSESSING
POTENTIAL HUMAN RISK FROM EXPOSURES
TO 2,3,7,8-TETRACHLORODIBENZODIOXIN

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INTRODUCTION

Numerous regulatory initiatives are being driven by the Environmental Protection Agency's (EPA's) assessment of the potential human risk posed by 2,3,7,8-tetrachlorodibenzo-dioxin (TCDD). Because EPA's Cancer Assessment Group has determined that a 1 in 1,000,000 cancer risk exists for a Lifetime Average Daily Dose (LADD) as low as 6 femtograms (6×10^{-15} grams)/kilogram/day (EPA 1985), numerous regulatory initiatives have sought to control TCDD to extremely low levels.

By contrast, many other nations have derived human exposure control limits of 1 to 10 picograms (1 to 10×10^{-12} grams/kilogram/day). It is therefore important to recognize, as detailed in this paper, the relevant scientific evidence that demonstrates the advisability of revising EPA's LADD to fall in line with the views of international experts.

EPA has also employed a Toxicity Equivalency Factor (TEF) scheme to determine control limits for other chlorinated dibenzodioxins, as well as for chlorinated dibenzofurans. The Agency has further indicated the same

scheme may be applied to brominated dibenzodioxins and dibenzofurans. Because the TCDD toxicity determination is the base number from which these other control limits are derived, it is vitally important that the TCDD assessment be scientifically appropriate and technically supportable.

The driving regulatory force of EPA's extremely low recommended control limit for TCDD is symptomatic of a general over-concern about potential human toxicity of chlorinated dibenzodioxins and dibenzofurans. The United States and Europe have expended huge resources in an effort to determine if there has been any impact on human health of exposures to such substances, but have not found any obvious concerns given current limited exposures. Scarce and valuable resources are being devoted to examine non-obvious and less major concerns with full knowledge that zero impact can never be scientifically proven. There will always be uncertainty in the numbers, and additional effort can only reduce the uncertainty by small increments -- never eliminate it. At the same time, EPA is implementing ever more stringent rules and requirements for dibenzodioxins and dibenzofurans under FIFRA, TSCA, RCRA, and CERCLA.

CMA is concerned that there is no plan for deciding when society has reached a point of diminishing return on the use of national resources investigating alleged human problems related to dibenzodioxin and dibenzofuran exposure. Before further substantial expenditures are mandated, EPA

should reassess the health criteria upon which these regulatory initiatives are based. As one reviewer (Tschirley 1986) recently concluded:

What the agency has not done -- and might be said to have a responsibility to do -- is to try to dispel the public's fear on the basis of the evidence that exposure to low concentrations of TCDD in the environment appears not to have serious chronic effects on human beings.

The importance of EPA's current determination of TCDD toxicity is illustrated by the fact that the control limits employed by EPA are about 1,000 times more restrictive than the levels determined by other international expert groups who have reviewed the same evidence. Specifically, its TCDD recommended human exposure control level is 160 to 1,600 times more restrictive than the levels recommended by various non-U.S. regulatory agencies and expert panels, including a Swiss expert group (Schlatter, et al., 1985); a Canadian expert panel (Ontario Criteria Document 1985); a West German expert group (Appel, et al., 1985); and a Dutch expert group (Van der Heijden, et al., 1982). The EPA control limits are also about 10 times more restrictive than a U.S. Food and Drug Administration assessment of the same data (FDA 1983).

Accordingly, the CMA Panel on Dibenzodioxins and Dibenzofurans has prepared this Working Paper discussing the

scientific evidence that has led other expert groups to disagree with EPA's assessment of TCDD. In this paper, we:

(1) Note the extensive human data on exposures to TCDD and their results, which find some toxic effects (especially chloracne) in highly exposed manufacturing workers and industrial accident victims, but no consistent data indicating any carcinogenic or other life-threatening diseases in humans.

(2) Review the extensive animal data on TCDD with special emphasis on the lifetime studies that evaluated chronic toxicity and carcinogenic potential. We also review the mechanistic and dose-response data, relied on heavily by other review panels, that indicate TCDD carcinogenicity is most appropriately considered a threshold-based phenomenon to which an "uncertainty" or "margin of safety" factor can be applied in deriving an acceptable human LADD.

I. EPIDEMIOLOGY STUDIES HAVE NOT
DEMONSTRATED THAT TCDD CAUSES
CANCER OR OTHER LIFE-THREATENING
DISEASES IN HUMANS.

In the late 1970's concern that TCDD impurities in various pesticides caused cancer, especially soft tissue sarcomas, was raised by a series of Swedish epidemiology studies (Hardell 1981; Hardell, et al., 1982; Hardell and Sandstrom 1979; Eriksson, et al., 1981; Hardell and Eriksson 1981; Axelson 1980). More recent data from studies

of similarly exposed pesticide applicators in New Zealand (Smith, et al., 1983; Smith, et al., 1984) and Vietnam (U.S. Air Force 1983; U.S. Air Force 1985) and forestry and agricultural workers in Sweden (Wiklund & Holm, 1986) have found no such association.

In addition, critical scientific review of the original Swedish studies, as well as examination of results of studies of manufacturing workers exposed to TCDD in the U.S. (Cook, et al., 1980; Ott, et al., 1980; Zack and Suskind 1980; Zack and Gaffey 1983) and in Europe (Theiss, et al., 1982; Dallderup and Zellenrath 1983), have led most reviewers to conclude that there is no significant epidemiology evidence of an association between TCDD and human cancer or other life-threatening disease.

The Expert Committee (including Drs. O. Hutzinger, G. L. Plaa, S. Safe, E. Y. Spencer and B. Birmingham) that reported to the Ontario Canada Ministry of Environment in its Scientific Criteria Document on PCDDs and PCDFs, for example, concluded (at 1-13):

Epidemiological studies to date do not present sufficient evidence to establish a causal relationship between exposure to PCDDs or PCDFs and a chronic human health effect relating to carcinogenesis, coronary disease or impairment of the immune system.

The American Medical Association's Council on Scientific Affairs (1984) similarly concluded that although many

adverse effects of dioxins had been found in exposed animals:

Except for chloracne, ... TCDD has not demonstrated comparable levels of biologic activity in man; that is to say, no long-term effects on the cardiovascular and central nervous systems, the liver, the kidney, the thymus and immunologic defenses, and the reproduction function -- in the male, female or offspring -- has been demonstrated.

It is true that even this extensive body of epidemiologic data cannot prove an absence of risk for low level TCDD exposures, but no such body of data ever will exist. On the other hand, these data provide assurance that significant adverse human effects are unlikely at low exposures. These data, moreover, caution strongly against exaggerated interpretation of the laboratory animal evidence, as discussed next, to establish guidelines for human exposure limits.

II. LIFETIME STUDIES OF TCDD IN ANIMALS
SHOW A CONSISTENT NO-OBSERVED-
ADVERSE-EFFECT LEVEL OF AT LEAST
1 NANOGRAM/KILOGRAM/DAY.

Given the absence of data indicating long-term debilitating effects of TCDD exposure in man, most expert review groups and governments have sought to establish human control limits based on the substantial animal toxicity data base. TCDD has been tested in a variety of toxicity tests using various animal species.

The animal studies considered most appropriate for determining lifetime exposure control limits for man are the lifetime animal studies evaluating chronic toxicity and carcinogenic potential. These long-term animal studies consistently have shown a no-observed-adverse-effect level (NOAEL) of at least 1 nanogram/kilogram/day. The preponderance of data thus supports derivation of a lifetime human exposure control limit of approximately 10 picograms/kilogram/day based on the existence of these NOAELs and application of a 100 times "uncertainty" or "margin of safety" factor.

A. Animal Toxicity Studies Have Adequately Defined the No-Observed-Adverse-Effect Levels for Non-Cancer Effects of TCDD.

TCDD has been administered to a variety of species in standard toxicologic studies. Apart from the lifetime animal studies discussed next, the studies of reproductive and teratogenic effects are most significant to human health risk assessment. The Ontario Expert Committee summarized those studies (Ontario Criteria Document 1985 at 3-132):

Data from teratological (reproductive effects) studies in rats and mice indicate that 2,3,7,8-TCDD causes embryolethality and/or fetotoxicity. A 3-generation reproduction study of rats was associated with decreased fertility and neonatal survival in the first and second generations.

NOELs for these teratogenic and reproductive effects over the range 0.001 to 0.03 μ g 2,3,7,8-TCDD/kg have been reported.

As the Ontario Report further notes, TCDD has been found to affect the fetus only at doses equivalent to those which produce adult toxicity.

An additional margin of safety should be inherent in any extrapolation from TCDD animal results given the data indicating the lesser sensitivity of humans. Reviews by both Neal (1983) and Tschirley (1986) found man to be less sensitive to acute TCDD effects than tested laboratory animals, including rats, mice and guinea pigs.

Data concerning actual human exposures to TCDD confirms this analysis. Perhaps the most valuable human data for evaluating teratogenic, fetotoxic, and reproductive risk are those obtained in the Seveso region following the 1976 accident. Unlike other human exposures to TCDD, Seveso involved severe exposure to women of child-bearing age. The Seveso exposures caused no increase in spontaneous abortion, birth defects, or any abnormalities in the growth and development of children in utero at the time of the accident. (Marni, et al., 1982:) In addition, the Kligman study which demonstrated that humans voluntarily exposed to TCDD by dermal application suffered no adverse effects at doses well above those which produce chloracne in test rabbits, also suggests that people are less sensitive than test animals.

Taking all of these considerations into account, the application of a 100-fold "uncertainty" or "safety margin" for TCDD to the NOAEL defined in the animal studies is a conservative approach to establishment of lifetime human control limits.

B. Lifetime Animal Studies of
Chronic Toxicity/Carcinogenicity
Have Established a No-Observed-
Adverse-Effect Level for TCDD
of at Least 1 Nanogram/Kilogram/Day.

Almost all reviews of the evidence of TCDD carcinogenicity in animals have focused on the Kociba, et al. (1978) study in Sprague-Dawley rats. This study, in agreement with other bioassays conducted in other rat strains and in mice, established a lifetime NOAEL for chronic toxicity/carcinogenic response of at least 1 nanogram/kilogram/day. The Kociba study is considered the most pertinent animal study for deriving long-term human exposure control limits because it was conducted with state-of-the-art procedures to evaluate the dose-response pattern for both chronic toxicity and potential carcinogenicity.

Detailed pathologic examination in the Kociba study of an extensive list of tissues from rats given the high dose level of 0.1 µg/kg/day revealed the presence of toxicologic lesions. The liver was the primary target organ. Only at this highest and overly-toxic dose level, which exceeded the maximal tolerated dose and shortened the lifespan of female

rats, was there a carcinogenic response following lifetime treatment.

