8/16/13

CM Christiansen / Town of Phelps mtg. Wausau

CS - Town looking to work w/ us & CMC to take property; what are obstacles, what are risks?

JR - break site down into 2 parts

1) Upland / known issues - soil cleanup

2) Sediments / Unknown

1) soil cleanup left resid contam > indust D.C, so cleanup incl deed restr We'd be OK w/ recording subsequent affidavit that would allow public use ⇒ mitigation of DC pathway is what we need.

2) Sediment issues NRT ⇒ what are pathways we're trying to address?

L.P. - whole fish data from N. Twin Lk shows no risk

B.F. - Risk assessment pathway followed previously showed risk (eco & potential human health)

- stuck on cap vs mass removal

- Public $ to complete cleanups

* - Can we sample seds at "bowl" at outlet of N. Twin Lake?

- CM Christiansen Co. owns only the Pole Yard; other properties owned by other

Christiansen entities

- Next steps
  - Town is interested in acquisition, working w/ CMC Co Inc, et. al
  - their interest might ramp up level of interest from DNR
  - J.R. Thomas suggested moving towards negotiated agreement
    - Eric C would be interested if it spells out endpoint & future liabilities
- Proposed technical mtg in near future
  - Outcome of tech mtg could be term sheet for sed agreement. This could be rolled into negotiated agreement
- Town needs response back by early November / basically need us (CMC & DNR)

CM Christiansen Meeting

Friday, August 15, 2013

Agenda

Welcome and Introductions

Agenda Repair

Overview of past work

Current status

Applicable regulatory standards

Remedial options

Next steps

Issues of interest to the Town of Phelps

CORRESPONDENCE/MEMORANDUM

State of Wisconsin

DATE: September 26, 2013 FILE REF:

TO: Pat Stevens – AD/8
Mark Giesfeldt – RR/5

FROM: Chris Saari – Ashland

SUBJECT: C.M. Christiansen Co. Contaminated Sediment Issues, Town of Phelps, Vilas County

The following is intended to provide context for a possible case discussion on September 26th. I apologize for my lack of brevity, but this is a rather complicated site.

Background:

- The C.M. Christiansen Co. operated a wood treatment facility on the outskirts of Phelps from 1954 until 1981, treating power poles with a 5% pentachlorophenol (PCP) solution.
- The facility was located adjacent to Military Creek, which is a Class 1 trout stream. Military Creek drains into North Twin Lake approximately 1,200 feet downstream of the site. North Twin Lake is classified as an Outstanding Resource Water under s. NR 102.10(1m), Wis. Adm. Code.
- DNR performed a Superfund Preliminary Assessment/Site Inspection at the site in 1993 and identified soil, groundwater and sediment contamination. Soil and groundwater contaminants were mainly PCP and polynuclear aromatic hydrocarbons (PAH). The main contaminants of concern in the sediments are dioxins/furans, which are known byproducts formed during the manufacturing of PCP.
- The RP conducted a site investigation of soil and groundwater impacts between 1995 and 1998.
- In April 1998, the RP entered into a Spill Response Agreement with DNR under s. 292.11(7)(d), Wis. Stats. This agreement spelled out the RP's responsibilities to complete the site investigation and implement remedial actions to address the contamination in soil, groundwater and sediments.
- A remedial action to address soil contamination (excavation and off-site disposal) was completed in 1999. Post-remedial monitoring suggests that groundwater contaminants are attenuating.
- DNR performed a Superfund Expanded Site Inspection in 2003 to further delineate groundwater and sediment impacts.
- Between 2004 and 2010, DNR and the RP met on several occasions to try to negotiate a mutually acceptable remedy for the sediment impacts. The RP believes that the sediment contamination is stable and not causing harm and should be left alone, or perhaps capped in place.
- The RP has claimed limited funds are available to complete the sediment investigation and cleanup. It should be noted that all sediment, surface water and toxicity sampling conducted to date has been completed at DNR's expense.
- The sediment data collected to date indicates that sediment concentrations exceed Probable Effects Concentrations from DNR's Consensus Based Sediment Quality Guidelines. Furthermore, limited toxicity testing indicates ecological affects are likely from the sediments. However, it also appears that the extent of impacts is relatively limited (at least in comparison to other sediment sites).
- The RP's consultant (Natural Resource Technology or NRT) was working through a risk assessment approach in 2010 when DNR suggested that rather than spending the RP's limited funds on risk assessment, that money could be spent removing the relatively small volume of contaminated sediments. NRT responded by providing a conceptual plan for limited removal and no post-remedial monitoring. DNR and the RP traded comments on the matter through 2010.

Current Status:

- The Town of Phelps approached DNR in 2012 about the possibility of acquiring the site. The Town hopes to use the property as a trailhead for the regional bicycle and snowmobile trail systems.
- Acquisition is planned via tax foreclosure, with the Town taking advantage of the Local Governmental Unit exemption in s. 292.11(9), Wis. Stats. Proceedings could begin as soon as this month. The Town has also been negotiating with the RP about acquiring (through donation and/or purchase) other, non-site properties within the Town to assist with potential development opportunities in the Town.
- DNR met with the RP and the Town Board in July and August 2013 in an attempt to identify outstanding issues and to come to an agreement on how to address the sediment contamination.
- DNR will be meeting with the RP and NRT on September 27th to discuss technical issues related to the sediment contamination and options for a path forward.

Outstanding Issues:

- The RP has technically been out of compliance with the sediment portion of the Spill Response Agreement since late 1998. However, DNR has pursued cooperation rather than enforcement to try to reach an acceptable outcome.
- DNR offered our ability to pay process to the RP to confirm the alleged lack of funds. However, because the RP is a corporation, the ability to pay determination would need to go through the Department of Justice, and the RP was not interested in pursuing that option.
- As mentioned above, DNR proposed a sediment removal approach in 2010 in lieu of a risk assessment, as a more productive use of the RP's funds. The counterproposal from NRT was deemed by DNR to be unacceptable, and we have essentially been in a stalemate since that time.
- During both of the previously mentioned July and August meetings, one of the Town Board members has rather forcefully asked about the potential for sediment contamination in North Twin Lake. To date, no sediment samples have been collected in the lake, and very limited fish data has been inconclusive in terms of impacts to the resource.
- During an internal DNR discussion on September 25th, we agreed that our current approach is not working. In an effort to accommodate the RP's limited funding claims and desire for closure certainty, we have tried to bend our code requirements and policies to fit an incomplete investigation into a compromised cleanup plan.

Proposed Approach:

- The NOR Region RR program, NOR Waters program and central office sediment staff feel that the best approach at this point is to ask the RP to prove their claims that the sediment contamination poses little or no risk in its current condition. This will involve completing the investigation (as required by the Spill Response Agreement) and going ahead with the risk assessment approach that NRT had proposed prior to 2010. This is obviously a change from what we have been asking for over the past 3+ years.
- This change in approach might also complicate the Town of Phelps' plans to acquire the property and open it up for public use. However, this proposed change in use from closed industrial to open public land plays a large part in our thinking that a full characterization is needed here.

cc: John Robinson – Wausau

State of Wisconsin \ DEPARTMENT OF NATURAL RESOURCES

North Central District Headquarters
Box 818
Rhinelander, Wisconsin 54501
(715)362-7616

Carroll D. Besadny
Secretary

September 25, 1987

Mr. Philip Christensen
C. M. Christensen Company
Lake Street
Phelps, Wisconsin 54554

Dear Mr. Christensen:

On August 25, 1987, I had an opportunity to meet with Don Grass as it relates to the old pole dipping operation in Phelps. The purpose of my visit was to first look at the waste chemicals that were involved in a breakin earlier this summer. Upon reviewing the site, it appears that all the chemicals have been removed and were in the possession of Mr. Grass. Upon reviewing the information available, it is possible that these materials may be hazardous as defined by both State and Federal regulations. You are required under State law to determine if the material is hazardous. If so, the material will have to be properly disposed of. I have enclosed a list of such facilities for your information.

The second area of concern centered on the dipping operaton at the old pole plant. Upon reviewing the site, I found areas where the smell of diesel fuel could still be noted in the soil, as well as penta sludge on the ground in the areas of the old dip tank.

Wisconsin's hazardous waste and groundwater laws do regulate operations which may or have discharged materials which may cause environmental problems. Recently, we have had a number of situations where pentachlorophenol from dipping operations have caused substantial environmental problems. Because of the potential for problems at this site, as well as the observed materials, I am requesting that you contact a consultant firm to do an in-field conditions report to determine what impacts this operation may have had on the groundwater and wetlands at this facility.

Such an investigation would include groundwater monitoring, soil samples and other related activities to determine what materials are present and their impacts on the environment. I am requesting that you inform the Department within 14 days as of the date of this letter of your intentions. A draft scope of work should be submitted within 60 days.

If you have any questions concerning this matter, please do not hesitate in contacting me at the District Office, (715)362-7616.

Sincerely,

Gary Kulibert
District Solid Waste Coordinator

GK:da
Enc.
cc: Bureau of Solid Waste, SW/3
D. K. Tyler, Woodruff
Vilas County Sheriff's Dept., Courthouse, Eagle River, WI 54521

C.M.CHRISTIANSEN CO.

MANUFACTURERS & DISTRIBUTORS
(715)545-2333
• VILAS COUNTY •

PHELPS • WISCONSIN 54554

C.M. CHRISTIANSEN, FOUNDER
K.K. CHRISTIANSEN, PRESIDENT
P.C. CHRISTIANSEN, VICE PRES. & GEN. MGR.
M.M. SAUCKE, SECRETARY &
[redacted], TREASURER

October 1, 1987

Mr. Gary Kulibert
District Solid Waste Coordinator
STATE OF WISCONSIN
Department of Natural Resources
North Central District Headquarters
Box 818
Rhinelander, WI. 54501

Dear Mr. Kulibert:

In prompt reply to your letter dated September 25, 1987, my comments are as follows:

1) We began pole treating in 1954.

2) We treated our last poles in 1978. We have been out of the treating business since that time.

3) The minimal inventory of chemicals for analysis on hand (now in Mr. Crass' home basement is as follows:

   1½ lbs $Ca(OH)_2$ KNO_3 mix (white powder)
   3/4 Quart $AGNO_3$ (liquid)
   1/6 Pint VOLHARD indicator

   How do we dispose of all? (We need none of it!)

4) Who were the children that broke into our locked building (where the chemicals were stored), and what disposition has been made (or will be made) regarding this illegal entry? What is our legal recourse?

5) You neglected to enclose (first paragraph of your letter) "a list of such facilities".

6) Please note enclosed copy of a letter out of your office dated October 4, 1973, signed by Mr Morehouse, Waters Management Investigator, which was our "Bible" until we closed shop (copy sent to your Woodruff Office).

Some few years ago we responded to a State questionnaire regarding our treating operation here. I believe we were (and had been) inoperative for a number of years then. The single and only reason we discontinued treating operations was owing to our

1) Inability to obtain Western Red Cedar poles for the power transmission industry and
2) No demand for telephone poles (they went undergroung) and
3) The general poor business climate - lack of demand for power transmission poles (also increased usage of underground cable, etc.)
4) Finally, our Pole Division Manager of many years retired. That was it!

Fortunately, it seems, we got out of the business, one way or another. I am indeed sorry fine businesses must fold at some point in time, but we made room for the Cable industry. Unfortunately, we cannot manufacture cable in Phelps, Vilas County, or do you have some connections?

Under the foregoing circumstances, I don't feel we need to be obligated to go to all the expense of what you might have thought necessary. We have done what was requested and were given assurances we were not derelict.

Respectfully submitted,

C. M. CHRISTIANSEN CO.

P. C. Christiansen,
President & Chief Executive Officer

PCC/ms

Encl: Copy of Morehouse Letter of 10/4/73, File No. 3530

No copies to anyone in your department!

P.S. I will not authorize the payment for a long-dead horse, especially one who was good for many years to a number of local families!

P.C.C.

State of Wisconsin \ DEPARTMENT OF NATURAL RESOURCES

L. P. Voigt
Secretary

North Central District Headquarters
Box 818
Rhinelander, Wisconsin 54501

IN REPLY REFER TO: 3530

October 4, 1973

C. M. Christensen Company
Phelps
Wisconsin 54554

Attention: Mr. Donald Crass, Pole Yard Manager

Gentlemen:

This is in confirmation of our discussion with Mr. Crass at the pole yard at Phelps, Wisconsin, relative to treated poles and the possibility of it leaching into adjacent Mill Creek. We were able to determine that the poles are treated by being submerged in a large tank, after which they are removed and stacked to dry along the side of the tank and on the adjacent area. There appears to be a slope of 15 degrees toward Mill Creek and heavy rains could wash residue from the poles into the creek. Our examination, however, found no heavy concentration of this residue as evidenced by the vegetation in the area.

It appears that there is no problem at the present time and that no material does actually reach the creek. We do urge caution and extreme care in this operation, not only to prevent a future problem here, but also to insure protection for Mill Creek. We know of your interest in the waters of the Phelps area and we do appreciate your cooperation in future protective measures that you may employ to reduce the possibility of any contamination of the creek.

Very truly yours,

L. E. Morehouse

L. E. Morehouse
Waters Management Investigator

LEM:ab
cc: Ed Brick
District Headquarters
Area Office - Woodruff

State of Wisconsin \ DEPARTMENT OF NATURAL RESOURCES

North Central District Headquarters
Box 818
Rhinelander, Wisconsin 54501
(715)362-7616

Carroll D. Besadny
Secretary

November 3, 1987

4400

Mr. C. P. Christiansen
President & Chief Executive Officer
C. M. Christiansen Company
Phelps, Wisconsin 54554

Dear Mr. Christiansen:

I received your October 1, 1987, response to my September 25, 1987, letter concerning the old pole plant. Enclosed is a list of companies that handle analysis, transportation, packaging and proper disposal of hazardous waste. As I stated in my original letter, you as a generator are required under state and federal laws to properly insure this material is handled. The people enclosed are licensed by the State of Wisconsin and should be able to provide you with the necessary services.

In answer to your question about the children that broke into your locked building, I would advise you to contact Vilas County Sheriff's Department. They are the individuals who are doing that investigation.

As for my concerns about the old pole dipping operation, as I stated in my earlier letter, you and your company have responsibilities and obligations under state law to carry out an environmental investigation on this property. Should you choose not to do the investigation as you indicated in your letter, I will be advising my staff to begin either developing an administrative order requiring the investigation or the placing of this site on the CERC list for Superfund investigation. Please be advised that the State or U.S. EPA can conduct an investigation of this property. We have the obligation and statutory authority to seek reimbursement of cost for our time and the funds spent.

If you have any other questions concerning this subject or we can advise you in anyway, please feel free to contact us at our District Office, (715)362-7616.

Sincerely,

Gary F. Kulibert
District Solid Waste Coordinator

GFK:da
Enc.
cc: Paul Didier, SW/3
D. Tyler, Woodruff

WISCONSIN
DEPT. OF NATURAL RESOURCES
George E. Meyer
Secretary

State of Wisconsin \ DEPARTMENT OF NATURAL RESOURCES

North Central District Headquarters
Box 818
Rhinelander, Wisconsin 54501
TELEPHONE 715-369-8900
TELEFAX 715-369-8932

August 16, 1994

IN REPLY REFER TO: 4190
CASETRACK# 94-NCEE-141

CERTIFIED MAIL

Mr. Phil Christiansen
1 Lake Street - County Hwy. E
P.O. Box 100
Phelps, WI 54554

SUBJECT: NOTICE OF VIOLATION AND ENFORCEMENT CONFERENCE

Dear Mr. Christiansen:

This notice is to advise you that the Department of Natural Resources (Department) has reason to believe that you may be in violation of Wisconsin's solid and hazardous waste and spill regulations at your property located in Townships 41 and 42 North-Range 11 East.

The Department conducted a Site Inspection in the area of the old wood treating site on September 29, 1993. Results showed that hazardous substances were found in the soils, the sediments and surface water of Military Creek and groundwater.

Also, an investigation was conducted on a complaint that the disposal of 25+ drums occurred on the C.M. Christiansen/Sylvan Products Company site. During an interview with you, by Mr. Randy Falstad of the Department on May 26, 1993, you admitted to directing the disposal of 30 drums and are aware of the location of the buried drums.

The Department also has a concern that other miscellaneous items were buried on your property in violation of waste disposal regulations.

Based on the information stated above the Department believes that you are in violation of hazardous substance spill and waste disposal regulations.

Under Wisconsin law, the Department is responsible for enforcing statutes and administrative rules relating to the reporting and remediation of hazardous substance spills or discharges under s. 144.76, Stats., and to the disposal of hazardous waste under s. 144.60 to 144.70, Stats. Persons who may be responsible for such hazardous substance spills or for hazardous waste disposal should know their responsibilities under the law and act accordingly.

Section 144.76(3), Stats., states that "A person who possesses or controls a hazardous substance which is discharged or who causes the discharge of a hazardous substance shall take the actions necessary to restore the environment to the extent practicable and minimize the harmful effects from the discharge to the air, lands, or waters of the state."

The Department believes that you are responsible for restoring the environment at this site under s. 144.76, Stats. This includes first investigating the extent of the contamination, then selecting and implementing the most appropriate remedial action. Wisconsin Administrative Codes NR 700 through 728 establish requirements for interim actions, public information, site investigations, design and operation of remedial action systems, and case closure. Wisconsin Administrative Code NR 140 establishes groundwater standards. To ensure that your investigation and cleanup actions comply with Wisconsin's regulations, you should hire a professional environmental consultant who understands what needs to be done.

The Department is authorized to seek injunctive or other appropriate relief for violations of Wisconsin's hazardous substance laws, including forfeitures of no more than $5000.00 for each violation, pursuant to s. 144.99, Stats. Each day of continued violation is a separate offense.

The Department requests that you attend an enforcement conference to discuss this notice. Please be prepared at the conference to discuss your plans for coming into compliance with the hazardous substance and waste disposal regulations. The conference has been scheduled for the following day:

TIME: 10:00 a.m.
DATE: August 29, 1994
PLACE: Department of Natural Resources
107 Sutliff Avenue
Rhinelander, WI. 54501

If you have any technical questions regarding the rules and regulations concerning this site, please contact Mr. Scott Watson at 715-369-8961. If you have any questions concerning this notice, please contact me at 715-369-8935.

Sincerely,
NORTH CENTRAL DISTRICT

Michelle DeBrock-Owens
Environmental Enforcement Specialist

cc: Enforcement File, Rhinelander
CASETRACK File, Rhinelander
Tom Jerow, Rhinelander
Scott Watson, Rhinelander
Gary Kulibert, Rhinelander
Linda Meyer, LC/5
Randy Falstad, Wausau

WISCONSIN
DEPT. OF NATURAL RESOURCES

State of Wisconsin \ DEPARTMENT OF NATURAL RESOURCES

Tommy G. Thompson, Governor
George E. Meyer, Secretary

101 S. Webster St.
Box 7921
Madison, Wisconsin 53707-7921
Telephone 608-266-2621
FAX 608-267-3579
TDD 608-267-6897

April 17, 1998

Elizabeth Gamsky Rich
Whyte, Hirschboeck, Dudek, S.C.
111 East Wisconsin Ave., Suite 2100
Milwaukee, WI 53202-4894

Subject: C.M. Christiansen Co., Inc. Spill Response Agreement

Dear Elizabeth:

I have enclosed one of the fully-executed duplicate originals of the above-referenced agreement. As I indicated in the voice-mail message that I left for you earlier today, the agreement became effective on April 17, 1998 when it was signed by DNR Secretary George Meyer.

The Department appreciates your client's willingness to sign this agreement and we look forward to working with you and your client as the agreement is implemented. Thank you.

Sincerely,

Linda Meyer

Linda Meyer
Staff Attorney
Bureau of Legal Services

cc: Michelle DeBrock Owens - NOR (Rhinelander)
——> Chris Saari - Brule

SPILL RESPONSE AGREEMENT

1. This Agreement is entered into pursuant to s. 292.11(7)(d), Wis. Stats., and shall be construed in a manner consistent with s. 292.11, Wis. Stats. The Department of Natural Resources ("the Department") and the C.M. Christiansen Company, Inc., a Michigan corporation ("CMC") hereby agree that CMC will conduct the activities listed below in compliance with the following schedule, except as provided in paragraph 2 of this agreement:

No	Activity	Compliance Date
1	Submittal to DNR of a Revised Source Control Soil Remedial Action Options Report, that complies with the requirements of s. NR 722.13, Wis. Adm. Code	Within 30 days after the effective date of this agreement
2	Submittal to DNR of an Update to Military Creek Sediment Sampling Plan, that complies with the relevant requirements of ss. NR 716.07, 716.09 and 716.13, Wis. Adm. Code	Within 30 days after the effective date of this agreement
3	Submittal to DNR of a Proposed Groundwater Monitoring Plan	Within 30 days after the effective date of this agreement
4	Military Creek Sampling Start	On or before May 30, 1998, unless an extension is granted by DNR because of adverse weather, or within 30 days after CMC receives DNR comments on the Updated Military Creek Sediment Sampling Plan, whichever is later

5	Submittal to DNR of Soil Remediation System Design that complies with the requirements of ss. NR 724.09 and 724.11 and the relevant requirements of 724.13, Wis. Adm. Code, and application for any permits, variances and other approvals required from DNR	Within 60 days after the effective date of this agreement
6	Start Soil Remedial Action Implementation, including free product removal	On or before the later of June 1, 1998, or within 30 days after CMC or its contractors receive all permits, variances and DNR approvals needed for soil remedial action implementation, including without limitation DNR approval of the Revised Source Control Soil Remedial Action Options Report, and System Design
7	Soil Remediation Construction Completion	Within 90 days after the start of soil remediation construction
8	Submittal to DNR of a Soil Remedial Construction Documentation Report, that complies with the requirements of s. NR 724.15, Wis. Adm. Code	Within 90 days after completion of soil remediation construction
9	Submittal to DNR of Military Creek Investigation Report, that complies with the requirements of s. NR 716.15, Wis. Adm. Code	Within 90 days after completion of the Military Creek sediment sampling

10	Submittal to DNR of a Military Creek Remedial Action Options Report (which may include an evaluation of institutional controls and other non-remedial actions, if appropriate) that complies with the requirements of s. NR 722.13, Wis. Adm. Code, if remediation action is necessary.	Within 60 days after CMC or its contractor receives DNR approval of the Military Creek Investigation Report
11	Implementation of Groundwater Monitoring Plan	In compliance with the schedule contained in the DNR-approved Groundwater Monitoring Plan

2. CMC will perform all of the work required under this agreement within the time limits set forth herein, unless the schedule is amended by mutual agreement of the parties or unless performance is delayed by events that constitute a "force majeure." The Department will not unreasonable refuse to amend the agreed-upon schedule if CMC submits credible evidence to the Department that new developments in the case require that the schedule be changed. For purposes of this agreement, a "force majeure" is an event arising from causes beyond the control of CMC or an entity controlled by CMC which delays or prevents performance of any work required by this agreement. Increases in cost or changes in economic circumstances do not by themselves constitute a force majeure. However, an event that would otherwise constitute a force majeure shall be deemed a force majeure even though such an event also results in increased costs or changed economic circumstances. CMC shall notify the Department in writing no later than ten (10) business days after CMC becomes aware of any event that CMC contends is a force majeure. If the Department agrees that a delay is attributable to a force majeure, the time period for performance under this agreement shall be extended by adding the time period attributable to the delay caused by the force majeure event to the deadlines specified in this agreement. Nothing in this agreement, including this force majeure provision is intended to expand any obligation which CMC may have pursuant to s. 292.11(3), Wis. Stats.