At the intermediate dose level of 0.01 $\mu\text{g}/\text{kg}/\text{day}$, there was no definite carcinogenic response, despite the fact that this dose was high enough to produce some toxicity. In the primary target organ, the liver, the maximal response was the formation of hyperplastic nodules originating from the liver cells. At the lowest dose level of 0.001 $\mu\text{g}/\text{kg}/\text{day}$, there was no carcinogenic response, and no other adverse effect was associated with this lifetime exposure to TCDD.

NCI bioassay results in Osborne-Mendel rats are in agreement with the results observed in the Sprague-Dawley rats in the Kociba study. In the NCI study, TCDD induced liver neoplasms in female rats only at the high dose of 0.07 $\mu\text{g}/\text{kg}/\text{day}$. No carcinogenic effects were observed at a daily dose of 0.0014 $\mu\text{g}/\text{kg}/\text{day}$.

TCDD has also been administered to mice in long-term studies. The report is ambiguous (Toth 1979), but even if a true carcinogenic response was produced at the middle dose level of 0.7 μg TCDD/kg/week, this dose is equivalent to the daily dose of 0.1 $\mu\text{g}/\text{kg}/\text{day}$ demonstrated to be carcinogenic to rats in the Kociba study. The Toth study found no carcinogenic effects in mice at the lower dose of 0.03 $\mu\text{g}/\text{kg}/\text{day}$.

Upon reviewing these lifetime studies, the Canadian experts concluded (at 1-11):

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Those studies involving oral administration (2,3,7,8-TCDD is most toxic using this route of exposure) have reliable dose-response data and indicate clear NOELs (0.001 to 0.0014 µg/kg/day) for tumour incidence.

In general, 2,3,7,8-TCDD administration was associated with relatively few histologically different tumour types. The onset of these tumours appeared late in the study and generally at similar time to onset of similar, but less frequent, tumors in the control animals.

Although 2,3,7,8-TCDD has been found to be carcinogenic in rats and mice, it is difficult at this stage to predict the ability of this compound to induce tumours in humans.

In sum, long-term cancer studies of TCDD in several strains of both rats and mice have shown neither chronic toxicity nor carcinogenicity at lifetime doses of 1 nanogram/kilogram/day.

- C. The Animal Bioassays and Other Studies on the Mechanism of Action of TCDD Show That the Carcinogenic Response Observed in Animals Is Reflective of a Promotion Mechanism Rather than a Genotoxic Mechanism, Indicating Lifetime Human Exposure Control Limits Are Most Appropriately Derived on an "Uncertainty" or "Margin of Safety" Basis.

Recent reviewers have deliberated on the proper interpretation for human risk assessment of carcinogenic responses from administration of TCDD to animals. Each of these assessments has focused on the absence of genotoxic potential and have identified an indirect promotion mechanism as the likely cause of the tumors seen in laboratory animals.

Accordingly, these reviewers have all applied an "uncertainty" or "margin of safety" analysis to the NOAELs found in the definitive and sensitive long-term animal studies to determine human control limits.

Many scientists, including Pereira (1985) of EPA, have recognized the need for differentiation between carcinogens that mechanistically interact directly with DNA (genotoxic) and those that do not (non-genotoxic). Initiators are genotoxic agents that penetrate the cell nucleus and damage or alter the DNA genetic material of the cell. By contrast, promoters or modifying agents produce a carcinogenic response as an indirect effect of organ toxicity or by impairing the body's defense mechanisms against carcinogenic initiators.

Current theory of some scientists assumes that the genotoxic potential of initiators may indicate the lack of a threshold for carcinogenic effects. For promoters, on the other hand, it is generally agreed that a threshold for the carcinogenic response exists (Pereira 1985). This threshold would be indicated by the dose-response data defining the NOAEL for organ toxicity or impairment of bodily defense mechanisms. In the absence of detailed quantitative information about the exact mechanism of action, most authorities thus recommend, in line with an increasing scientific consensus, using a conservative "uncertainty" or "margin of safety" factor to protect human health.

These considerations apply to TCDD, as it is generally agreed it is not a cancer initiator. Short term assays indicate TCDD is not genotoxic. Various mechanisms of TCDD carcinogenicity have been investigated, each of which points to the conclusion that TCDD is acting as a promoting or modifying agent, for example, through tissue damage found at the same doses at which a carcinogenic response is observed.

TCDD does not covalently bind to DNA or RNA (Poland and Glover 1979), does not induce DNA repair synthesis (Althaus, et al., 1982), and is essentially devoid of any mutagenic activity (Wassom 1977; Kociba 1984). In an in vivo cytogenetics screening study conducted for FDA, Green and Moreland (1975) found no chromosomal aberrations in the bone marrow of male rats treated with TCDD. A subsequent study by Green, et al., (1977), limited by the fact that controls were not used, reported "only weakly positive" results, while an earlier study by Khera and Ruddick (1973) was negative for dominant lethal mutations in Wistar rats.

In addition, Poland and Glover (1979) tested the DNA binding potential of TCDD in the liver of Sprague-Dawley rats and found that the maximum potential DNA binding by TCDD is 10,000 to 1,000,000 times less than that of most chemical carcinogens. They thus concluded, "it is unlikely that TCDD-induced oncogenesis is through a mechanism of covalent binding to DNA and somatic mutation."

Taken together, these studies provide strong evidence that TCDD does not interact with or damage cellular genetic material to produce heritable genetic changes. TCDD is therefore unlikely to cause cancer via a genotoxic mechanism.

As the Ontario Expert Committee concluded (at 1-10):

2,3,7,8-TCDD does not form DNA adducts, i.e., it does not chemically bind to DNA. Therefore it is unlikely to cause mutations by chemically changing DNA directly.

This compound has been extensively tested in in vitro microbial mutagenicity tests, such as the Ames test, with mainly negative results. More limited information is available from in vitro and in vivo mammalian test systems for mutagenicity and clastogenicity.

On the other hand, considerable evidence indicates that TCDD acts through one or more non-genetic mechanisms as a promoting or modifying agent. These mechanisms depend upon the occurrence of TCDD-induced toxicity or physiological alterations which, in turn, enhance or promote the growth of tumors. Dose levels below those needed to produce toxicity or physiological alterations are unlikely to increase tumor incidence.

The lifetime study of TCDD rats by Kociba, et al. (1978), for example, showed a carcinogenic response only at dose levels that induced toxicity. As detailed above, the lowest dose level (0.001 µg/kg/day) was a NOAEL for such toxicity, and no carcinogenic effects were observed. It is

well-known that recurrent tissue injury and repair commonly leads to tumors in affected organs of laboratory animals. Thus, one very likely mechanism for TCDD production of tumors is recurrent tissue injury and regenerative repair within the affected organ.

The non-genetic mechanisms involved in the intermediate toxic or physiological effect occurred only above the 0.001 µg/kg/day NOAEL defined in the lifetime toxicity studies. Accordingly, with lifetime exposure levels at or below 0.001 µg/kg/day, one would expect no intermediate toxicity or physiological alteration and therefore no tumor promotion.

The subsequent study by Pitot, et al. (1980), supports the non-genotoxic interpretation. Pitot tested "the hypothesis that the liver cancer associated with chronic administration of TCDD might arise from the promoting activity of the compound, presumably stimulating cells already spontaneously initiated by dietary and other environmental carcinogens." The strain of "rats and the TCDD dosage regimen" used "were chosen to resemble closely the conditions" in the Kociba study. Dr. Pitot concluded: "TCDD is a potent promoting agent for hepatocarcinogenesis."

In addition to the promotion of liver tumors in rats reported by Pitot, another study by Poland, et al. (1982) reported TCDD to be a promoter of skin tumors in hairless mice after treatment with known cancer-initiating agents

such as N-methyl-N-nitrosoguanidine (MNNG) or dimethylbenzanthracene (DMBA). Another more recent study by Abernethy, et al. (1984) reported TCDD to be a promoter of the transformation of C₃H/10T 1/2 cells that had been initiated with MNNG. Overall, these studies provide compelling evidence that TCDD acts as a cancer promoter in animal bioassays.

In sum, strong evidence exists that TCDD acts not by a genotoxic mechanism but rather by one or more non-genetic mechanisms that promote or enhance tumor growth. As the Canadian expert group concluded:

Results of short term genotoxicity tests suggest that 2,3,7,8-T₄CDD is not genotoxic in a classical sense and does not act directly on the chromosomes or the DNA molecule itself. Consequently, 2,3,7,8-T₄CDD appears to produce tumours in rodents by an indirect mechanism.

The Ontario expert committee thus concluded that an acceptable LADD for TCDD could be derived by applying an "uncertainty" or "margin of safety" factor of 100 to the NOAEL of 1 nanogram/kg/day. This LADD of 10 picograms/kg/day is, as noted above, consistent with other Swiss, West German and Dutch expert conclusions.

In sum, based on detailed review of the available data, international experts have determined the appropriate level of concern for lifetime exposure to TCDD is 1,000 times higher than EPA has determined. Given the many Agency initiatives being driven by this unduly high estimate of TCDD

potency, it is imperative that EPA reassess its 1985 determination.

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INTERIM PROCEDURES FOR ESTIMATING RISKS ASSOCIATED WITH EXPOSURES TO MIXTURES
OF CHLORINATED DIBENZO-p-DIOXINS AND DIBENZOFURANS (CDDs AND CDFs)

DRAFT

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INTERIM PROCEDURES FOR ESTIMATING RISKS ASSOCIATED WITH EXPOSURES TO
MIXTURES OF CHLORINATED DIBENZO-p-DIOXINS AND -DIBENZOFURANS (CDDs and CDFs) 1/

I. SUMMARY

The U.S. Environmental Protection Agency (EPA) is often confronted with the need to determine the risks associated with exposure to materials such as soot, incinerator fly ash, industrial wastes, and soils which contain complex mixtures of chlorinated dibenzo-p-dioxins (CDDs) and chlorinated dibenzofurans (CDFs). Recognizing the public and toxicological concern generated by these chemicals and the significant gaps in our ability to evaluate the human health potential of these compounds by existing procedures, the CDD/CDF Technical Panel of the Risk Assessment Forum (Forum) is recommending an interim method to aid in the assessment of the human health risks posed by mixtures of CDDs/CDFs until data gaps are filled.