3. This agreement shall become effective on the date that it is signed by both CMC and the Department.

STATE OF WISCONSIN
DEPARTMENT OF NATURAL RESOURCES

By George R. Meyer, Secretary 4/17/98

C.M. CHRISTIANSEN CO., INC., a Michigan corporation

By _____
Printed Name: ERIC R. CHRISTIANSEN
Title: PRESIDENT

Use of Dioxin TEFs in Calculating Dioxin TEQs at CERCLA and RCRA Sites

May 2013

Purpose

This fact sheet provides information on the use of the 2005 World Health Organization (WHO) dioxin toxicity equivalence factors (TEFs) to calculate dioxin toxicity equivalence (TEQ) at Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and Resource Conservation and Recovery Act (RCRA) sites contaminated with dioxins, furans, and polychlorinated biphenyls (PCBs). The approach provided in this fact sheet is for use at newly evaluated sites as well as for re-evaluating sites that have been previously cleaned up or screened from further consideration.

Background

Dioxins are a group of compounds that share distinct chemical structures and characteristics. The term dioxin commonly refers to the compound in this group considered most toxic, 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD). Dioxin-like is a description used for compounds that have chemical structures, physico-chemical properties, and toxic responses similar to TCDD. Dioxin-like compounds (DLCs), including polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like polychlorinated biphenyls (PCBs), typically are found in mixtures with TCDD at CERCLA and RCRA sites and other contaminated properties. The EPA Toxics Release Inventory Program issued a final rule (EPA 2007) requiring that facilities report the released mass (grams) of individual DLCs in addition to reporting the released mass of TCDD.

The evaluation of TCDD and DLCs at CERCLA and RCRA sites includes consideration of the toxicity (i.e., cancer risks and non-cancer effects) of these contaminants. In the absence of toxicity values for DLCs, TEFs are used as a measure of the toxicity of the DLCs relative to TCDD. Concentrations of DLCs measured in media are modified by TEFs to determine the dose of each DLC in a medium that is equivalent to a dose of TCDD. The modified DLC doses are expressed in terms of TCDD toxicity equivalence (TEQ). The DLC TEQ concentrations are used, rather than the DLC concentrations measured in media, for site evaluations including site characterization, risk assessment, cleanup level development and confirmatory sampling.

The U.S. Environmental Protection Agency (EPA) Office of Research and Development released the *Recommended Toxicity Equivalence Factors (TEFs) for Human Health Risk Assessments of 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Dioxin-Like Compounds* (EPA 2010), recommending the use of the 2005 human and mammalian WHO TEF values for DLCs. For additional information on the use of the 2005 WHO TEFs at CERCLA and RCRA sites, refer to EPA's 2010 TEF document.

This document does not impose any requirements or obligations on EPA, the states, other federal agencies, or the regulated community. It is important to understand that this document does not

substitute for statutes that EPA administers or their implementing regulations, nor is it a regulation itself. Thus, this document does not impose legally binding requirements on EPA, the states, or the regulated community, and may not apply to a particular situation based upon the specific circumstances. Rather, the document provides information that may be used at particular sites, as appropriate, given site-specific circumstances.

Frequently Asked Questions

Q: What are toxicity equivalence factors (TEFs)?

A: 2,3,7,8-tetrachlorodibenzo-p-dioxin (or TCDD) and DLCs, including polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like polychlorinated biphenyls (PCBs), typically occur as mixtures in environmental media. The toxicity of DLCs can be addressed by considering their toxicity relative to TCDD. EPA recommends using updated TEFs to assess human health risks from exposure to dioxin-like compounds (EPA 2010). A TEF for a DLC is a measure of the compound's toxicity relative to TCDD, which is assigned a TEF of 1. For example, 1,2,3,4,7,8-hexachloro-dibenzo-*p*-dioxin is considered one tenth as toxic as TCDD and has therefore been given a TEF of 0.1.

Q: For which media are the TEFs used?

A: The TEFs are most appropriate for dioxin exposures via the oral exposure route. Generally, the ingestion pathway for TCDD drives risk CERCLA and RCRA assessments. The TEFs can be used for evaluating the risk posed by the ingestion of soil, sediments, water, and fish contaminated with TCDD and DLCs.

Q: What is the basis for using the TEF approach for DLCs?

A: The TEF approach is based on the concept of dose addition, under which it is assumed that the toxicokinetics and toxicodynamics for all DLCs are similar, and that the DLCs act by a common toxic mode of action (i.e., for all DLCs, effects are mediated through aryl hydrocarbon receptor binding). Further, this approach assumes that toxicological interactions do not occur among the DLCs within the environmental mixtures being assessed (e.g., synergism and antagonism do not occur).

Q: What is toxicity equivalence (TEQ)?

A: For a single DLC, dioxin toxicity equivalence (TCDD TEQ) is the product of the concentration of the DLC in an environmental mixture and its corresponding TEF; total TEQ for the mixture is the sum of the individual TCDD TEQs across the DLCs. The TCDD TEQ provides a means for determining the toxicity of a mixture of DLCs, in the absence of toxicity values for these DLCs.

The EPA's *Recommended Toxicity Equivalence Factors (TEFs) for Human Health Risk Assessments of 2,3,7,8- Tetrachlorodibenzo-p-dioxin and Dioxin-Like Compounds* (EPA

2010) provides a formula (reproduced below) for calculating the exposure concentration for *n* DLCs in a mixture, in TCDD TEQ. Exposure to the *ith* individual PCDD, PCDF, or PCB compound is expressed in terms of an equivalent exposure of TCDD by computing the product of the concentration of the individual compound (*Ci*) and its assigned *TEFi*. TEQ is then calculated by summing these products across the *n* DLCs present in the mixture.

$$TEQ = \sum_{i=1}^{n} (C_i \times TEF_i)$$

- C_i *Individual TCDD or DLC concentration in environmental media.*
- TEF_i *Toxicity Equivalence Factor assigned for TCDD or the DLC.*
- *TEQ* *TCDD toxicity equivalence.*

Sample calculation:

Using the 2005 WHO TEFs (Van den Berg et. al. 2006), the TEQ for each DLC is estimated by multiplying the measured DLC concentration by the TEF corresponding to the DLC. The TEQ for the media sample is determined by summing the individual TEQ for TCDD with DLCs in the mixture. For example:

Individual concentration of TCDD and DLCs in an environmental sample:
2,3,7,8 TCDD.....10 ppt (parts per trillion)
2,3,4,7,8- PeCDF .....30 ppt
PCB 126..... 20 ppt

TEFs:
2,3,7,8 TCDD.....1
2,3,4,7,8- PeCDF 0.5
PCB 126.....0.1

Individual TEQ:
2,3,7,8 TCDD.....10 ppt × 1 = 10 ppt TEQ
2,3,4,7,8- PeCDF .....30 ppt × 0.5 = 15 ppt TEQ
PCB 126.....20 ppt × 0.1 = 2 ppt TEQ

Total TEQ
10 ppt + 15 ppt + 2 ppt = 27 ppt TEQ

Q: For which exposure pathways are the TEFs used?

A: In addition to the ingestion pathway, the TEFs may be applied to other exposure routes (i.e., dermal or inhalation), as an estimate, assuming exposures to DLCs via these routes can be quantified. When included in an assessment, the fractional contribution of oral, dermal, and inhalation route exposures to the predicted TEQ should be identified.

In the absence of dermal toxicity values, a route-to-route (oral to dermal) extrapolation can be done using the oral toxicity value and adjusting for absorption through skin. This Office of Solid Waste and Emergency Response policy is described in Section 4.1 of the *Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment) Final* (EPA 2004). The availability of a dermal absorption factor for TCDD allows for the use of the TEFs in evaluating dermal exposure.

The EPA Integrated Risk Information System (IRIS) does not include toxicity values for estimating the risk posed by the inhalation of TCDD (either via particulates or volatiles). The EPA Regional Screening Tables (EPA 2012) provide dioxin soil screening levels for the inhalation pathway based on the California EPA reference concentration (RfC) and unit risk factor for TCDD. Inhalation risk based on particulate emissions from soil, estimated using the California EPA RfC for TCDD, shows that the contribution of the inhalation pathway compared to the ingestion pathway is well below 1%.

Q: Are dioxin TEFs applied in assessing both cancer risks and non-cancer health effects?

A: The EPA 2010 TEF document (EPA 2010) recommends that the TEFs be used for all effects mediated through aryl hydrocarbon receptor binding by the DLCs, including cancer and noncancer effects.

Q: How is the EPA 2010 report *Recommended Toxicity Equivalence Factors (TEFs) for Human Health Risk Assessments of 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Dioxin-Like Compounds* to be applied at CERCLA and RCRA sites?

A: The TEF approach has previously been used at CERCLA and RCRA sites. The EPA is now recommending the use of the 2005 human and mammalian WHO TEF values for DLCs, as discussed in the EPA 2010 TEF report (EPA 2010). This report provides updates to the 1998 WHO TEF values (Van den Berg et al 1998), based on a number of factors, including new toxicity values and the need to consider impurities in test compounds.

Some of the 2005 WHO TEFs have increased and some have decreased in value, compared to the 1998 WHO TEFs. The relative importance of the TEF changes largely depends on the mixture being evaluated. For example, the TEF for 2,3,4,7,8-pentachlorodibenzofuran was reduced from 0.5 to 0.3 and the TEF for PCB 169 increased from 0.01 to 0.03. See Attachment A for a comparison of the WHO 1998 and 2005 TEFs.

Underlying assumptions of the TEF method include: a) the toxicokinetics and the toxicodynamics of TCDD and DLCs are similar; b) the dose-response curves of TCDD and DLCs are similarly shaped; c) the aryl hydrocarbon receptor mediates most if not all of the biologic and toxic effects of the DLCs; and d) the kinetics and potency of various DLCs are generally similar between species (EPA 2000, EPA 2008). EPA recommends that risk assessors identify the fraction of the total TEQ attributable to TCDD (for which

uncertainty is relative low) and attributable to DLCs (for which uncertainty is somewhat higher).

Q: The EPA issued a report in 2010 on the use of dioxin TEFs for human health risk assessments. Does the Agency have information on the use of TEFs for ecological risk assessments?

A: Yes. In 2008, the EPA issued the *Framework for Application of the Toxicity Equivalence Methodology* for *Polychlorinated Dioxins, Furans, and Biphenyls in Ecological Risk Assessment* (EPA 2008).

Q: How are the dioxin TEFs used at PCB sites?

A: There are 209 PCB chemical compounds, or congeners; 12 of the 209 PCB congeners are considered dioxin-like. If dioxin-like PCBs are of concern at a PCB site, the PCB cleanup level will need to meet a site-specific dioxin TEQ cleanup level. In this case, two PCB cleanup levels are calculated. One cleanup level is calculated for total PCBs (i.e., for all PCB congeners present), based on toxicity values for total PCBs. The other PCB cleanup level is calculated so that it meets a site-specific dioxin TEQ cleanup level. This second PCB cleanup level depends on the TEQ (i.e., concentration x TEF) of dioxin-like PCBs in the PCB-contaminated media along with any TCDD and other DLCs present, and considers toxicity values for TCDD. The more stringent of the two PCB cleanup levels is selected.

For example, the PCB soil cleanup level that will meet a site-specific dioxin TEQ soil cleanup level can be calculated as:

$$PCB_{\text{cleanup level for TCDD/DLCs}} = PCB_{\text{soil concentration}} \times TEQ_{\text{cleanup level}} / TEQ_{\text{soil concentration}}$$

Where:

- $PCB_{\text{cleanup level for TCDD/DLCs}}$ — PCB soil cleanup level that meets the dioxin TEQ soil cleanup level.
- $PCB_{\text{soil concentration}}$ — Soil concentration of total PCBs.
- $TEQ_{\text{cleanup level}}$ — Dioxin TEQ soil cleanup level.
- $TEQ_{\text{soil concentration}}$ — Soil TEQ concentration of TCDD and DLCs, (i.e. other dioxins, furans and dioxin-like PCBs).