The Technical Panel has reviewed a spectrum of approaches for making such assessments, consistent with EPA's Guidelines for the Health Risk Assessment of Chemical Mixtures and has concluded that a direct biological assessment of the toxicity of complex mixtures of CDDs/CDFs is preferred. A validated bioassay that can plausibly be applied to such mixtures is not now available, although promising research is in progress in the area. An alternative approach involves explicit analysis and toxicological determination of each of the constituent CDD/CDF congeners. The data required for such an approach also need to be developed and are not likely to be generated soon. The Forum therefore concludes that, as an interim science policy measure, a reasonable estimate of the toxic

1/ See Appendix A for the nomenclature and conventions used in this paper.

risks associated with a mixture of CDDs/CDFs can be made by taking into account the distribution of CDD/CDF congeners or homologues and the likely relative toxicity of these compounds. This document describes the recommended interim procedure for generating the "2378-TCDD equivalence" of complex mixtures of CDDs/CDFs, based on congener- or homologue-specific data, and for using such information in assessing risk. (The recommendations are summarized in the rightmost column of Table 1.)

The Forum acknowledges that this procedure is not based on a thoroughly established scientific foundation. Instead, the approach represents a consensus recommendation for interim science policy, subject to change as additional data are available. The approach is judged to be applicable to mixtures of CDDs/CDFs, but should not be construed as being applicable as well to mixtures of other chemicals.

The basis of this approach, i.e., the assignment of toxicity equivalence factors (TEFs) is subject to revision as new scientific data become available in the future. Consequently, risk assessors and risk managers are urged to use informed discretion, noting specific problems on a case-by-case basis, when deciding to which situations the procedure can be applied. The Forum urges the support of research to broaden the scientific basis for this approach and develop the more preferred approaches.

II. THE NEED FOR A PROCEDURE FOR ASSESSING THE RISK ASSOCIATED WITH EXPOSURE TO COMPLEX MIXTURES OF CDDs/CDFs

During the late 1970s, the Agency was faced with assessing the human health significance of exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD).

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In preparation for the cancellation hearings for the herbicides 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and Silvex, the Agency generated risk assessments for several toxic responses for 2,3,7,8-TCDD. The quantitative cancer risk assessment developed by the Carcinogen Assessment Group was later adapted for use in the Water Quality Criteria (WQC) Document for 2,3,7,8-TCDD (U.S. EPA, 1984a). In addition to carcinogenicity concerns, the WQC document contains an assessment of systemic toxicity based on reproductive effects resulting from exposure to 2,3,7,8-TCDD.

Later, it became clear that exposure situations exist in the country which involve more than 2,3,7,8-TCDD alone. Data on emissions from combustion sources (e.g., hazardous waste and municipal waste incinerators) and contents of waste from certain industrial production processes indicate that the majority of the 75 CDDs and 135 CDFs can be detected in the environment.

In recent years, the reporting of at least homologue-specific data for the CDDs and CDFs has become commonplace, and the Agency has taken some steps to address the significance of these findings. For example, the current draft of the Health Assessment Document for Polychlorinated Dibenzo-p-Dioxins prepared for the Office of Air Quality, Planning, and Standards (U.S. EPA, 1984b) contains a quantitative risk assessment for a mixture of hexachlorodibenzo-p-dioxins (HxCDDs) based on carcinogenicity studies conducted by the National Cancer Institute. These concerns have also led to regulatory action; e.g., several industrial wastes containing tetra-, penta-, hexachlorodioxins, and -dibenzofurans were recently designated by the Agency as EPA hazardous wastes.

Faced with increasing amounts of isomer- and homologue-specific data, and recognizing the significant potency and structure-activity relationships exhib-

ited in in vivo and in vitro studies of CDDs and CDFs, the Technical Panel perceives a need to address more generally the potential risks posed by the congeners other than 2,3,7,8-TCDD and the mixture of HxCDDs. ^{2/} Detailed consideration of the toxicity of the vast majority of the CDDs/CDFs is limited by the lack of a complete toxicological data base on most of the congeners. Further, it is unlikely that many long-term test results will be available soon. For example, research on 2,3,7,8-TCDD has been under way for more than two decades at an estimated cost of more than one hundred million dollars. Although this chemical has been investigated to a much greater extent than any of the other CDDs/CDFs, unanswered questions remain. Therefore, the Forum believes that an interim science policy position should be adopted for use in assessing risks associated with CDD/CDF mixtures, until more definitive scientific data are available.

III. APPROACHES TO HAZARD ASSESSMENT FOR CDD/CDF MIXTURES

A. The Ideal Approach -- Long-Term, Whole-Animal Toxicity Assay of Mixtures

Under ideal conditions, an assessment of the toxicity of a mixture of chemicals is best accomplished by direct evaluation of its toxic effects, e.g., by determining the effects of chronic exposure in an experimental animal (U.S. EPA, 1985). Such an assessment is time-consuming and costly and would theoretically

^{2/} In the early 1980s, the Agency developed a method for an approximate assessment of the risks of the emission of CDDs/CDFs associated with the high-temperature incineration of PCBs and combustion of municipal waste (U.S. EPA, 1981; U.S. EPA, 1982); see Table 1. The procedure presented in this document is a refinement of that approach. A comparison of a variety of methods is included in Appendix B.

have to be performed for each of the many mixtures of environmental importance. Therefore, this idealized approach would cause unacceptable delays in addressing the potential health risks associated with exposures to CDD/CDF mixtures.

B. A Promising Approach -- Short-Term, Biological Assay of Mixtures

An alternative, and perhaps more achievable, approach to hazard assessment of a mixture is a short-term assay that indirectly provides a measure of the mixture's potential toxicity. In the case of mixtures containing CDDs and CDFs, short-term assays are under development that directly determine the 2,3,7,8-TCDD-like response which could be used as a measure of the toxicity of the mixture as a whole. Such assays, which take advantage of the similar toxic end points induced by CDDs and CDFs, and have been used to assess the potential health hazards of exposure to CDD/CDF-contaminated soot from PCB fires (Eadon, 1982; Gierthy and Crane, 1984; Gravitz et al., 1983), and for predicting the potential toxicity of incinerator fly ash (Rizzardini, et al., 1983; Sawyer, et al., 1983).

The development of such "mixture assays" is progressing rapidly. While additional work is required to more fully validate the assay findings for specific toxic end points, especially chronic effects, and aspects of pharmacokinetics need to be considered, an increasing body of data demonstrate correlations with subchronic effects of CDDs/CDFs (Safe et al., 1985). The Forum, recognizing the importance of this approach in implementing its regulatory strategy for 2,3,7,8-TCDD-like chemicals, strongly encourages research in this area.

C. A Reductionist Approach -- Additivity of Toxicity of Components

In the absence of a fully developed "mixture assay," the components in a mixture of CDDs and CDFs could theoretically be identified and quantified

by analytical chemists. Then the toxicity of the mixture could be estimated by adding the toxicity contributed by each of its components. In the case of most environmental mixtures, however, this method would be of limited value since congener-specific analyses for the 75 CDDs and 135 CDFs potentially present in the mixture are seldom available. In addition, there is little information available on the toxic potency of most of these congeners. Therefore, this approach is not viable at this time; nor is it likely to be feasible in the near future.

D. An Interim Approach -- 2378-TCDD Toxicity Equivalence Factors (TEFs)

The Forum recommends a fourth alternative for estimating the risks associated with exposure to complex mixtures of CDDs/CDFs. In this approach, as in approach C above, information is obtained on the concentrations of homologues and/or congeners present in the mixture. Then, using the available toxicological data and reasoning on the basis of structure-activity relations, the significance of the exposure to each of the components is estimated and expressed as an "equivalent amount of 2378-TCDD." Combining this information with hazard information on 2,3,7,8-TCDD, and assuming additivity of effects, the risks associated with the mixture of CDDs/CDFs can be estimated if exposure is known. Key to the approach are the 2378-TCDD Toxicity Equivalence Factors (TEFs) which are derived in Section IV.

The general approach using TEFs as outlined here is not unique; several organizations have used similar approaches (see Table 1).

At one extreme, all CDDs/CDFs could be assumed to be as toxic as 2,3,7,8-TCDD (all TEFs = 1). This position is not recommended since the limited long-term data (2-year cancer bioassays) on 2,3,7,8-TCDD and a mixture of 2378-HxCDDs

(and the greater body of short-term data on many CDDs/CDFs) indicate that such an assumption is overly conservative. At the other extreme one could totally ignore the presence of CDDs/CDFs other than those for which adequate long-term data are available (most TEFs = 0). This position is not recommended in light of the similar toxic properties of several of these compounds and the structure-activity relationship demonstrated for effects resulting from less than lifetime exposures.

Instead, the Forum recommends that the TEF procedure presented below be adopted as a matter of science policy on an interim basis, subject to revision as new experimental data become available. Based on the available scientific information, the Forum believes that this approach represents an appropriate means of approximating the potential risk of exposure to mixtures of CDDs and CDFs for purposes of risk management.

The approach will enable the Agency to deal with many, but not all, of its problems; e.g., assigning priority to Superfund sites, estimating the extent to which a hazardous waste site should be cleaned up, guiding decisions on which manufacturing wastes can be delisted as EPA hazardous wastes, and estimating risks associated with the emission of CDDs/CDFs from combustion sources.

The remainder of this document discusses the TEF approach in greater detail, illustrates its use in risk assessment, and identifies additional research, the results of which would provide information for adjustments to this interim approach.

IV. THE 2378-TCDD TOXICITY EQUIVALENCE FACTORS (TEFs) APPROACH TO ASSESSING THE TOXICITY OF COMPLEX MIXTURES OF CDDs/CDFs

2,3,7,8-TCDD is one of 75 CDDs. Exceptionally low doses of this compound elicit a wide range of toxic responses in many animals., e.g., adverse reproduc-

tive effects, thymic atrophy, and a "wasting syndrome" leading to death. The EPA's Carcinogen Assessment Group (CAG) has determined that there is sufficient evidence to conclude that 2,3,7,8-TCDD and a mixture of two 2378-HxCDDs are probable human carcinogens. The CAG quantitative assessment indicates that these chemicals are among the most potent animal carcinogens evaluated by the Agency to date. Limited data suggest that some of the other CDDs may have other toxic effects similar to those of 2,3,7,8-TCDD, again at very low doses.

Moreover, these toxicity concerns are not restricted to CDDs. Limited experimental data, supplemented by structure/activity relationships in in vitro tests that are correlated with in vivo toxic effects of CDFs indicate that some of these compounds exhibit "2,3,7,8-TCDD-like" toxicity (Bandiera et al., 1984; Okey et al., 1984; Safe et al., 1985).

The biochemical mechanisms leading to the toxic response resulting from exposure to CDDs and CDFs are not known in detail. However, experimental data have accumulated which suggest that an important role in the development of systemic toxicity resulting from exposure to these chemicals is played by an intracellular protein, the Ah receptor, the putative product of a gene locus designated Ah. This receptor binds halogenated polycyclic aromatic molecules, including CDDs and CDFs. It has been postulated that the Ah locus controls several pleiotropic responses: a limited, but widely expressed gene complex that includes the structural genes for AHH expression, and, in a few organs, such as skin and thymus, a second gene complex regulating cell proliferation and differentiation (Knutson and Poland, 1980; Neal, et al., 1982; Greenlee et al., 1985a).