The PCB soil cleanup level that will meet a site-specific dioxin TEQ soil cleanup level is compared to the site-specific soil cleanup level for total PCBs to select the more stringent of the two, ensuring that the remedy will be protective for both PCB and dioxin-like PCB (along with any TCDD and other DLC) exposures.

The following is a sample calculation:

$$PCB_{\text{cleanup level for TCDD/DLCs}} = 5{,}000 \text{ ppt PCBs} \times 50 \text{ ppt TEQ} / 500 \text{ ppt TEQ}$$

$PCB_{\text{cleanup level for TCDD/DLCs}} = 500$ ppt PCBs

In this example, one tenth of the total PCB concentration is due to dioxin-like PCBs, as well as any TCDD and other DLCs present (i.e., the dioxin-like PCB TEQ concentration, along with any TCDD and other DCLs present, is 500 ppt TEQ). For a soil dioxin cleanup level of 50 ppt TEQ, the corresponding PCB soil cleanup level that would not exceed the soil dioxin cleanup level is 500 ppt PCBs.

Additional Resources

This fact sheet provides information on the use of the 2005 WHO TEFs to calculate TEQs at CERCLA and RCRA sites. Additional information on evaluating TCDD and DLCs at these sites can be found online at: http://epa.gov/superfund/health/contaminants/dioxin/dioxinsoil.html

Attachment A "Recommended Toxicity Equivalence Factors (TEFs) for Human Health Risk Assessments of Polychlorinated Dibenzo-p-dioxins, Dibenzofurans, and Dioxin-Like Polychlorinated Biphenyls" provides the 2005 updates to the 1998 WHO TEFs.

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ATTACHMENT A

Recommended Toxicity Equivalence Factors (TEFs) for Human Health Risk Assessment of Polychlorinated dibenzo-*p*-dioxins, Dibenzofurans, and Dioxin-Like Polychlorinated Biphenyls[1]

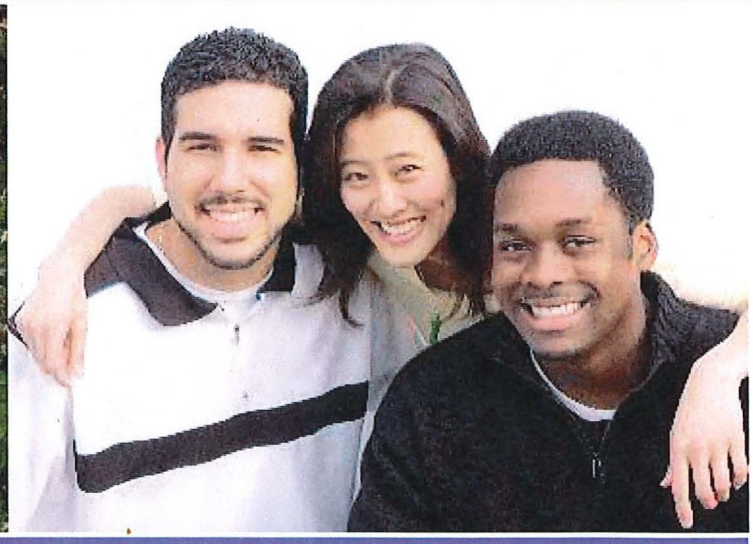
Compound	1998 TEF[2]	2005 TEF[3]
Polychlorinated dibenzo-*p*-dioxins (*PCDDs*)		
2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin (TCDD)	1	1
1,2,3,7,8-Pentachloro dibenzo-*p*-dioxin (PeCDD)	1	1
1,2,3,4,7,8-Hexachloro- dibenzo-*p*-dioxin (HxCDD)	0.1	0.1
1,2,3,6,7,8-Hexachloro- dibenzo-*p*-dioxin (HxCDD)	0.1	0.1
1,2,3,7,8,9-Hexachloro- dibenzo-*p*-dioxin (HxCDD)	0.1	0.1
1,2,3,7,8,9-Heptachloro- dibenzo-*p*-dioxin (HpCDD)	0.01	0.01
Octachloro-dibenzo-*p*-dioxin (OCDD)	**0.0001**	**0.0003**
Polychlorinated dibenzofurans (*PCDFs*)		
2,3,7,8-Tetrachlor-dibenzofuran (TCDF)	0.1	0.1
1,2,3,7,8-Pentachloro-dibenzofuran (PeCDF)	**0.05**	**0.03**
2,3,4,7,8-Pentachloro-dibenzofuran (PeCDF)	**0.5**	**0.3**
1,2,3,4,7,8-Hexachloro-dibenzofuran (HxCDF)	0.1	0.1
1,2,3,6,7,8-Hexachloro-dibenzofuran (HxCDF)	0.1	0.1
1,2,3,7,8,9-Hexachloro-dibenzofuran (HxCDF)	0.1	0.1
2,3,4,6,7,8-Hexachloro-dibenzofuran (HxCDF)	0.1	0.1
1,2,3,4,6,7,8-Heptachloro-dibenzofuran (HpCDF)	0.01	0.01
1,2,3,4,7,8,9-Heptachloro-dibenzofuran (HpCDF)	0.01	0.01
Octachloro-dibenzofuran (OCDF)	**0.0001**	**0.0003**
Polychlorinated biphenyls (*PCB* congener number)		
3,3',4,4'-Tetrachloro-biphenyl (77)	0.0001	0.0001
3,4,4',5-Tetrachloro-biphenyl (81)	**0.0001**	**0.0003**
3,3',4,4',5-Pentachloro-biphenyl (126)	0.1	0.1
3,3',4,4',5,5'-Hexachloro-biphenyl (169)	**0.01**	**0.03**
2,3,3',4,4'-Pentachloro-biphenyl (105)	**0.0001**	**0.00003**
2,3,4,4',5-Pentachloro-biphenyl (114)	**0.0005**	**0.00003**
2,3',4,4',5-Pentachloro-biphenyl (118)	**0.0001**	**0.00003**
2',3,4,4',5-Pentachloro-biphenyl (123)	**0.0001**	**0.00003**
2,3,3',4,4', 5-Hexachloro-biphenyl (156)	**0.0005**	**0.00003**
2,3,3',4,4',5'-Hexachloro-biphenyl (157)	**0.0005**	**0.00003**
2,3',4,4',5,5'-Hexachloro-biphenyl (167)	**0.00001**	**0.00003**
2,3,3',4,4',5,5'-Heptachloro-biphenyl (189)	**0.0001**	**0.00003**

[1] Numbers in bold indicate a change in TEF value.
[2] Source: van den Berg et al. (1998); available at: http://www.cerc.usgs.gov/pubs/center/pdfDocs/90970.pdf
[3] Source: van den Berg et al. (2006); WHO's Web site on dioxin TEFs, available at: http://www.who.int/ipcs/assessment/tef_update/en/

EPA
United States
Environmental Protection
Agency

EPA/100/R 10/005 | December 2010
www.epa.gov/osa

Recommended Toxicity Equivalence Factors (TEFs) for Human Health Risk Assessments of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Dioxin-Like Compounds



Office of the Science Advisor
Risk Assessment Forum

EPA/100/R-10/005
December 2010

Recommended Toxicity Equivalence Factors (TEFs) for Human Health Risk Assessments of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Dioxin-Like Compounds

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC 20460

NOTICE

This report has been subjected to the Agency's peer and administrative review and has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

ABSTRACT

This document describes the U.S. Environmental Protection Agency's (EPA's) updated approach for evaluating the human health risks from exposures to environmental media containing dioxin-like compounds (DLCs). 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and DLCs are structurally and toxicologically related halogenated aromatic hydrocarbons. The EPA recommends that the toxicity equivalence factor (TEF) methodology, a component mixture method, be used to evaluate human health risks posed by these mixtures, using TCDD as the index chemical. The EPA recommends the use of the consensus TEF values for TCDD and the DLCs published in 2005 by the World Health Organization. EPA Program Offices and Regions have historically used TEF values in their risk assessments; this document recommends the 2005 WHO consensus TEFs, but does not address specific risk assessment applications of TEFs. The EPA recommends these TEFs be used for all effects mediated through aryl hydrocarbon receptor binding by the DLCs including cancer and noncancer effects. Using information that summarizes the range of relative toxicities of the DLCs, the EPA recommends that, for major risk assessments as determined by U.S. EPA Program Offices or Regions, the conduct of a sensitivity analysis be considered to illustrate the impact the TEFs have on the toxicity equivalence (TEQ) value. The EPA will update all of these recommendations in the future based on the evaluation of new toxicity data for the DLCs, updates to available relative potency (ReP) data, including statistical summaries of RePs for individual DLCs, and the results of new consensus processes undertaken to update the TEF approach.

Preferred citation:
U.S. EPA (Environmental Protection Agency). (2010) Recommended Toxicity Equivalence Factors (TEFs) for Human Health Risk Assessments of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Dioxin-Like Compounds. Risk Assessment Forum, Washington, DC. EPA/600/R-10/005.

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LIST OF ABBREVIATIONS

AhR	aryl hydrocarbon receptor
DLC	dioxin-like compound
ECEH	European Centre for Environmental Health
ED_{50}	effective dose that causes an effect in 50% of the test units
IPCS	International Programme on Chemical Safety
NAS	National Academy of Science
ReP	relative potency or relative effect potency
ReP_{1997}	World Health Organization ReP database developed in 1997
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TEF	toxicity equivalence factor
TEQ	toxicity equivalence
EPA	U.S. Environmental Protection Agency
WHO	World Health Organization

LIST OF ABBREVIATIONS OF DIOXINS AND DIOXIN-LIKE COMPOUNDS

Polychlorinated biphenyls:

TCB	tetrachlorinated biphenyl
PeCB	pentachlorinated biphenyl
HxCB	hexachlorinated biphenyl
HpCB	heptachlorinated biphenyl
OCB	octachlorinated biphenyl
PCB	polychlorinated biphenyl

Polychlorinated dibenzo-p-dioxins:

TCDD	tetrachlorinated dibenzo-*p*-dioxin
PeCDD	pentachlorinated dibenzo-*p*-dioxin
HxCDD	hexachlorinated dibenzo-*p*-dioxin
HpCDD	heptachlorinated dibenzo-*p*-dioxin
OCDD	octachlorinated dibenzo-*p*-dioxin
PCDD	polychlorinated dibenzo-*p*-dioxin

Polychlorinated dibenzofurans:

TCDF	tetrachlorinated dibenzofuran
PeCDF	pentachlorinated dibenzofuran
HxCDF	hexachlorinated dibenzofuran
HpCDF	heptachlorinated dibenzofuran
OCDF	octachlorinated dibenzofuran
PCDF	polychlorinated dibenzofuran

KEY TERMS

Dioxin-like: A description used for compounds that have chemical structures, physico-chemical properties, and toxic responses similar to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Because of their hydrophobic nature and resistance towards metabolism, these chemicals persist and bioaccumulate in fatty tissues of animals and humans. Certain members of the dioxin, furan, and polychlorinated biphenyl (PCB) family are termed "dioxin-like" in this document and are assigned toxic equivalence factor (TEF) values.

Index Chemical: The chemical selected as the basis for standardization of toxicity of components in a mixture. The index chemical must have a clearly defined dose-response relationship. For dioxin like compounds (DLCs), TCDD is typically specified as the index chemical. (In some studies used to develop RePs, PCB_{126} has been used as the index chemical.)

Relative Potency (ReP): The ratio of the potency of a compound to the standard toxicant in that specific study; a concept similar to toxic equivalence but based on a single study, species, or matrix, etc., and not integrated with other RePs to obtain a general TEF.

Toxic Equivalence Factors (TEFs): TEFs are consensus estimates of compound-specific toxicity/potency relative to the toxicity/potency of an index chemical. TEFs are the result of expert scientific judgment using all of the available data and taking into account uncertainties in the available data.