In several mouse strains, the expression of toxicity of 2,3,7,8-TCDD-related compounds, including cleft palate formation, liver damage, effects on

body weight gain, thymic involution, and chloracnegenic response, has been correlated with their binding affinity for the Ah receptor, and with their ability to induce several enzyme systems, some of which have been linked to the expression of carcinogenicity (Poland and Knutson, 1982; Bandiera et al., 1984; Madhukar et al., 1984; Poland et al., 1985; Safe et al., 1985; Vickers et al., 1985). Structure-activity studies also link the enhanced in vitro cell differentiation caused by these compounds to the presence of the Ah receptor (Greenlee et al., 1985b).

However, it has also been noted that the cytosolic receptor concentration alone may not be the sole determinant of the capacity for AHH induction (Neal, 1985; Okey and Vella, 1984). In interspecies comparisons there are poor correlations between the amount of cellular Ah receptor, its ability to bind 2,3,7,8-TCDD, and AHH induction (Denison and Wilkinson, 1985; Gasiewicz and Rucci, 1984; Neal, 1985); and in the mouse the development of TCDD-induced liver toxicity cannot be ascribed solely to the presence of the Ah receptor (Greig et al., 1984).

A recent review concludes that although there are inconsistencies across species in the Ah receptor's being the sole mechanism of toxicity of CDDs and CDFs, the data suggest that the binding of these compounds to the receptor is in some way related to some of the biological effects they cause in experimental animals (Neal, 1985)

Table 2 summarizes information on a variety of end points elicited by CDDs/ CDFs: acute toxicity, carcinogenicity, reproductive effects, receptor binding, enzyme induction, and in vitro cell transformation. For ease of comparison, the data are normalized to unity for 2,3,7,8-TCDD. For example, 2378-HxCDDs have about 5% the Ah receptor binding strength of 2,3,7,8-TCDD. Their repro-

ductive toxicity and carcinogenic potency are, respectively, about 1% and 4% that of 2,3,7,8-TCDD. Kociba and Cabey (1985) recently presented similar data.

The structure/activity generalizations based on the data in Table 2 support the generalizations in the literature concerning the congeners that are most likely to be of toxic concern (Poland and Knutson, 1982; Gasiewicz and Rucci, 1984; Bandiera et al., 1984). That is, congeners that are substituted in the lateral 2, 3, 7, and 8 positions are likely to exhibit toxic effects at lower doses than other congeners. This includes the 15 tetra-, penta-, hexa- and heptachlorinated CDDs and CDFs listed in Table 3. 3/

3/ The Technical Panel is aware that some investigators (e.g., Grant, 1977; Olie et al, 1983; Commoner et al., 1984; and Ontario, 1982, 1984) have broadly defined congeners of concern to include those tri- to hepta- congeners which are substituted with at least three chlorines in the four lateral (2, 3, 7, and 8) positions. The toxicity data (Table 2) do not argue strongly for this extended range of concern. Further, the increased level of complexity invoked by including these additional congeners is to suggest a greater level of accuracy and resolution than the Technical Panel believes is presently warranted by the TEF approach.

The Technical Panel is also aware that receptor binding data suggest a relatively high potential toxicity for 1,2,4,6,7-PeCDF. Examination of stereochemical models show that the 4 and 6 positions of CDFs exhibit partial overlap with the lateral chlorine groups of 2,3,7,8-TCDD (Bandiera et al., 1984). However, this increased receptor binding activity is not reflected in an increased potency of 1,2,4,6,7-PeCDF as an enzyme inducer (cf. Table 2), an end point which has been shown to correlate with subchronic toxicity (Safe et al., 1985). Therefore, the Technical Panel is treating 1,2,4,6,7-PeCDF as a "non-2378-congener" at this time; however, additional data could lead to a change in this position.

1,2,3,6,7- and 2,3,4,6,7-PeCDF are almost as potent as 2378-PeCDF in the induction of AHH activity in human lymphoblastoid cells in vitro (see Table 2). However, because this assay seems to yield relative potencies that do not agree with other short-term tests, and because dose-response data are not available for this assay, these data are not included in the overall evaluation at the present time.

The "2378-TCDD equivalence factors" (TEFs) listed in Tables 1 and 3 were assigned using the following criteria:

1. Information on carcinogenic potency based on long-term animal studies takes precedence.
2. Where carcinogenic activity has not been demonstrated, information on systemic effects is used in the following manner:
 - a. Data on reproductive effects take priority because of the significance of the end point in humans and because the estimated human exposure levels potentially resulting in reproductive and carcinogenic effects are very similar.
 - b. Data on acute lethality is accorded very low priority since a correlation between LD₅₀s chronic effects has not been established for these compounds.
 - c. The data currently available on systemic effects (e.g., body or organ weight losses, hepatotoxicity) are not sufficient for use in developing TEFs. Such data are used to provide qualitative support for these assignments.
3. In the interpretation of the data from in vitro test systems, more weight is placed on data from receptor binding interaction and oxidative enzyme induction, because for these effects the correlations with in vivo systemic effects (immunotoxicity, body weight loss) are strongest.

The above criteria were applied as follows:

1. Since the primary concern is with chronic effects, the relative carcinogenicity responses (Table 2) for 2,3,7,8-TCDD and the mixture of two 2378-HxCDDs ^{4/} were used to generate the TEF for 2378-PeCDD.

The TEF for 2378-PeCDD (0.5) is the arithmetic mean of the carcinogenic potency values for 2,3,7,8-TCDD (1) and 2378-HxCDDs (0.04). Data on receptor binding, enzyme induction, and cell keratinization generally support this value.
2. 2,3,7,8-TCDF is assigned a TEF of 0.1 primarily because it is 1 to 2 orders of magnitude (OMs) less potent than 2,3,7,8-TCDD in reproductive toxicity tests. Also, it is about one OM less potent than 2,3,7,8-TCDD in the in vitro tests.
3. The 2378-PeCDF congeners are assigned a TEF of 0.1 due to the responses seen in in vitro tests. Greater reliance was placed on the animal

^{4/} See Appendix A, item 6, for explanation of notation.

enzyme induction studies due to the more significant correlations observed between this end point and subchronic responses than have been observed with the receptor binding end point. The human cell data were accorded less weight because these experiments were conducted at only one exposure concentration.

4. Because in vitro data in general show HxCDFs to be about one tenth as potent as PeCDFs, their TEF is assigned a value of 0.01 (0.1/10). Further, the data generally suggest that CDFs are somewhat less toxic than the analogous CDDs. Therefore, the TEF for 2378-HxCDFs should be less than that of the 2378-HxCDDs (0.04).
5. The 2378-HpCDDs and 2378-HpCDFs are assigned TEFs 3 OM less than that for 2,3,7,8-TCDD because the enzyme induction potencies of these congeners differ from that of 2,3,7,8-TCDD by about this factor.
6. Based on the data in Table 2, the non-2378-substituted isomers are 1 to 3 OMs less potent than the 2378-substituted isomers. Since these data are limited to in vitro systems, a factor of 0.01 is applied to the non-2378-substituted, as compared to the 2378-substituted congeners.

With the exception of 2,3,7,8-TCDD, the 2378-HxCDDs, and 2378-TCDF, the TEFs are not based on the results of major animal (reproductive, carcinogenic) studies. Generally, TEFs are based on estimates of the relative toxicity in in vitro tests whose relationship to the chronic effects of concern is largely presumptive. However, as discussed above, studies on systemic effects continue to reinforce the view that the short-term assays provide important fundamental information on the toxicity of the CDDs/CDFs.

In summary, the Forum concludes that there is a sufficiently plausible basis for the TEF approach of estimating risks associated with exposures for CDDs/CDF and recommends that the Agency adopt the approach, on an interim basis, as a matter of science policy. The TEFs should be revised as additional scientific information is developed. It should be noted that this general approach to estimating such CDD/CDF risks has been taken by other regulatory groups (see Table 1 and Appendix B).

V. APPLICATIONS TO RISK ASSESSMENT

In general, an assessment of the human health risk of a mixture of CDDs and CDFs, using the TEF approach, involves the following steps:

1. Analytical determination of the CDDs and CDFs in the sample.
2. Multiplication of congener concentrations in the sample by the TEFs in Table 1 to express the concentration in terms of 2378-TCDD equivalents.
3. Summation of the products in step 2 to obtain the total 2378-TCDD equivalents in the sample.
4. Determination of human exposure to the mixture in question, expressed in terms of 2378-TCDD equivalents.
5. Combination of exposure from step 4 with toxicity information on 2,3,7,8-TCDD (usually carcinogenicity and/or reproductive effects) to estimate risks associated with the mixture.

In cases in which the concentrations of the 15 congeners of concern are known:

$$\begin{aligned} \text{2378-TCDD Equivalents} = & (\text{TEF of each 2378-CDD/CDF congener} \times \text{the} \\ & \text{concentration of the respective congener}) + \\ & (\text{TEF of each non-2378 CDD/CDF congener} \times \text{the} \\ & \text{concentration of the respective congener}) \end{aligned}$$

Samples of this calculation for several environmental mixtures are provided in Table 4.

In cases where only the concentration of homologous groups is known, i.e., no isomer-specific data are available, different approaches are possible. For example, the assumption that the 2378-congeners of concern constitute all of the CDDs and CDFs present in the mixture is likely to provide an upper-bound, most conservative estimate of the toxicity. Alternatively, one could assume

that the occurrence of each of the congeners in the mixture has equal probability (Olie et al., 1983; Commoner et al., 1984). For instance, 2,3,7,8-TCDD is one of 22 possible TCDDs and would constitute about 4% of a mixture of isomers occurring with equal probability. In other situations particular knowledge of chemical reaction parameters, process conditions, and results from related studies (e.g., congener distributions in emissions from combustion sources) might enable one to estimate the relative occurrence of 2378-congeners. However, one must be careful to explicitly explain and justify whatever assumptions are made. Table 5 illustrates the results obtained using different methods to estimate the proportion of 2378 to non-2378 isomers in the absence of analytical data for individual isomers.

The calculated 2378-TCDD equivalents can then be used to assess the health risk of a mixture. As an explicit example, consider a municipal solid waste (MSW) combustor whose particulate emissions, the CDD/CDF mixture in question, are the same as the electrostatic precipitator (ESP) catch cited in columns 5 and 6 of Table 4. The sample is estimated to contain 32 ppb 2378-TCDD equivalents; i.e., 32 picograms of 2378-TCDD equivalents per milligram of mixture. Suppose that an exposure analysis indicates that a person living downwind from the incinerator receives an average daily dose of 1 ng of the mixture/kg body weight resulting from inhalation (i.e., without consideration of other possible routes of exposure). This exposure estimate is combined with the upper-bound carcinogenic potency of 2,3,7,8-TCDD (1.6×10^5 per mg/kg-day [U.S. EPA, 1984c]) to generate the upper 95% limit of the excess risk of developing cancer (from inhalation exposure alone) for a person living downwind from the facility emitting the mixture under consideration, assuming lifetime exposure:

Upper 95% limit of excess cancer risk resulting from inhalation exposure

$$\begin{aligned} &= [\text{potency}] \times [\text{exposure}] \\ &= [1.6 \times 10^5 \text{ per mg 2,3,7,8-TCDD/kg-day}] \times \\ &[32 \text{ pg TCDD/mg mixture} \times 10^{-9} \text{ mg 2,3,7,8-TCDD/pg} \times 1 \text{ ng mixture/kg-day} \\ &\quad \times 10^{-6} \text{ mg mixture/ng mixture}] \end{aligned}$$

VI. COMPARISON OF TEF APPROACH WITH RESULTS OF BIOLOGICAL TESTING

A limited number of in vivo and in vitro approaches have been employed in assessing the toxicity of complex mixtures of CDDs and CDFs. While the results from these attempts are not definitive, it is instructive to compare those results with the results from the TEF approach proposed here.

Eadon et al. (1982) investigated the toxicity of CDD/CDF-contaminated soot associated with a fire involving PCB-containing electrical equipment. Using the results from acute in vivo toxicity (LD₅₀) studies in which the soot was the test substance, the researchers determined that it had the acute toxicity expected of material containing about 50 times the amount of 2,3,7,8-TCDD actually found by GC/MS analysis.

Table 5 illustrates the results of employing the TEF approach through three different procedures, each of which depends upon the results of GC/MS analysis of the soot. In the first instance (A, in Table 5), the analytical data have been consolidated to totals within a homologous class. These concentrations are treated as if they consisted completely of 2378-members of the class and, therefore, are multiplied by the TEF appropriate for the 2378-members of the class. The resulting estimate of 2378-TCDD equivalents by this procedure is about 80.

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In procedure B the assumption is made that the occurrence of each of the congeners in a homologous class is equally probable; e.g., the concentration of 2,3,7,8-TCDD is 1/22 (about 5%) of the concentration of the total TCDDs. This approach leads to an estimate of the total 2378-TCDD equivalents of 8.

A rather unique data base exists in the case of the soot from this fire in that an extensive isomer-specific analysis of the sample is available (as cited in Des Rosiers, 1984). Therefore, the full array of TEFs from Table 1 (using the current EPA recommendations) can be applied. This procedure (C in Table 5) results in an estimate of roughly 50 for the total 2378-TCDD equivalents in the sample.

As might be expected, the most conservative of these procedures, A, leads to the highest estimate. Approach B (using theoretical probability of occurrence) leads to an estimate that is about 10-fold lower than the isomer-specific results C, reflecting the fact that the 2378-congeners are present in somewhat higher than "equal probability" proportions in this particular soot sample. Given the complexity of the analysis involved, the approximate nature of the TEF method, and the vagaries of the assay, a major feature of note in Table 5 regarding the soot samples is that the results of procedures A, B, and C span a range of only one order of magnitude and bracket the bioassay estimate.

In a separate study, Sawyer et al. (1983) published results of homologue-specific CDD and CDF concentrations in fly ash from four municipal solid waste combustors which are amenable to treatment by the TEF methodology. In addition, extracts from the fly ash samples were analyzed by three bioassay techniques (AHH induction, EROD induction, and receptor binding).

These data suggest that the TEF approach is likely to be a useful interim tool for the rough (order of magnitude) estimation of the toxicity of complex

mixtures of CDDs and CDFs. The availability of additional data comparing the results of analytical and biological assays will enable a conclusion regarding the preferred method of estimating TEFs (e.g., method A or B of Table 5).

VII. RESEARCH NEEDS

The Forum recommends that research be conducted that will enable the development of assays to directly assess the toxicity of mixtures of CDDs and CDFs. In addition, research should be conducted in order to provide a firmer basis for, and to guide appropriate modification of the TEF approach. The following areas of research are appropriate for these purposes:

1. Validation and completion of the in vitro test data such as those listed in Table 2.
2. Investigation of the relationships between short-term in vivo and in vitro tests and the toxic end points of concern; i.e., carcinogenicity, reproductive toxicity, immunotoxicity, and other significant human health effects resulting from CDD/CDF exposure.
3. Determination of the toxic potencies of metabolites of CDDs and CDFs in in vitro tests, relative to the potencies of the parent compounds. As pointed out by several reviewers, this would enable a refinement of the TEF approach.
4. Investigation of additional short-term assays which can test the mechanistic hypotheses underlying the TEF approach.

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TABLE 1. SOME APPROACHES TO ESTIMATING RELATIVE TOXICITIES OF PCDDs AND PCDFs

Basis/ compound	Swiss ^a	Grant ^b Olle ^c Commoner ^d	New York State ^e	Ontario ^f	FDA ^g	CA ^h	EPA ⁱ 1981	EPA current recommend.
(Basis)	Enzyme		LD ₅₀	Various effects	Various effects			Various effects
Mono thru di tri	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0
2378-TCDD other TCDDs	1 0.01	1 0	1 0	1 0.01	1 0	1 0	1 1	1 0.01
2378-PeCDDs other PeCDDs	0.1 0.1	0.1 0	1 0	1 0.01	0 0	1 0	0 0	0.5 0.005
2378-HxCDDs other HxCDDs	0.1 0.1	0.1 0	0.03 0	1 0.01	0.02 0.02	1 0	0 0	0.04 0.0004
2378-HpCDDs other HpCDDs	0.01 0.01	0.01 0	0 0	1 0.01	0.005 0.005	1 0	0 0	0.001 0.00001
OCDD	0	0	0	0	<0.00001	1	0	0

^aSwiss Government, 1982.^bGrant, 1977.^cOlle et al., 1983.^dCommoner et al., 1984.^eEaton et al., 1982.^fOntario, 1982.^gU.S. DHHS, 1983.^hGravitz et al., 1983.ⁱU.S. EPA, 1981.

(continued on the following page)

Basis/ compound	Swiss ^a	Grant ^b Olie ^c Commoner ^d	New York State ^e
(Basis)	Enzyme		LD ₅₀
2378-TCDFs	0.1	0.1	0.33
other TCDFs	0.1	0	0
2378-PeCDFs	0.1	0.1	0.33
other PeCDFs	0.1	0	0
2378-HxCDFs	0.1	0.1	0.01
other HxCDFs	0.1	0	0
2378-HpCDFs	0.1	0.01	0
other HpCDFs	0	0	0
OCDF	0	0	0

TABLE 1. (continued)

Ontario ^f	FDA ^g	CA ^h	EPA ⁱ 1981	EPA current recommend.
Various effects	Various effects			Various effects
0.02	0	1	0	0.1
0.0002	0	0	0	0.001
0.02	0	1	0	0.1
0.0002	0	0	0	0.001
0.02	0	1	0	0.01
0.0002	0	0	0	0.0001
0.02	0	1	0	0.001
0.0002	0	0	0	0.00001
0	0	0	0	0

TABLE 2. POTENCIES OF DIOXINS RELATIVE TO 2,3,7,8-TCDD

Chemical	Guinea pig LD ₅₀	Carcinogenicity	Reproductive/teratogenic effects	Receptor binding	Enzyme Induction		Cell keratin.	Flat (XB) cell assay	Immunotoxicity in vitro
					AHH	EROD			
					Animal cells	Human cells			
CDDs:									
Mono thru tri	<10 ^{-4e}	-	--	.001-.01 ^e	<.001 ^f	--	--	.01 ^e	.00 ^g
2378-TCDD	1 ^a	1 ^b	1 ^{c,f}	1 ^e	1 ^e	1 ^m	1 ^g	1 ^j	10.0 ⁿ
TCDDs	<.001 ^a	--	<.001 ^k	<.01-.16 ^e	<.001-.029	--	--	<.001-.01 ^e	--
2378-PeCDD	.67 ^a	--	--	1 ^e	.02-.29	--	--	.5 ^e	--
PeCDDs	.002 ^a	--	--	--	<.001 ^g	--	--	--	--
2378-HxCDDs	.03 ^a	.04 ^b	.01 ^c	.05 ^e	.001-.19	--	--	.005 ^e	--
HxCDDs	--	--	--	--	<.001 ^g	--	--	--	--
2378-HpCDDs	.004 ^a	--	--	--	.002-.0049 ^f	--	--	--	--
HpCDDs	.002 ^a	--	--	--	<.001 ^f	--	--	--	--
OCDD	--	--	<.00001 ^k	--	<.001 ^f	--	--	--	--

^a McKinney and McConnell, 1982; Moure et al., 1979.^b U.S. EPA, 1984a.^c Murray et al., 1979; Schwetz et al., 1973; Weber et al., 1984.^d Handlira et al., 1983.^e Knutson and Poland, 1980.^f Bradlaw et al., 1979.^g Bradlaw et al., 1980.^h Handlira et al., 1984.ⁱ Hassoun et al., 1984.^j Gierthy and Crane, 1985.^k Weber et al., 1984.^l Poland et al., 1979.^m Nagayama et al., 1985a,b.ⁿ Poland et al., 1976.^o Dencker et al., 1985.^p Greenlee et al., 1985b.

(Table continued on the following page)

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TABLE 2(continued)

Chemical	Guinea pig LD ₅₀	Carcinogenicity	Reproductive/teratogenic effects	Receptor binding	Enzyme Induction		Cell keratin.	Flat (XH) cell assay	Immunotoxicity in vitro
					AHH	EROD			
					Animal cells	Human cells			
CDFs:									
Mono thru tri	--	--	--	<.001-.02d,h	<.001d	<.001d	--	.001e	--
2378-TCDF	.28;.5a	--	.3-.13f,k	.3e;.24h;.4l	.01-.4f,h,m	.4m	.1h	.05e	.1J
TCDFs	--	--	--	.001-.05d,e	<.001d;.04m	.4m	<.005d	--	--
2378-PeCDF	--	--	--	.13d;.7e;.6h	<.3d;.4m	.8m	.1d	--	--
12467-PeCDF	--	--	--	.15h	.002h	--	<.001h	--	--
PeCDFs	--	--	--	.001-.1d,e	<.001-2d,n,m	.6m	<.001h	--	--
2378-HxCDFs	.017a	--	--	.04-.5e,h	.05-.2h,m	.9m	.1-.5h	--	--
HxCDFs	--	--	--	.001e,h	.001m;.002h	--	.006h	--	--
2378-HpCDFs	--	--	--	--	.004g	--	--	--	--
HpCDFs	--	--	--	<.001h	<.001f	--	--	--	--

TABLE 3. CDD/CDF ISOMERS OF MOST TOXIC CONCERN^a

Dioxin		Dibenzofuran	
Isomer	TEF ^b	Isomer	TEF ^b
2,3,7,8-TCDD	1	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	0.5	1,2,3,7,8-PeCDF	0.1
		2,3,4,7,8-PeCDF	0.1
1,2,3,4,7,8-HxCDD	0.04	1,2,3,4,7,8-HxCDF	0.01
1,2,3,7,8,9-HxCDD	0.04	1,2,3,7,8,9-HxCDF	0.01
1,2,3,6,7,8-HxCDD	0.04	1,2,3,6,7,8-HxCDF	0.01
		2,3,4,6,7,8-HxCDF	0.01
1,2,3,4,6,7,8-HpCDD	0.001	1,2,3,4,6,7,8-HpCDF	0.001
		1,2,3,4,7,8,9-HpCDF	0.001

^a In each homologous group, the relative toxicity factor for the isomers not listed above is 1/100 of the value listed above.