Toxic Equivalence (TEQ): TEQ is the product of the concentration of an individual DLC in an environmental mixture and its corresponding TCDD TEF for that compound.

PREFACE

This document updates the U.S. Environmental Protection Agency's (EPA's) approach for evaluating the human health risks from exposures to environmental media containing 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and dioxin-like compounds (DLCs). It is intended for guidance only. It provides guidance to EPA Regional and Program Offices. EPA Program Offices and Regions have historically used TEF values in their risk assessments; this document recommends the 2005 WHO consensus TEFs, but does not address specific risk assessment applications of TEFs. It does not establish any substantive "rules" under the Administrative Procedure Act or any other law and will have no binding effect on EPA or any regulated entity. Rather, it represents a statement of current policy. The EPA's National Center for Environmental Assessment developed the initial draft of this document, which was then reviewed and completed by a Technical Panel under the auspices of EPA's Risk Assessment Forum. EPA made the document available for public comment during a 30 day public comment period in September 2009, and an expert peer-review panel discussed the document in a teleconference open to the public on October 22, 2009. The public comments received by EPA were provided to the peer-review panel members prior to the October 2009 teleconference for their consideration in making comments and recommendations to EPA. The peer-review report, and EPA response to comments, is available at http://www.epa.gov/raf/hhtefguidance/index.htm.

The Risk Assessment Forum was established to promote scientific consensus within EPA on difficult and controversial risk assessment issues and to ensure that this consensus is incorporated into appropriate risk assessment guidance. To accomplish this, the Risk Assessment Forum assembles experts from throughout EPA in a formal process to study and report on these issues from an Agency-wide perspective.

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INTRODUCTION

This document describes the U.S. Environmental Protection Agency's (EPA's) updated approach for evaluating the human health risks from exposures to environmental media containing 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and dioxin-like compounds (DLCs). TCDD and DLCs, including polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs), are structurally and toxicologically related halogenated dicyclic aromatic hydrocarbons.[1]

EPA's chemical mixtures guidelines and guidance documents (U.S. EPA, 1986, 2000) call for the use of whole mixture data or data on a sufficiently similar mixture as preferred risk assessment methods. However, when data are not sufficient to apply these methods, the EPA also recommends component-based approaches. In such situations, the EPA has recommended use of the Toxicity Equivalence Factor (TEF) Methodology and the World Health Organization's (WHO's) TEFs to evaluate the risks associated with exposure to mixtures of TCDD and DLCs for human health (U.S. EPA, 1987, 1989, 2003) and ecological risk assessments (U.S. EPA, 2008). The WHO has used a process based on consensus judgment of scientific expert panels to develop TEFs for mammals, birds, and fish and has re-evaluated them on a schedule of approximately every 5 years (Ahlborg et al., 1994; van den Berg et al., 1998, 2006; also see WHO's Web site for the dioxin TEFs, available at: http://www.who.int/ipcs/assessment/tef_update/en/). After evaluating the empirical data on TCDD and some DLCs, WHO reconfirmed that the combined effects of these compounds generally are consistent with dose additivity, a key underlying assumption of the TEF methodology (van den Berg et al., 2006). In this document, the EPA is updating its human health approach by adopting the mammalian TEFs for DLCs recommended in the WHO's 2005 reevaluation of TEFs for human exposures to DLCs (van den Berg et al., 2006). EPA Program Offices and Regions have historically used TEF values in their risk assessments; this document recommends the 2005 WHO consensus TEFs, but does not address specific risk assessment applications of TEFs.

[1]For further information on the chemical structures of these compounds, see U.S. EPA (2003, 2008).

THE TEF METHODOLOGY

This section briefly describes the TEF methodology, which is based on the concept of dose addition. Application of this methodology in human health risk assessment has been described and reaffirmed for use by the Agency in EPA's *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000). Under dose addition, the toxicokinetics and the toxicodynamics of all components are assumed to be similar and the dose-response curves of the components of a mixture are assumed to be similarly shaped.[2] Following these assumptions, the combined toxicity of the individual components can be estimated using the sum of their doses, which are scaled for potency relative to that of another component of the mixture for which adequate dose-response information is available (U.S. EPA, 2000).

In practice, the scaling factor for each DLC is typically based on a comparison of its toxic potency to that of a designated index chemical. For DLCs, TCDD is typically specified as the index chemical. However, the WHO 2005 (van den Berg et al., 2006) panel also used PCB_{126} as an index chemical for some DLCs in some studies used to develop relative potency estimates; the panel invoked transitivity, that is, by quantifying both the toxicity of a DLC relative to PCB_{126} and PCB_{126} to TCDD, the toxicity of the DLC relative to TCDD was estimated (RePs; Haws et al., 2006).[3] The index chemical is well-studied toxicologically and must have a dose-response function to apply the methodology to an environmental mixture. The

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[2] The TEF methodology has traditionally required that the dose response curves of the DLCs be parallel. In recent years, EPA's guidance documents on chemical mixtures risk assessment have moved away from the strict dose-response requirement of parallelism because of the variability inherent in showing such a phenomenon when dose-response data across mixture components are typically from different labs, different experimental designs or dose levels, and various strains, species, and genders of experimental animals. Further, it can be difficult to evaluate the shapes of dose response curves from experimental studies in the low dose region of interest in risk assessment. For the EPA's relative potency factor method, which is based on dose-addition, only similarly shaped dose response curves are required (satisfied, for example, by modeling the mixture components using the same dose-response functional form, or grouping chemicals by common slope parameters or by a common maximum effect) and may be limited to a range of exposure conditions, including dose level, frequency and route (U.S. EPA, 2000, 2002).

[3] For some compounds in some toxicity studies, the WHO panel compared the toxicity of DLCs to that of PCB_{126} during their development of estimates of RePs (Haws et al., 2006). When developing RePs based on comparing effects of DLCs to those of PCB_{126}, the WHO panel invoked transitivity; that is, by quantifying both the toxicity of a DLC relative to PCB_{126} and PCB_{126} to TCDD, one could estimate the toxicity of the DLC relative to TCDD. Given the TEF for PCB_{126} was 0.1, WHO (2005) multiplied the PCB_{126}-based ReP by 0.1. Based on Hawes et al. (2006), a total 114 RePs were developed for the mono-ortho PCBs in the TEF database. PCB126 served as the index chemical for 29 (25.4%) of these. For the nonortho-PCBs in the same database, if PCB126 is excluded from the nonortho PCBs in the TEF database, then PCB126 served as the index chemical for 18 of 91 (20%) of the RePs.

toxicological data considered for these comparisons of toxic potency are from both in vitro and in vivo studies as well as structure-activity relationships and are based on the following classes of measure: biochemical changes, toxicity, and carcinogenicity. A comparative measure from an individual toxicity assay is termed an estimate of relative potency (ReP).[4] Based on the RePs that may be estimated from multiple toxicological assays, each individual PCDD, PCDF, and PCB is assigned a single scaling factor termed the TEF. By definition, the TEF for TCDD is 1.0; when PCB_{126} serves as an index chemical the value of its TEF is 0.1 (U.S. EPA, 1989, 2000, 2003, 2008; van den Berg et al., 1998, 2006).

To apply TEFs to an environmental mixture of DLCs, each individual compound's exposure concentration is multiplied by its specific TEF, yielding the individual PCDD, PCDF, or PCB dose that is equivalent to a dose of the index chemical. These index chemical equivalent doses are then summed. To estimate risk associated with the mixture, the dose-response function for the index chemical is evaluated at this sum, which is an estimate of the total index chemical equivalent dose for the mixture components being considered.

Equation 1 is the formula for calculating exposure concentration for n DLCs in a mixture in TCDD toxic equivalence (TEQ). Exposure to the i^{th} individual PCDD, PCDF, or PCB compound is expressed in terms of an equivalent exposure of TCDD by computing the product of the concentration of the individual compound (C_i) and its assigned TEF_i. TEQ is then calculated by summing these products across the n DLC present in the mixture. For human health risk assessment, the TEQ may be evaluated using TCDD dose-response data and used to assess the risk posed by exposures to mixtures of TCDD and DLCs.

$$TEQ = \sum_{i=1}^{n} (C_i \times TEF_i) \qquad \text{(Eq. 1)}$$

[4]The term "relative effect potency" (ReP) also is used at times. This term is distinguished from the 'relative potency factors' (RPF) method, which is a general dose additive method described in U.S. EPA (2000). van den Berg et al. (2006) evaluated RePs based on biochemical and toxicological endpoints (also see related discussion in Haws et al., 2006).

BACKGROUND

There is a long history of the development of TEFs and the TEF methodology, dating back to the 1980s (see Table 1 for details). Early EPA documents recommended the use of the TEF approach for specific PCDDs and PCDFs for environmental risk assessment (U.S. EPA, 1987, 1989). The PCBs that displayed dioxin-like activity were added to the available TEFs for DLCs in 1994 (Ahlborg et al., 1994). Then, in 1997, consensus TEFs were assigned to the DLCs during a meeting held by the WHO (van den Berg et al., 1998); in 2003, EPA recommended the use of the 1997 WHO mammalian TEFs for human health risk assessment (U.S. EPA, 2003).

Besides the inherent assumption of dose additivity that underpins the TEF approach (i.e., the toxicokinetics and the toxicodynamics of all components are assumed to be similar and the dose-response curves of the components of a mixture are assumed to be similarly shaped), limitations in the available toxicity data for the DLCs resulted in a number of additional assumptions that were associated with this approach as implemented. These assumptions included:

- the Ah receptor mediates most if not all of the biologic and toxic effects of TCDD and the DLCs;
- the applicability of extrapolations from short-term bioassays to long-term health effects;
- similarities between interspecies kinetics and potency;
- appropriateness of high-dose to low-dose extrapolations; and
- the constancy of TEF relationships for different exposure routes, health endpoints, and dose levels

(U.S. EPA, 1989, 2000, 2003; see also Birnbaum and DeVito [1995] and Birnbaum [1999]).

Toxic effects of a DLC induced through mechanisms other than the Ah receptor are not accounted for in this method. Similarly, the TEF methodology does not account for the interactions of TCDD and DLCs with each other or with other chemicals to which individuals are exposed. (U.S. EPA [2000] defines the term "interaction" to refer to effects resulting from a mixture of chemicals that are greater than or less than those anticipated to occur as a

Table 1. Background and history of TEFs for risk assessment of DLCs

Publication	Description of historical context
OME, 1984	First to conclude that PCDDs and PCDFs share a common mechanism of action (activation of the AhR) and that a toxic equivalency approach should be used to compare equivalent group concentrations to TCDD.
U.S. EPA, 1986	EPA Guidelines for chemical mixtures risk assessment endorse EPA use of dose addition approaches for chemicals with the same mode of action.
Eadon et al., 1986	First to describe a TEF-like approach.
U.S. EPA, 1987	Recommends EPA use a TEF approach, applying it to specific PCDDs and PCDFs instead of to equivalent group concentrations.
NATO, 1988	Concludes TEF approach is the best available interim approach for PCDD/PCDF risk assessment. Presents an international TEF scheme.
U.S. EPA, 1989	EPA adopts the international TEF scheme developed by NATO (1988) for use in developing interim estimates of risk from exposure to PCDDs and PCDFs.
Barnes et al., 1991	EPA holds workshop. Guiding criteria for TEF approaches are developed. Concludes that PCBs displaying dioxin-like activity meet the criteria for inclusion in the TEF scheme.
Ahlborg et al., 1994	Develops first set of global consensus TEFs. Adds PCBs, including di-ortho congeners.
van den Berg et al., 1998	Develops second set of global consensus TEFs. Uses database compiled by the Karolinska Institute. Deletes di-ortho PCBs from the concept. Recognizes that TEFs for fish and birds need to be differentiated from humans. Acknowledges that in vivo results are more important than in vitro results.
U.S. EPA, 2000	Supplemental guidance for chemical mixtures risk assessment describes TEF and Relative Potency Factor methods. Endorses these for use by EPA.
U.S. EPA, 2003 (NAS Review draft)	This draft document recommends van den Berg et al. (1998) TEFs for EPA human health risk assessment. Provides details on historical development of TEFs.
Haws et al., 2006	Refines Karolinska Institute ReP database. Updates the literature. Deletes duplicate entries. Presents study exclusion criteria and deletes RePs based on studies not meeting the criteria. Presents statistical summaries of the RePs for each DLC.
van den Berg et al., 2006	Develops third set of global consensus TEFs. Uses Haws et al. (2006) database. Incorporates new literature including NTP (2006) study results. Holds stakeholder meeting at the beginning of the evaluation. Articulates shortcomings of the present TEF system. Identifies other potential compounds for inclusion in the TEF scheme.
NAS, 2006	Supports the use of the TEF approach by EPA to assess DLCs.
U.S. EPA, 2008	Recommends van den Berg et al. (2006) TEFs for EPA ecological risk assessments.
U.S. EPA, 2010 (this document)	Recommends van den Berg et al. (2006) TEFs for EPA human health risk assessments. Recommends the conduct of a sensitivity analysis be considered for major assessments as determined by U.S. EPA Regions or Program Offices.

AhR = aryl hydrocarbon receptor; NATO = North Atlantic Treaty Organization.

consequence of a specified definition of additivity, typically dose-addition or response addition.) To capture the uncertainty in these assumptions, all TEFs were provided as order-of-magnitude estimates, and the EPA described their application as a "useful interim approach" (U.S. EPA, 1989).

A set of guiding criteria were developed for TEF approaches (Barnes et al., 1991; U.S. EPA, 1991, 2000). These criteria included the development of TEFs through scientific consensus. The assignment of global consensus TEFs for the DLCs, including the dioxin-like PCBs, has been reevaluated as new data have become available (e.g., Ahlborg et al., 1994) and through consensus judgment of expert panels (e.g., WHO deliberations detailed in van den Berg et al., 1998, 2006). The TEF values published in van den Berg et al. (1998) were recommended for use by EPA in its National Academy of Science (NAS) review draft dioxin reassessment (U.S. EPA, 2003). In its review, NAS supported the use of the TEF approach (NAS, 2006, p. 8), stating that "Even with the inherent uncertainties, the committee concludes that the TEF methodology provides a reasonable, scientifically justifiable, and widely accepted method to estimate the relative potency of DLCs."

In 2005, a WHO expert panel updated TEF values for DLCs (van den Berg et al., 2006). They reaffirmed the characteristics necessary for inclusion of a compound in the WHO's TEF approach (van den Berg et al., 1998). These include:

- Structural similarity to polychlorinated dibenzo-*p*-dioxins or polychlorinated dibenzofurans;
- Capacity to bind to the aryl hydrocarbon receptor (AhR);
- Capacity to elicit AhR-mediated biochemical and toxic responses; and
- Persistence and accumulation in the food chain.

van den Berg et al. (2006) also reevaluated the support for assuming dose additivity and observing parallel dose-response curves. Evaluations of a number of studies of DLCs, including a mixture study from the National Toxicology Program that evaluated neoplastic and non-neoplastic endpoints (Walker et al., 2005), led the panel to state that the observed toxicity is consistent generally with these two assumptions underlying the TEF approach. In addition, the

NAS supported the use of an additivity assumption in its report on EPA's NAS review draft dioxin reassessment (U.S. EPA, 2003), concluding that "from an overall perspective, this assumption appears valid, at least in the context of risk assessment. Additivity in biochemical and toxic responses by the indicated DLCs has been supported by numerous controlled mixture studies in vitro and in vivo and is scientifically justifiable" (NAS, 2006, p. 80).

The TEF values were revised further by evaluating new toxicological data in conjunction with statistical summaries of available in vivo RePs formed using a mammalian ReP database (Haws et al., 2006). The database was comprised of ReP values from all identified studies that could yield an estimate of a ReP for a DLC; the RePs were not weighted according to study characteristics (e.g., in vivo, in vitro, chronic, acute, etc.). Haws and collaborators extended the original WHO ReP database, developed at the Karolinska Institute (ReP_{1997} database) in which some studies were represented more than once in the form of dissertations, conference proceedings, and/or peer-reviewed publications.[5] In the development of a refined ReP database, Haws et al. (2006) applied a set of study exclusion criteria to the ReP_{1997} database to identify RePs that likely provided "the most representative measure of a biological response." If a study met any of the exclusion criteria, the RePs derived from the study were not included in the quantitative analyses of all RePs. Haws et al. (2006) modified the ReP_{1997} database using the following exclusion criteria:

- Replicate RePs, when RePs from the same original study were presented in multiple publications.
- Multiple RePs from a single study that used different assays to measure the same response. In this case an effort was made to identify the single most representative ReP from a study.
- Study included only a single dose level of test and/or reference compound.
- Data omitted from the final peer-reviewed publication.

[5]The ReP_{1997} database was used in the WHO-European Centre for Environmental Health (ECEH)/International Programme on Chemical Safety (IPCS) TEF evaluation in 1997 and included not only published manuscripts, but also manuscripts in press, conference proceedings, theses, dissertations, and unpublished studies through June of 1997 that compared compounds to TCDD or PCB 126. Since the ReP_{1997} database was intended to be all inclusive, some studies are represented more than once in the form of dissertations, conference proceedings, and/or peer-reviewed publications.

- Authors indicated in the original publication that the ReP is not valid due to experimental problems.
- Data entry errors.
- ReP based on replicates in an in vitro study (average value calculated and retained).
- ReP based on non-AhR-mediated response.
- ReP based on nonmammalian species.
- Response for test or reference compound not statistically different from controls and not biologically meaningful.
- Reference compound (e.g., TCDD) not included in study or in identical study from the same laboratory.
- Multiple RePs derived from the same data using different calculation techniques.
- Multiple RePs reported for laboratory validation study (samples sent to two different labs for analysis and RePs calculated for both).
- Multiple RePs calculated based on different test conditions.
- RePs based on data at end of study and at end of some extended recovery period.
- ReP based on mixtures study.
- ReP from an unpublished study that could not be obtained.

The most recent WHO TEFs were developed using a refined approach. The WHO expert panel considered data from Haws et al. (2006) who present summary statistics of the RePs for each DLC, calculated from the assembled in vivo and in vitro studies that were not eliminated by the exclusion criteria. For each individual DLC, the WHO expert panel examined where the existing TEF value from van den Berg et al. (1998) fell within that DLC's in vivo ReP statistical summary developed in Haws et al. (2006). If it fell above the 75th percentile of the ReP statistical range, then they reviewed the basis of the 1998 TEF value, evaluated whether new data would impact the TEF and either confirmed the 1998 value or derived an updated TEF value. If it fell below the 75th percentile, the panel examined the database to identify the RePs having the most influence on the TEF value, evaluated the new data, and derived an updated TEF value (van den Berg et al., 2006). Because the ReP statistical ranges were unweighted relative to study type

and quality, the TEFs were determined using point estimates from toxicological studies, not by using specific points within the ReP ranges. A stepwise scale was used to assign the TEFs using half order of magnitude increments on a logarithmic scale (e.g., 0.03, 0.1, 0.3, etc.) instead of the increments used in previous efforts (e.g., 0.01, 0.05, 0.1, etc.), with uncertainty assumed to be at least ± half a log.[6]

[6]For example, the uncertainty for a TEF of 0.1 can be described as being within the interval of 0.03 and 0.3, and for a TEF value of 0.3, within an interval of 0.1 and 1. These estimates are generated by multiplying (dividing) the TEF value by half a log (i.e., 3.16).

UNCERTAINTIES IN THE TEF APPROACH

As is true for any risk assessment approach, uncertainties exist relative to data quality and evaluation, strength of biological rationale, and ability to determine whether the assumptions of the method being applied have been met. Application of the TEF approach to the human health risk assessment of DLCs carries with it some of these uncertainties which have been discussed in detail elsewhere in the literature. (For example, see discussions in Haws et al. [2006], NAS [2006], EPA [2000, 2003], and van den Berg et al. [1998, 2006].) The following uncertainties associated with application of the TEF approach are briefly described for the reader:

UNCERTAINTY IN TEF METHOD ASSUMPTIONS

- Dose additivity under the TEF method assumes a common mode of toxic action mediated through AhR binding and downstream biochemical and toxic responses. There is some evidence suggesting that some toxicities associated with some DLCs may be mediated through other ligands and processes (i.e., not mediated through the AhR). Effects mediated by other mechanisms (AhR independent) are not accounted for by the TEF method.

- Dose additivity under the TEF method assumes parallel dose-response curves. This is supported by some empirical data, but, in practice, parallelism is difficult to show for all DLCs and exposure scenarios, particularly in the low response region of most interest in environmental risk assessment.

- Dose additivity under the TEF method assumes that toxicological interactions are not occurring at environmental levels of the DLCs. Some data suggest that combined exposures of some DLCs may have antagonistic, rather than additive, effects; these could be species-specific. It may also be noted that joint toxic action of dioxins with non dioxin-like compounds could result in additive or nonadditive responses.

- Under the TEF method, the TEF of a DLC is assumed to be equivalent for all exposure scenarios, for all end points of concern, and all are full agonists. The ranges of RePs shown in the Haws et al. (2006) database demonstrate the uncertainty in this assumption as the ranges represent RePs from various study types and endpoints.

- Under the TEF method, it is assumed that RePs from animal studies are predictive of RePs in humans. However, the human AhR demonstrates some differences when compared to the AhR from experimental animal species.

UNCERTAINTY IN THE PROCESSES AND DATA USED TO DERIVE TEFs

- Expert scientific judgment, which depends on the knowledge and evaluations of the expert scientists involved, was used to select the DLCs included in the WHO TEF approach by evaluating experimental data against specific criteria (van den Berg et al., 2006). It may be noted that not all of the DLCs identified in releases from anthropogenic sources are included.

- Expert judgment and a consensus process were used to derive the WHO 2005 TEFs (van den Berg et al., 2006), including evaluation of information from the Haws et al. (2006) database.

- The kinds of information available for comparing the responses to individual DLCs to those of the index compound are highly variable across chemicals, including many types of and numbers of in vivo (including different test species) and in vitro studies. In addition, a number of different methods are employed to calculate REP values (Haws et al., 2006). (See additional discussions of this below under the section on Sensitivity Analysis Limitations.)

The uncertainty in TEQ estimates and in the TEF methodology accounts for only some of the overall uncertainty in a risk assessment of DLCs. TEQ uncertainty only pertains to the confidence associated with the estimation of TCDD equivalents in a mixture. There is also uncertainty associated with assessing exposures to environmental mixtures of TCDD and DLCs and with quantitatively linking health effects to the TCDD and DLC exposures. In addition, the value of a TEQ is highly dependent on the DLC exposure estimates used in the TEQ calculations.

RECOMMENDATIONS

When data on a whole mixture or a sufficiently similar mixture are not available for DLCs, the EPA recommends use of the WHO consensus mammalian TEF values from van den Berg et al. (2006) in the assessment of human health risks posed by exposure to mixtures of TCDD and DLCs, using TCDD as the index chemical. These TEFs are presented in Table 2. The TEF methodology is most applicable to situations where exposures are predominantly to mixtures of dioxins, furans and PCBs, and the goal of the assessment is to analyze the health risks posed by the mixture, not from exposure to individual compounds or single classes of compounds. Thus, other approaches may be considered when exposures are to single compounds or chemical classes.[7]

The EPA agrees with van den Berg et al. (2006) that the TEFs are most appropriate for dioxin exposures via the oral exposure route. The bioavailability of DLCs encountered through various sources of oral exposure needs to be evaluated in risk analyses. The TEFs may be applied to other exposure routes (i.e., dermal or inhalation), as an interim estimate or as a component of the sensitivity analysis, assuming exposures to DLCs via these routes can be quantified. Uncertainties associated with such applications should be identified. EPA recommends that, if considered in an assessment, the fractional contribution of oral, dermal, and inhalation route exposures to the predicted TEQ be identified.