^b TEF = Toxicity Equivalence Factor = relative toxicity assigned.

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TABLE 4. PCDDs/PCDFs IN SOME ENVIRONMENTAL SAMPLES

Isomer	TEF	Air partics. St. Louis ^e		MSW ESP dust ^c		Lake sediment ^e		1982 Milorganite ^d		MSW fly ash ^f			
		CDD/F conc. (ppb)	TCDD eqts.	CDD/F conc. (ppb)	TCDD eqts.	CDD/F conc. (ppb)	TCDD eqts.	CDD/F conc. (ppt)	TCDD eqts.	Ontario CDD/F conc. (ppt)	TCDD eqts.	Oslo CDD/F conc. (ppt)	TCDD eqts.
TCDDs	1	0.2	0.2	5	5	0	0	206	206	541	541	ND	--
PeCDDs	0.5	1	0.5	10	5	0.1	0.05	--	--	467	234	11	5.1
HxCDDs	0.04	1.2	0.048	160	6.4	0.34	0.014	2768	110.7	591	24	51	2
HpCDDs	0.001	25	0.025	120	0.12	0.5	0.001	7600	7.6	434	6.43	119	0.1
OCDD	0	170	--	260	--	1.3	--	60000	--	467	--	186	--
TCDFs	0.1	--	--	40	4	0.13	0.013	--	--				
PeCDFs	0.1	--	--	80	8	0.14	0.014	--	--				
HxCDFs	0.01	--	--	280	2.8	0.38	0.004	--	--				
HpCDFs	0.001	--	--	160	0.16	1.13	0.001	--	--				
OCDF	0	--	--	40	--	0.14	--	--	--				
Total TCDD eqts.			0.08		32		0.10		324		799		7.1

^aU.S. EPA, 1984d.^bCooper Engineers, 1984.^cRappe, 1984.^dLamparski et al., 1984.^eCzuwa and Hites, 1984.^fTong et al., 1984.^gDes Rosiers, 1984.

(continued on the following page)

TABLE 4. (continued)

		Thermal degradation prods. from dielectric fluids ^a				Jap. MSW ^b				Commercial CPs				Soot from PCB fire ^g	
Isomer	TEF	Run 8-13-40		Run 8-30-61 ASKL		Pt. A TEF		Pt. B TEF		246TCPC		PCPC			
		CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.
		(ng)		(ug)		[1b/MMBTU(x10 ⁻⁶)]				(ppm)		(ppm)		(ppm)	
TCDDs															
2378	1	0	0	0	0	0.1	0.1	0.58	0.58	<0.1	--	<0.1	--	0.6	0.6
other	0.01													0.6	0.01
PeCDDs															
2378	0.5	0	0	0	0	0.07	0.035	0.47	0.24	<0.1	--	<0.1	--	2.5	1.25
other	0.002													2.5	0.01
HxCDDs															
2378	0.04	0	0	0	0	0.04	0.002	0.36	0.014	<1	--	2.5	0.1	1.1	0.04
other	0.0004													3.6	0
HpCDDs															
2378	0.001	0	0	330	0.33	0.02	<0.001	0.08	<0.001	<1	--	175	0.18	3	0
other	0.00001													4	0
OCDD	0	0	0	37	0	0.01	0	0.04	0	<1	--	500	--	2	--

(continued on the following page)

TABLE 4. (continued)

		Thermal degradation prods. from dielectric fluids ^a				Jap. MSW ^b				Commercial CPs				Sopt from PCB fire ⁹	
		Run 8-13-40		Run 8-30-61 ASKL		Pt. A TEF		Pt. B TEF		246TCPC		PCPC			
Isomer	TEF	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.	CDD/F conc.	TCDD eqts.
		(ng)		(ug)		[1b/MMBTU(10 ⁻⁶)]				(ppm)		(ppm)		(ppm)	
TCDFs															
2378	0.1	690	69	1400	140	1.31	0.131	1.25	0.125	1.5	0.15	<0.1	--	12	1.2
other	0.001													16	0.01
PeCDFs															
2378	0.1	43	4.3	6400	640	0.38	0.038	0.46	0.046	17.5	1.75	<0.1	--	358	35.8
other	0.001													312	0.3
HxCDFs															
2378	0.01	7	0.07	910	9.1	0.06	0.006	0.06	0.006	36	3.6	<0.3	--	670	6.7
other	0.0001													295	0.03
HpCDFs															
2378	0.001	0	0	29	0.029	0.01	<.001	0.02	<.001	4.8	0.005	19	0.019	285	0.29
other	0.00001													172	0
OCDF	0	0	0	3.4	0	0.004	0	0.01	0	<1	--	25	--	40	--
Total TCDD eqts.		73		789		0.3		1.02		5.5		0.3		46	

TABLE 5. USE OF THE TEF APPROACH

Isomer	TEF	Propn. factor	PCB fire soot ^a				MSW fly ash ^b				
			CDD/F conc. (ppm)	TCDD eqts. (ppm)			Sample 1		Sample 2		
				CDD eqts. (ppb)			CDD/F conc. (ppb)	TCDD eqts. (ppb)	CDD/F conc. (ppb)	TCDD eqts. (ppb)	
				AC	BC	CC				AC	BC
Total TCDDs	1	1	1.2	1.2			85	85	2.7	2.7	
2378 TCDDs	1	0.05	1.2		0.2	0.6	85		2.7		0.1
other TCDDs	0.01	0.95	1.2		-- ^d	--	85		2.7		--
Total PeCDDs	0.5	1	5.0	2.5			213	107	6.6	3.3	
2378 PeCDDs	0.5	0.07	5.0		0.2	1.3	213		6.6		0.2
other PeCDDs	0.005	0.93	5.0		--	--	213		6.6		--
Total HxCDDs	0.04	1	4.7	0.2			354	14.2	11.6	0.5	
2378 HxCDDs	0.04	0.3	4.7		0.1	--	354		11.6		0.1
other HxCDDs	0.0004	0.7	4.7		--	--	354		11.6		--
Total HpCDDs	0.001	1	7	--		--	184	0.2	5.7	--	
2378 HpCDDs	0.001	0.5	7		--	--	184		5.7		--
other HpCDDs	0.00001	0.5	7		--	--	184		5.7		--

^a Des Rosiers, 1984, assuming only homologue-specific concentrations are known (for isomer-specific analyses; see Table IV).

^b Sawyer et al., 1983.

^c A = estimated assuming 2378-isomers constitute 100% of a homologous group.

B = estimated assuming occurrence of all isomers in a homologous group is equally probable (thus using the proportionality factor in column three).

C = estimated by utilizing isomer-specific analyses (see Table IV).

^d Values rounding off to less than 0.1 are omitted.

(continued on the following page)

TABLE 5. (continued)

Isomer	TEF	Propn. factor	PCB fire soot ^a				MSW fly ash ^b					
			CDD/F conc. (ppm)	TCDD eqts. (ppm)			Sample 1		Sample 2			
				AC	BC	CC	CDD/F conc. (ppb)	TCDD eqts. (ppb)		CDD/F conc. (ppb)	TCDD eqts. (ppb)	
								AC	BC		AC	BC
Total TCDFs	0.1	1	28	2.8			209	20.9		7.0	0.7	
2378 TCDFs	0.1	0.03	28		0.1	1.2	209		0.6	7.0	--	
other TCDFs	0.001	0.97	28		--	--	209		0.2	7.0	--	
Total PeCDFs	0.1	1	670	67			549	54.9		17.8	1.8	
2378 PeCDFs	0.1	0.07	670		4.7	35.8	549		3.8	17.8	0.1	
other PeCDFs	0.001	0.93	670		0.6	0.3	549		0.5	17.8	--	
Total HxCDFs	0.01	1	965	9.7			1082	10.8		32.1	0.3	
2378 HxCDFs	0.01	0.25	965		2.4	6.7	1082		2.7	32.1	0.1	
other HxCDFs	0.0001	0.75	965		0.1	--	1082		0.1	32.1	--	
Total HpCDFs	0.001	1	460	0.5			499	0.5		10.9	--	
2378 HpCDFs	0.001	0.50	460		0.2	0.3	499		0.2	10.9	--	
other HpCDFs	0.00001	0.50	460		--	--	499		--	10.9	--	
Total TCDD equivalents (TEF):												
TEF estimate:				84	9	46		294	26		9 1	
AHH bioassay:				--	--	--		4			-- --	
EROD bioassay:				--	--	--		5			-- --	
Receptor binding assay:				--	--	--		32			4 --	
Acute toxicity bioassay:				58	--	--		--			-- --	

(continued on the following page)

Table 5. (continued)