TCDD and DLCs are associated with several different human health effects. Nearly all TCDD and DLC experimental data appear to be consistent with the hypothesis that binding to the AhR is the first step in a series of biochemical, cellular, and tissue changes that ultimately lead to toxic responses observed in both experimental animals and humans. The general basis for the TEF scheme is the assumption that the AhR mediates most if not all of the dioxin-like biological and toxic effects induced by compounds included in the WHO 2005 TEF approach (Safe, 1990; Okey et al., 1994; Birnbaum, 1994; Hankinson, 1995). Binding to the receptor

[7]For example, if the exposure is dominated by the single class of PCBs, then an alternative approach for evaluating human health risk might include use of the PCB cancer slope factors on Integrated Risk Information System (U.S. EPA, 1997). Also, when PCB exposures do not involve significant amounts of PCDDs and PCDFs, EPA (1996) provides another alternative methodology that might be useful for PCB mixture cancer dose-response assessment. However, in these cases, risks associated with other chemical exposures, i.e., not PCBs, would still need to be addressed.

Table 2. Recommended toxicity equivalence factors (TEFs) for human health risk assessment of polychlorinated dibenzo-*p*-dioxins, dibenzofurans, and dioxin-like polychlorinated biphenyls

Compound	TEF
Polychlorinated dibenzo-*p*-dioxins *(PCDDs)*	
2,3,7,8-TCDD	1
1,2,3,7,8-PeCDD	1
1,2,3,4,7,8-HxCDD	0.1
1,2,3,6,7,8-HxCDD	0.1
1,2,3,7,8,9-HxCDD	0.1
1,2,3,4,6,7,8-HpCDD	0.01
OCDD	0.0003
Polychlorinated dibenzofurans *(PCDFs)*	
2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDF	0.03
2,3,4,7,8-PeCDF	0.3
1,2,3,4,7,8-HxCDF	0.1
1,2,3,6,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDF	0.1
2,3,4,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,4,7,8,9-HpCDF	0.01
OCDF	0.0003
Polychlorinated biphenyls* *(PCBs)*	
3,3',4,4'-TCB (77)	0.0001
3,4,4',5-TCB (81)	0.0003
3,3',4,4',5-PeCB (126)	0.1
3,3',4,4',5,5'-HxCB (169)	0.03
2,3,3',4,4'-PeCB (105)	0.00003
2,3,4,4',5-PeCB (114)	0.00003
2,3',4,4',5-PeCB (118)	0.00003
2',3,4,4',5-PeCB (123)	0.00003

Table 2. Recommended toxicity equivalence factors (TEFs) for human health risk assessment of polychlorinated dibenzo-p-dioxins, dibenzofurans, and dioxin-like polychlorinated biphenyls (continued)

Compound	TEF
2,3,3',4,4', 5 -HXCB (156)	0.00003
2,3,3',4,4',5'-HxCB (157)	0.00003
2,3',4,4',5,5'-HxCB (167)	0.00003
2,3,3',4,4',5,5'-HpCB (189)	0.00003

*Note: TEFs that were previously assigned to PCB 170 and PCB 180 (Ahlborg et al., 1994) were withdrawn during the WHO-ECEH/IPCS TEF re-evaluation in 1997, and a TEF for PCB 81 was established, such that the number of PCB compounds with TEFs assigned was reduced from 13 to 12 (van den Berg et al., 1998). The numbers in parentheses following each PCB are the PCB congener numbers.

Source: van den Berg et al. (2006); WHO's Web site on dioxin TEFs, available at: http://www.who.int/ipcs/assessment/tef_update/en/.

appears to be necessary—but not sufficient—to generate the wide variety of toxic effects caused by dioxin-like halogenated aromatic hydrocarbons (Sewall and Lucier, 1995; DeVito and Birnbaum, 1995). In this document EPA assumes that all cancer and noncancer effects of TCDD and DLCs are AhR dependent. The EPA recommends these TEFs be used for all cancer and noncancer effects that appear to be mediated through AhR binding by the DLCs. EPA recognizes that this issue will require further evaluation as additional toxicity data become available. Eventually, endpoint-specific TEFs or separate TEFs for systemic toxicity and carcinogenicity endpoints may need to be developed.

van den Berg et al. (2006) also identified a number of candidate compounds that may need to be included in future developments of TEFs for DLCs:

- PCB 37
- Polybrominated dibenzo-*p*-dioxins and polybrominated dibenzofurans (PBDFs)
- Mixed halogenated dibenzo-*p*-dioxins and mixed halogenated dibenzofurans
- Hexachlorobenzene

- Polychlorinated naphthalenes and polybrominated naphthalenes
- Polybrominated biphenyls

EPA will consider an update of the recommendations in this document when TEFs for these candidate compounds are developed. At a minimum, if occurrence or exposure data are available for these candidate compounds, this information should be included as part of a qualitative risk characterization.

For analytic transparency, the EPA recommends that the fraction of the TEQ attributable to each PCDD, PCDF, or PCB compound be identified in the risk characterization (Table 2 lists the DLCs considered to be members of PCDD, PCDF, or PCB groups.) Further, the contributions of each chemical class, i.e., the PCDDs, PCDFs, and dioxin-like PCBs, should also be identified. Alternatively, the analysis could examine 2,3,7,8-TCDD alone, all dioxin congeners, and the dioxin-like compounds (PCBs and PCDFs) in three separate analyses. The compounds and class(es) making the largest contributions to the TEQ should be specified as appropriate to the assessment (see example in Text Box 1). In addition, the implications of the fraction of the TEQ attributable to TCDD should be discussed in the analyses because the dose-response data for TCDD are used to evaluate risks, and the confidence in the risk estimate increases with increases in the fraction of the TEQ attributable to TCDD. Finally, if multiple routes are considered in an assessment, the fractional contribution of the compounds and class(es) to each exposure route to the predicted TEQ should be identified.

Text Box 1. Example Risk Characterization

U.S. EPA (2003) notes that the majority of the TEQ (based on van den Berg et al., 1998) from dietary exposures is typically associated with the concentrations of only five compounds (i.e., TCDD, 1,2,3,7,8-PCDD, 2,3,4,7,8-PeCDF, 1,2,3,6,7,8-HxCDD, PCB 126) whose ReP variability appears to be small relative to other compounds.* Thus, if dietary exposures are important to the assessment being conducted, the fraction of the TEQ attributable to these five compounds should be presented and discussed in the risk characterization.

*Note that the TEF for 2,3,4,7,8-PeCDF changed from 0.5 to 0.3 from van den Berg et al., 1998 to 2006, respectively.

SENSITIVITY ANALYSIS

The EPA recommends that, for major risk assessments, as determined by U.S. EPA Program Offices or Regions, the conduct of a sensitivity analysis be considered to illustrate the impact the TEFs have on the TEQ value, which is consistent with good risk assessment practices (U.S. EPA, 2000). While ideally a full quantitative uncertainty analysis is desirable, currently

available ReP data that could be used to characterize the distributions of the TEFs are not suitable for use in simulation procedures (e.g., a Monte Carlo analysis) that are typically undertaken. Characterization of the underlying statistical distributions of the ReP data would be needed as input to a quantitative uncertainty analysis; the true probability distributions of the TEFs are not known at this time. The limitations in both the underlying ReP data and in the ability to statistically analyze them preclude a detailed evaluation of the various sources of heterogeneity inherent in a quantitative analysis of uncertainty. However, insightful sensitivity analyses can be conducted using estimated ranges of the TEFs.

A TEF sensitivity analysis has at least two purposes: (1) to identify plausible upper and lower estimates of the TEQ to assess the potential range the TEQ may have, and (2) to identify the influence of TEF values for specific compounds on the TEQ. One quantitative approach for identifying upper and lower TEQ estimates is presented in Eq. 2 and 3 below for n compounds with TCDD represented by compound $i = 1$ (see discussion of limitations of this approach below).

$$TEQ_U = \sum_{i=1}^{n} (C_i \times TEF_{iU}) \qquad \text{(Eq. 2)}$$

$$TEQ_L = \sum_{i=1}^{n} (C_i \times TEF_{iL}) \qquad \text{(Eq. 3)}$$

where:

TEQ_U = upper estimate of TEQ range

TEQ_L = lower estimate of TEQ range

C_i = concentration of the ith individual compound

TEF_{iU} = upper estimate of the ith compound's TEF; for $I = 1$, $TEF_{IU} = 1$

TEF_{iL} = lower estimate of the ith compound's TEF; for $I = 1$, $TEF_{IL} = 1$.

For the TEQ_U and TEQ_L estimates that are generated using Eq. 2 and 3, the fraction of the TEQ attributable to TCDD and to each DLC should be identified.

EPA is aware of two possible data choices for identifying compound specific TEF_{iU} and TEF_{iL} values. First, van den Berg et al. (2006) state that the TEFs are assumed to have

uncertainty of at least ± half a log (i.e., 3.16); thus, multiplying and dividing the compound specific TEFs by 3.16 could provide estimates of TEF_{iU} and i, respectively.

Second, the EPA is aware that Haws et al. (2006) has summarized statistical descriptions of the ReP values. Although limited to the available ReP data (i.e., not necessarily an unbiased sample of equivalence factors), the ReP ranges developed by Haws et al. (2006) may provide another source of data for TEF_{iU} and TEF_{iL} values to use in Eq. 2 and 3. Tables 3 and 4 present specific percentiles of the Haws et al. (2006) statistical summaries for the RePs derived from in vivo data and combined in vitro and in vivo data, respectively. The values for TEF_{iU} and TEF_{iL}, for example, could be based on the minimum and maximum data, the 10^{th} and 90^{th} percentiles, or the interquartile ranges from either Tables 3 or 4. Over time, this set of ReP values is expected to change with the availability of additional relevant studies.

To identify the influence of specific compounds on the TEQ, EPA recommends that the list of compounds that are most influential to the TEQ, as defined in Eq. 1, be further explored. For each of these, the sensitivity of the TEQ to changes in the TEF values for the individual compounds may be conducted (i.e., varying the TEF value for one compound at a time). The same statistical ranges described above can be used to identify alternative TEF values.

SENSITIVITY ANALYSIS LIMITATIONS

The suggested summations of TEF_i times C_i should not be interpreted as upper or lower bounds on confidence limits for the TEQ. These calculations only provide crude estimates of the range of the TEQ, and they are useful for comparing the impact that the TEF_i have on the TEQ in a sensitivity analysis. A summation using a specific percentile does not result in an estimate of the same percentile of the TEQ, but would likely overestimate that percentile for upper bound estimates and likely underestimate that percentile for lower bound percentiles. Thus, an overestimation of the TEQ range will increase as higher (lower) TEF percentiles are used in the summation.