MSW fly ash ^b								
Isomer	TEF	Propn. factor	CDD/F conc. (ppb)	Sample 3		Sample 4		
				TCDD eqts. (ppb)		CDD/F conc. (ppb)	TCDD eqts. (ppb)	
				AC	BC		AC	BC
Total TCDDs	1	1	12.9	12.9		2.4	2.4	
2378 TCDDs	1	0.05	12.9		0.6	2.4		0.1
other TCDDs	0.01	0.95	12.9		0.1	2.4		--
Total PeCDDs	0.5	1	37.5	18.8		7.9	4.0	
2378 PeCDDs	0.5	0.07	37.5		1.3	7.9		0.3
other PeCDDs	0.005	0.93	37.5		0.2	7.9		--
Total HxCDDs	0.04	1	75	3		9.7	0.4	
2378 HxCDDs	0.04	0.3	75		0.9	9.7		0.1
other HxCDDs	0.0004	0.7	75		--	9.7		--
Total HpCDDs	0.001	1	41.9	--		9.1	--	
2378 HpCDDs	0.001	0.5	41.9		--	9.1		--
other HpCDDs	0.00001	0.5	41.9		--	9.1		--
Total TCDFs	0.1	1	8.2	0.8		4.4	0.4	
2378 TCDFs	0.1	0.03	8.2		--	4.4		--
other TCDFs	0.001	0.97	8.2		--	4.4		--
Total PeCDFs	0.1	1	19.8	2.0		21.0	2.1	
2378 PeCDFs	0.1	0.07	19.8		0.1	21.0		0.1
other PeCDFs	0.001	0.93	19.8		--	21.0		--
Total HxCDFs	0.01	1	38.7	0.4		21.6	0.2	
2378 HxCDFs	0.01	0.25	38.7		0.1	21.6		0.1
other HxCDFs	0.0001	0.75	38.7		--	21.6		--
Total HpCDFs	0.001	1	20.6	--		16.6	--	
2378 HpCDFs	0.001	0.50	20.6		--	16.6		--
other HpCDFs	0.00001	0.50	20.6		--	16.6		--
Total TCDD equivalents (TEF):								
TEF estimate:				38	2		9	0.7
AHH bioassay:				4	--		2	--
EROD bioassay:				5	--		2	--
Receptor binding assay:				65	--		11	--
Acute toxicity bioassay:				--	--		--	--

TABLE 6. EXAMPLE OF A CALCULATION OF TCDD EQUIVALENTS
WHERE ISOMER-SPECIFIC CONCENTRATIONS ARE AVAILABLE

Isomer	Concentration (ppb)	Relative potency	TCDD equivalents (ppb)
2,3,7,8-TCDD	0.5	1	0.5
Other TCDDs	20	0.01	0.2
1,2,3,7,8-PeCDD	0.10	0.5	0.05
1,2,3,6,7,8-HxCDD	0.05	0.04	0.002
1,2,3,7,8,9-HxCDD	0.5	0.04	0.02
1,2,3,4,7,8-HxCDD	0.1	0.04	0.004
Other HxCDDs	50	0.004	0.02
2,3,7,8-TCDF	10.5	0.1	1.05
1,2,3,7,8-PeCDF	0.1	0.1	0.01
2,3,4,7,8-PeCDF	0.01	0.1	0.01
1,2,3,6,7,8-HxCDF	0.01	0.1	0.001
1,2,3,7,8,9-HxCDF	0.01	0.1	0.001
1,2,3,4,7,8-HxCDF	0.01	0.1	0.001
2,3,4,6,7,8-HxCDF	0.01	0.1	0.001
Other HxCDFs	1	0.001	0.001
Total			1.8

TABLE 7. CALCULATION OF TCDD EQUIVALENTS
WHERE ONLY HOMOLOGUE-SPECIFIC ANALYSES ARE AVAILABLE

Homologue	Concentration (ppb)	Relative potency	TCDD equivalents (ppb)
TCDDs	0.5	1	0.5
PeCDDs	0.5	0.5	0.25
HxCDDs	13	0.04	0.42
TCDFs	100	0.1	10.0
PeCDFs	150	0.1	15.0
HxCDFs	10	0.1	10.0
Total			36.0

APPENDIX A
NOMENCLATURE

The following terminology and abbreviations are used in this document:

1. The term "congener" refers to any one particular member of the same chemical family; e.g., there are 75 congeners of chlorinated dibenzo-p-dioxins.

2. The term "homologue" refers to a group of structurally related chemicals that have the same degree of chlorination. For example, there are eight homologues of CDDs, monochlorinated through octochlorinated.

3. The term "isomer" refers to substances that belong to the same homologous class. For example, there are 22 isomers that constitute the homologues of TCDDs.

4. A specific congener is denoted by unique chemical notation. For example, 2,4,8,9-tetrachlorodibenzofuran is referred to as 2,4,8,9-TCDF.

5. Notation for homologous classes is as follows:

Dibenzo-p-dioxin	D
Dibenzofuran	F

<u>No. of halogens</u>	<u>Acronym</u>	<u>Example</u>
1	M	2,4-DCDD
2	D	
3	Tr	
4	T	
5	Pe	1,4,7,8-TCDD
6	Hx	
7	Hp	
8	O	
1 through 8	CDDs and CDFs	

6. Dibenzo-p-dioxins and dibenzofurans that are chlorinated at the 2,3,7, and 8 positions are denoted as "2378" congeners, except when 2,3,7,8-TCDD is uniquely referred to; e.g., 1,2,3,7,8-PeCDF and 2,3,4,7,8-PeCDF are both referred to as "2378-PeCDFs."

APPENDIX 3
COMPARISON OF DIFFERENT APPROACHES TO CALCULATING
2378-TCDD EQUIVALENTS

Table III lists a number of different approaches to calculating 2378-TCDD toxicity equivalents. Five of the approaches (those that deal with 4-position 2378-substituted congeners, but not the 3-position substituted congeners) were applied to

1. The data in Table IV.
2. Some of the data included in Table I of the Report of the Citizens Advisory Committee on Resource Recovery in Brooklyn (March, 1985), produced by Ketcham and the Mt. Sinai School of Medicine.

A summary comparison of the relative results is found in Table B-1, with the supporting tables attached. (Note that the units of mass emission are not the same for all of the facilities. Therefore, comparison of absolute numbers between facilities may be invalid.)

These data indicate that, in general, the methods used by the Swiss government, New York State, and the U.S. EPA (the 1981 approach and the 1985 proposal) all generate results which are within an order of magnitude of each other. This suggests that, within the range considered, the results are not particularly sensitive functions of the TEFs selected.

The procedure recommended by the state of California, however, gives results which are roughly an order of magnitude higher than those generated by the other approaches. In general, the greater the contribution from the TCDDs, the greater the similarity in the results of the methods. This is due to the fact that all methods assign a TEF of 1 for 2,3,7,8-TCDD (and 1 to all TCDDs, when isomer-specific analyses are not available). Because higher chlorinated

CDDs and CDFs contribute significantly to the total, the disparity is greater between the CA results and those produced by the other methods, since CA assumes that all 2378-substituted CDDs/CDFs are as potent as 2,3,7,8-TCDD. The other methods acknowledge, to one degree or another, the reduced toxicity in higher chlorinated species; cf. Table 2.

TABLE B-1. RELATIVE 2378-TCDD EQUIVALENTS^a

Source	EPA '85	EPA '81	Swiss	NY	CA
St. Louis air part.	1	0.3	1	2	40
PCB fire soot (isomer-specific)	1	0.03	4	3	30
MSW ESP dust	1	0.2	3	2	30
Lake sediment	1	--	2	2	30
Milorganite	1	0.6	2	0.9	30
Oslo MSW flyash	1	--	1	2	20
Ontario MSW flyash	1	0.8	1	2	3
Jap. plant A	1	0.3	1	2	7
Jap. plant B	1	0.6	0.8	2	3
Albany	1	0.3	0.4	2	5
Wright-Pat. (best)	1	0.2	2	3	20
Wright-Pat. (worst)	1	0.4	2	2	20

^aCalculated using the Toxicity Equivalence Factors shown in Table 1.

TABLE B-2. CALCULATION OF 2378-TCDD TOXICITY EQUIVALENTS FOR ST. LOUIS AIR PARTICULATES
USING HOMOLOGUE-SPECIFIC DATA

Compound	CDD/F conc. (ppb)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0.2	1	0.2	1	0.2	1	0.2	1	0.2	1	0.2
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	1	0.5	0.5	0	0	0.1	0.1	1	1	1	1
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	1.2	0.04	0.048	0	0	0.1	0.12	0.03	0.036	1	1.2
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	25	0.001	0.025	0	0	0.01	0.25	0	0	1	25
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	170	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	NA	0.01	0	0	0	0.1	0	0.01	0	1	0
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	NA	0.001	0	0	0	0.1	0	0	0	1	0
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	NA	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			0.7		0.2		0.7		1.2		27.4

TABLE B-3. CALCULATION OF 2378-TCDD TOXICITY EQUIVALENTS FOR PCB FIRE SOOT
USING ISOMER-SPECIFIC DATA

Compound	CDD/F conc. (ppm)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppm)	TEFs	TEs (ppm)	TEFs	TEs (ppm)	TEFs	TEs (ppm)	TEFs	TEs (ppm)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0.6	1	0.6	1	0.6	1	0.6	1	0.6	1	0.6
TCDDs	0.6	0.01	0.006	1	0.6	0.01	0.006	0	0	0	0
2378-PeCDD	2.5	0.5	1.25	0	0	0.1	0.25	1	2.5	1	2.5
PeCDDs	2.5	0.005	0.0125	0	0	0.1	0.25	0	0	0	0
2378-HxCDD	1.1	0.04	0.044	0	0	0.1	0.11	0.03	0.033	1	1.1
HxCDDs	3.6	0.0004	0.00144	0	0	0.1	0.36	0	0	0	0
2378-HpCDD	3	0.001	0.003	0	0	0.01	0.03	0	0	1	3
HpCDDs	4	0.00001	0.00004	0	0	0.01	0.04	0	0	0	0
OCDD	2	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	12	0.1	1.2	0	0	0.1	1.2	0.33	3.96	1	12
TCDFs	16	0.001	0.016	0	0	0.1	1.6	0	0	0	0
2378-PeCDF	358	0.1	35.8	0	0	0.1	35.8	0.33	118.14	1	358
PeCDFs	312	0.001	0.312	0	0	0.1	31.2	0	0	0	0
2378-HxCDF	670	0.01	6.7	0	0	0.1	67	0.01	6.7	1	670
HxCDFs	295	0.0001	0.0295	0	0	0.1	29.5	0	0	0	0
2378-HpCDF	285	0.001	0.285	0	0	0.1	28.5	0	0	1	285
HpCDFs	172	0.00001	0.00172	0	0	0	0	0	0	0	0
OCDF	40	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			46		1.2		196		132		1332

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TABLE B-4. CALCULATION OF 2378-TCDD TOXICITY EQUIVALENTS FOR MSW ESP DUST
USING HOMOLOGUE-SPECIFIC DATA AND 2378 TEFs

Compound	CDD/F conc. (ppb)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	5	1	5	1	5	1	5	1	5	1	5
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	10	0.5	5	0	0	0.1	1	1	10	1	10
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	160	0.04	6.4	0	0	0.1	16	0.03	4.8	1	160
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	120	0.001	0.12	0	0	0.01	1.2	0	0	1	120
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	260	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	40	0.1	4	0	0	0.1	4	0.33	13.2	1	40
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	80	0.1	8	0	0	0.1	8	0.33	26.4	1	80
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	280	0.01	2.8	0	0	0.1	28	0.01	2.8	1	280
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	160	0.001	0.16	0	0	0.1	16	0	0	1	160
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	40	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			31		5		79		62		855

TABLE B-5. CALCULATION OF 2378-TCDD TOXICITY EQUIVALENTS FOR LAKE SEDIMENT
USING HOMOLOGUE-SPECIFIC DATA

Compound	CDD/F conc. (ppb)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)	TEFs	TEs (ppb)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0	1	0	1	0	1	0	1	0	1	0
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	0.1	0.5	0.05	0	0	0.1	0.01	1	0.1	1	0.1
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	0.34	0.04	0.0136	0	0	0.1	0.034	0.03	0.0102	1	0.34
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	0.5	0.001	0.0005	0	0	0.01	0.005	0	0	1	0.5
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	1.3	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	0.13	0.1	0.013	0	0	0.1	0.013	0.33	0.0429	1	0.13
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	0.14	0.1	0.014	0	0	0.1	0.014	0.33	0.0462	1	0.14
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	0.38	0.01	0.0038	0	0	0.1	0.038	0.01	0.0038	1	0.38
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	1.13	0.001	0.00113	0	0	0.1	0.113	0	0	1	1.13
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	0.14	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			0.1		0		1.2		0.2		2.7

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TABLE B-6. CALCULATION OF 2378-TCDD TOXICITY EQUIVALENTS FOR MILORGANITE
USING HOMOLOGUE-SPECIFIC DATA

Compound	CDD/F conc. (ppt)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	206	1	206	1	206	1	206	1	206	1	206
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	0	0.5	0	0	0	0.1	0	1	0	1	0
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	2768	0.04	110.72	0	0	0.1	276.8	0.03	83.04	1	2768
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	7600	0.001	7.6	0	0	0.01	76	0	0	1	7600
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	60000	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	NA	0.01	0	0	0	0.1	0	0.01	0	1	0
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	NA	0.001	0	0	0	0.1	0	0	0	1	0
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	NA	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			324		206		559		289		10600

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TABLE B-7. CALCULATION OF 2378-TCDD TOXICITY EQUIVALENTS FOR OLSO MSW FLY ASH
USING HOMOLOGUE-SPECIFIC DATA

Compound	CDD/F conc. (ppt)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	NA	1	0	1	0	1	0	1	0	1	0
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	11	0.5	5.5	0	0	0.1	1.1	1	11	1	11
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	51	0.04	2.04	0	0	0.1	5.1	0.03	1.53	1	51
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	119	0.001	0.119	0	0	0.01	1.19	0	0	1	119
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	186	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	NA	0.01	0	0	0	0.1	0	0.01	0	1	0
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	NA	0.001	0	0	0	0.1	0	0	0	1	0
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	NA	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			7.7		0		7.4		12.5		181

TABLE B-8. CALCULATION OF 2378-TCDD TOXICITY EQUIVALENTS FOR ONTARIO MSW FLY ASH
USING HOMOLOGUE-SPECIFIC DATA

Compound	CDD/F conc. (ppt)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)	TEFs	TEs (ppt)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	541	1	541	1	541	1	541	1	541	1	541
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	467	0.5	233.5	0	0	0.1	46.7	1	467	1	467
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	591	0.04	23.64	0	0	0.1	59.1	0.03	17.73	1	591
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	434	0.001	0.434	0	0	0.01	4.34	0	0	1	434
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	467	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	NA	0.1	0	0	0	0.1	0	0.33	0	1	0
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	NA	0.01	0	0	0	0.1	0	0.01	0	1	0
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	NA	0.001	0	0	0	0.1	0	0	0	1	0
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	NA	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			799		541		651		1026		2023

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TABLE B-9. CALCULATION OF 2378-TCDD TOXICITY EQUIVALENTS FOR MSW AT JAPANESE PLANT A
USING HOMOLOGUE-SPECIFIC DATA

Compound	CDD/F conc. ^a	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEFs ^a	TEFs	TEFs ^a	TEFs	TEFs ^a	TEFs	TEFs ^a	TEFs	TEFs ^a
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0.1	1	0.1	1	0.1	1	0.1	1	0.1	1	0.1
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	0.07	0.5	0.035	0	0	0.1	0.007	1	0.07	1	0.07
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	0.04	0.04	0.0016	0	0	0.1	0.004	0.03	0.0012	1	0.04
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	0.02	0.001	0.00002	0	0	0.01	0.0002	0	0	1	0.02
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	0.01	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	1.31	0.1	0.131	0	0	0.1	0.131	0.33	0.4323	1	1.31
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	0.38	0.1	0.038	0	0	0.1	0.038	0.33	0.1254	1	0.38
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	0.06	0.01	0.0006	0	0	0.1	0.006	0.01	0.0006	1	0.06
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	0.01	0.001	0.00001	0	0	0.1	0.001	0	0	1	0.01
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	0.004	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			0.3		0.1		0.3		0.7		2.0

^aUnits = lb/MM BTU(X10⁻⁶)

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TABLE B-10. CALCULATION OF 2378-TCDD TOXICITY EQUIVALENTS FOR MSW AT JAPANESE PLANT B
USING HOMOLOGUE-SPECIFIC DATA

Compound	CDD/F conc. ^a	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs ^a	TEFs	TEs ^a	TEFs	TEs ^a	TEFs	TEs ^a	TEF	TEs ^a
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0.58	1	0.58	1	0.58	1	0.58	1	0.58	1.1	0.58
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	0.47	0.5	0.235	0	0	0.1	0.047	1	0.47	1	0.47
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	0.36	0.04	0.0144	0	0	0.1	0.036	0.03	0.0108	1	0.36
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	0.08	0.001	0.00008	0	0	0.01	0.0008	0	0	1	0.08
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	0.04	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	1.25	0.1	0.125	0	0	0.1	0.125	0.33	0.4125	1	1.25
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	0.46	0.1	0.046	0	0	0.1	0.046	0.33	0.1518	1	0.46
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	0.06	0.01	0.0006	0	0	0.1	0.006	0.01	0.0006	1	0.06
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	0.02	0.001	0.00002	0	0	0.1	0.002	0	0	1	0.02
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	0.01	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			1.0		0.6		0.8		1.6		3.3

^aUnits = lb/MM BTU(X10⁻⁶)

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TABLE B-11. CALCULATION OF 2378-TCDD TOXICITY EQUIVALENTS FOR MSW AT ALBANY
USING HOMOLOGUE-SPECIFIC DATA

Compound	CDD/F conc. (ng/m ³)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ng/m ³)	TEFs	TEs (ng/m ³)	TEFs	TEs (ng/m ³)	TEFs	TEs (ng/m ³)	TEFs	TEs (ng/m ³)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0.45	1	0.45	1	0.45	1	0.45	1	0.45	1	0.45
TCDDs	14	0.01	0.14	1	14	0.01	0.14	0	0	0	0
2378-PeCDD	97	0.5	48.5	0	0	0.1	9.7	1	97	1	97
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	53	0.04	2.12	0	0	0.1	5.3	0.03	1.59	1	53
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	71	0.001	0.071	0	0	0.01	0.71	0	0	1	71
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	10	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	2.1	0.1	0.21	0	0	0.1	0.21	0.33	0.693	1	2.1
TCDFs	33	0.001	0.033	0	0	0.1	3.3	0	0	0	0
2378-PeCDF	21	0.1	2.1	0	0	0.1	2.1	0.33	6.93	1	21
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	4	0.01	0.04	0	0	0.1	0.4	0.01	0.04	1	4
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	1	0.001	0.001	0	0	0.1	0.1	0	0	1	1
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	2	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			54		14		22		107		250

TABLE B-12. CALCULATION OF 2378-TCDD TOXICITY EQUIVALENTS FOR WP AFB (BEST)
USING HOMOLOGUE-SPECIFIC DATA

Compound	CDD/F conc. (ng/m ³)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ng/m ³)	TEFs	TEs (ng/m ³)	TEFs	TEs (ng/m ³)	TEFs	TEs (ng/m ³)	TEFs	TEs (ng/m ³)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	0.4	1	0.4	1	0.4	1	0.4	1	0.4	1	0.4
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	0.4	0.5	0.2	0	0	0.1	0.04	1	0.4	1	0.4
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	1	0.04	0.04	0	0	0.1	0.1	0.03	0.03	1	1
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	3	0.001	0.003	0	0	0.01	0.03	0	0	1	3
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	3	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	8	0.1	0.8	0	0	0.1	0.8	0.33	2.64	1	8
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	3	0.1	0.3	0	0	0.1	0.3	0.33	0.99	1	3
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	4	0.01	0.04	0	0	0.1	0.4	0.01	0.04	1	4
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	9	0.001	0.009	0	0	0.1	0.9	0	0	1	9
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	2	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			1.8		0.4		3.0		4.5		28.8

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TABLE B-13. CALCULATION OF 2378-TCDD TOXICITY EQUIVALENTS FOR WP AFB (WORST)
USING HOMOLOGUE-SPECIFIC DATA

Compound	CDD/F conc. (ng/m ³)	EPA 1985		EPA 1981		Switzerland		New York		California	
		TEFs	TEs (ng/m ³)	TEFs	TEs (ng/m ³)	TEFs	TEs (ng/m ³)	TEFs	TEs (ng/m ³)	TEFs	TEs (ng/m ³)
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDD	4	1	4	1	4	1	4	1	4	1	4
TCDDs	0	0.01	0	1	0	0.01	0	0	0	0	0
2378-PeCDD	3	0.5	1.5	0	0	0.1	0.3	1	3	1	3
PeCDDs	0	0.005	0	0	0	0.1	0	0	0	0	0
2378-HxCDD	6	0.04	0.24	0	0	0.1	0.6	0.03	0.18	1	6
HxCDDs	0	0.0004	0	0	0	0.1	0	0	0	0	0
2378-HpCDD	32	0.001	0.032	0	0	0.01	0.32	0	0	1	32
HpCDDs	0	0.00001	0	0	0	0.01	0	0	0	0	0
OCDD	16	0	0	0	0	0	0	0	0	0	0
Mono to tri	x	0	0	0	0	0	0	0	0	0	0
2378-TCDF	31	0.1	3.1	0	0	0.1	3.1	0.33	10.23	1	31
TCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-PeCDF	15	0.1	1.5	0	0	0.1	1.5	0.33	4.95	1	15
PeCDFs	0	0.001	0	0	0	0.1	0	0	0	0	0
2378-HxCDF	23	0.01	0.23	0	0	0.1	2.3	0.01	0.23	1	23
HxCDFs	0	0.0001	0	0	0	0.1	0	0	0	0	0
2378-HpCDF	93	0.001	0.093	0	0	0.1	9.3	0	0	1	93
HpCDFs	0	0.00001	0	0	0	0	0	0	0	0	0
OCDF	8	0	0	0	0	0	0	0	0	0	0
Total 2378-TCDD equivalents			11.0		4		21.4		22.6		207