Issues with the assignment of the WHO 2005 TEFs (van den Berg et al., 2006) and the construction of the Haws et al. (2006) ReP database preclude the conduct of a quantitative uncertainty analysis and the calculation of confidence limits. Both of these issues may be important in interpreting the results of a sensitivity analysis. The WHO 2005 individual TEFs are not central tendency estimates of the available values (van den Berg et al., 2006), but instead

Table 3. Percentiles of in vivo ReP values

Congener	*n*	min	0.1	0.25	0.5	0.75	0.9	max	2005 TEF
1,2,3,4,6,7,8-HpCDD	12	0.001	0.004	0.007	0.01	0.01	0.02	0.04	0.01
1,2,3,4,6,7,8-HpCDF	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.01
1,2,3,4,7,8,9-HpCDF	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.01
1,2,3,4,7,8-HxCDD	15	0.008	0.03	0.05	0.06	0.09	0.1	0.4	0.1
1,2,3,4,7,8-HxCDF	6	0.01	0.03	0.04	0.05	0.07	0.1	0.2	0.1
1,2,3,6,7,8-HxCDD	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.1
1,2,3,6,7,8-HxCDF	11	0.003	0.01	0.02	0.08	0.09	0.1	0.2	0.1
1,2,3,7,8,9-HxCDD	1	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.1
1,2,3,7,8,9-HxCDF	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.1
1,2,3,7,8-PeCDD	36	0.04	0.1	0.2	0.4	0.6	0.8	2	1
1,2,3,7,8-PeCDF	20	0.003	0.009	0.01	0.02	0.08	0.1	1	0.03
2,3,4,6,7,8-HxCDF	3	0.02	0.02	0.02	0.02	0.06	0.08	0.1	0.1
2,3,4,7,8-PeCDF	82	0.007	0.05	0.1	0.2	0.3	0.7	4	0.3
OCDD	1	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003
OCDF	6	0.000004	0.00002	0.00004	0.00008	0.0006	0.001	0.002	0.0003
PCB105	16	0.0000005	0.000002	0.000009	0.00004	0.0001	0.001	0.002	0.00003
PCB114	2	0.0002	0.0002	0.0003	0.0003	0.0004	0.0004	0.0005	0.00003
PCB118	15	0.0000004	0.000002	0.000007	0.00002	0.00005	0.001	0.002	0.00003
PCB123	2	0.00003	0.00004	0.00004	0.00004	0.00005	0.0001	0.0001	0.00003
PCB126	86	0.0001	0.02	0.06	0.1	0.2	0.4	0.9	0.1

Table 3. Percentiles of in vivo ReP values (continued)

		Percentile							
Congener	***n***	**min**	**0.1**	**0.25**	**0.5**	**0.75**	**0.9**	**max**	**2005 TEF**
PCB156	16	0.000002	0.000005	0.00003	0.00006	0.0005	0.09	0.4	0.00003
PCB157	2	0.0004	0.0006	0.0007	0.001	0.001	0.002	0.002	0.00003
PCB167	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.00003
PCB169	15	0.000002	0.0004	0.003	0.02	0.2	0.6	0.7	0.03
PCB189	3	0.00004	0.00004	0.00005	0.00006	0.0001	0.0002	0.0002	0.00003
PCB77	16	0.000002	0.000006	0.00001	0.00006	0.0001	0.02	0.04	0.0001
PCB81		N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.0003
TCDF	17	0.006	0.008	0.01	0.03	0.1	0.3	0.5	0.1

Source: Haws et al. (2006) 2004 ReP Database, Figure A-4.

Table 4. Percentiles of combined in vivo and in vitro ReP values

		Percentile							
Compound	***n***	**min**	**0.1**	**0.25**	**0.5**	**0.75**	**0.9**	**max**	**2005 TEF**
1,2,3,4,6,7,8-HpCDD	18	0.001	0.004	0.01	0.01	0.03	0.04	0.1	0.01
1,2,3,4,6,7,8-HpCDF	2	0.02	0.05	0.1	0.2	0.2	0.3	0.3	0.01
1,2,3,4,7,8,9-HpCDF	2	0.02	0.02	0.02	0.03	0.04	0.04	0.04	0.01
1,2,3,4,7,8-HxCDD	21	0.01	0.04	0.05	0.08	0.1	0.4	0.6	0.1
1,2,3,4,7,8-HxCDF	13	0.01	0.04	0.04	0.07	0.3	0.5	4	0.1
1,2,3,6,7,8-HxCDD	5	0.03	0.03	0.04	0.04	0.06	0.1	0.2	0.1
1,2,3,6,7,8-HxCDF	18	0.003	0.01	0.03	0.07	0.1	0.1	0.2	0.1
1,2,3,7,8,9-HxCDD	6	0.01	0.02	0.03	0.05	0.06	0.07	0.07	0.1
1,2,3,7,8,9-HxCDF	2	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.1
1,2,3,7,8-PeCDD	45	0.04	0.1	0.2	0.4	0.6	0.8	2	1
1,2,3,7,8-PeCDF	28	0.003	0.01	0.01	0.05	0.1	0.1	1	0.03
2,3,4,6,7,8-HxCDF	10	0.01	0.01	0.04	0.2	0.3	0.3	0.3	0.1
2,3,4,7,8-PeCDF	99	0.01	0.05	0.1	0.2	0.5	1	4	0.3
OCDD	6	0.0003	0.0003	0.0003	0.0003	0.002	0.003	0.003	0.0003
OCDF	9	0.000004	0.00003	0.00004	0.001	0.002	0.002	0.003	0.0003
PCB105	26	0.0000005	0.000005	0.00001	0.0001	0.0003	0.002	0.07	0.00003
PCB114	8	0.0001	0.0002	0.0002	0.001	0.001	0.002	0.002	0.00003

Table 4. Percentiles of combined in vivo and in vitro ReP values (continued)

		Percentile							
Compound	***n***	**min**	**0.1**	**0.25**	**0.5**	**0.75**	**0.9**	**max**	**2005 TEF**
PCB118	25	0.0000004	0.000002	0.00001	0.00002	0.0005	0.002	0.08	0.00003
PCB123	6	0.000003	0.00001	0.00002	0.00004	0.0001	0.0004	0.0007	0.00003
PCB126	115	0.0001	0.01	0.05	0.1	0.2	0.4	0.9	0.1
PCB156	30	0.000002	0.00001	0.00004	0.0001	0.001	0.2	0.5	0.00003
PCB157	9	0.00004	0.0001	0.0001	0.0004	0.001	0.002	0.002	0.00003
PCB167	5	0.000002	0.000005	0.00001	0.00001	0.00001	0.0004	0.001	0.00003
PCB169	30	0.000002	0.0007	0.002	0.01	0.06	0.5	0.8	0.03
PCB189	5	0.000002	0.000005	0.00001	0.00004	0.00006	0.0001	0.0002	0.00003
PCB77	49	0.000002	0.00002	0.0001	0.001	0.02	0.1	0.5	0.0001
PCB81	12	0.00004	0.0006	0.004	0.01	0.01	0.02	0.05	0.0003
TCDF	30	0.01	0.01	0.03	0.08	0.2	0.3	0.6	0.1

Source: Haws et al. (2006) 2004 ReP Database, Figure A-2.

are assigned based on professional judgment using both information from the Haws et al. (2006) database and from the available toxicology data; thus, these TEFs cannot be evaluated using statistics relevant to a mean or median value.

Haws et al. (2006) discuss the limitations of the current ReP database for use in quantitative uncertainty analysis. The RePs were calculated using various approaches, ranging from comparing dose-response curves, to developing ratios of effective doses that cause an effect in 50% of the test units (ED_{50s}), to estimating values from graphs of dose-response data. The RePs also represent a wide variety of study types and endpoints, including biochemical changes, systemic toxicity and carcinogenicity; some of these data may provide estimates that are more consistent than others with individual PCDD, PCDF, or PCB compound toxicity at higher levels of biological organization and such considerations will need to be included in a risk characterization. Finally, Haws et al. (2006) note a number of issues associated with the dose-response data (e.g., nonparallel dose-response curves, differences in maximal response among PCDD, PCDF, or PCB compounds within a study, incomplete dose-response data due to insufficient dose levels). In addition, the number of RePs available varies widely across the congeners from $n = 2$ to $n = 115$ RePs. Thus, the Haws et al. (2006) database provides "statistical descriptions," not probability distributions, as the RePs in the database are not unbiased random samples of TEF values.

Although EPA recognizes the limitations associated with the use of the Haws et al. (2006) database in sensitivity analyses, EPA believes the benefits associated with the conduct of such an analysis outweigh the limitations. The development of a more refined ReP database and additional examination of the uncertainties inherent in a TEF process would improve TEF-based risk assessments.

CONCLUSIONS

When whole mixture data or data on a sufficiently similar mixture are not available for DLC exposures, the EPA recommends use of the consensus mammalian TEF values from van den Berg et al. (2006) in the assessment of human health risks posed by exposures to mixtures of TCDD and DLCs (see Table 2), using TCDD as the index chemical. EPA Program Offices and Regions have historically used TEF values in their risk assessments; this document recommends the 2005 WHO consensus TEFs, but does not address specific risk assessment applications of TEFs. Further, while ideally a full quantitative uncertainty analysis is desirable, currently available ReP data that could be used to characterize the distributions of the TEFs are not suitable for use in simulation procedures that are typically undertaken. Because limitations in both the underlying ReP data and in the ability to statistically analyze them preclude conduct of a full quantitative uncertainty analysis of the TEQs, the EPA recommends that conduct of a sensitivity analysis be considered when using TEFs in major risk assessments, as determined by EPA Program Offices or Regions. In conducting a TEF-based risk assessment the EPA suggests addressing the key risk characterization recommendations that have been discussed in this document and are summarized in Table 5. The EPA will update all of these recommendations in the future based on the evaluation of new toxicity data for the DLCs, updates to the ReP database including statistical summaries of RePs for individual DLCs, and the results of new consensus processes undertaken to update the TEF approach.

Table 5. Summary of risk characterization recommendations for TEF applications

1) Apply the TEF methodology to situations where exposures are predominantly to mixtures of dioxins, furans, and PCBs, and the goal of the assessment is to analyze the human health risks posed by the mixture.
2) Identify the fraction of the TEQ attributable to TCDD, each DLC, and to each chemical class, i.e., the PCDDs, PCDFs, and dioxin-like PCBs. Alternatively, the analysis of chemical classes could examine separately the contributions from 2,3,7,8-TCDD alone, all dioxin congeners, and the dioxin-like compounds (PCBs and PCDFs) to the TEQ.
3) When it is deemed appropriate to apply TEFs to a multiroute exposure as an interim approach, identify the fractional contributions of oral, dermal, and inhalation route exposures to the predicted TEQ. Within each route of exposure, identify the fractional contribution of each congener to the predicted TEQ and identify the fraction of the TEQ associated with each chemical class.
4) Address the implications of the identified fractional contributions to the TEQ for the risk assessment being conducted, in particular, their impacts on the overall confidence in the analytic results.
5) Include occurrence or exposure data, if available, for the following compounds as part of a qualitative risk characterization:
   - PCB 37
   - Polybrominated dibenzo-*p*-dioxins and polybrominated dibenzofurans
   - Mixed halogenated dibenzo-*p*-dioxins and mixed halogenated dibenzofurans
   - Hexachlorobenzene
   - Polychlorinated naphthalenes and polybrominated naphthalenes
   - Polybrominated biphenyls
6) For major risk assessments as determined by EPA Program Offices or Regions, EPA recommends the conduct of a sensitivity analysis be considered to characterize the impact of TEF variability on the TEQ.
   - For the TEQ_U and TEQ_L estimates that are generated, identify the fraction of the TEQ attributable to TCDD, each DLC and each chemical class.
   - Identify the TEF_i values that are most influential to changing the TEQ estimate.

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2005 Re-evaluation of human and mammalian toxic equivalency factors (TEFs)

Last reviewed/updated
16 November 2011

During the last assessment in 1997 at the WHO/IPCS expert consultation in Stockholm, it was agreed to re-evaluate TEF values on a regular basis, preferably at five-year intervals. Such a re-evaluation should be based on new scientific information published in the peer reviewed literature subsequent to the last expert consultation.

To follow this recommendation and to take account of a vast amount of new scientific studies, WHO organized an expert workshop to review and assess all new information and to recommend updated TEF values for dioxins, furans, and dioxin-like PCBs as appropriate.

An expert workshop was held on 28 to 30 June 2005 at WHO Headquarters in Geneva. Preceding the workshop on 27 June, was a Public Session, to give interested parties an opportunity to express their views on the subjects to be addressed in the workshop and for follow-up activities.

During the workshop, the expert group developed and applied a systematic decision scheme to review existing TEFs, using the WHO 98 TEF values (Van den Berg et al., EHP 106, 1998) and the recently published updated database of relative potencies (REP) (Haws et al., ToxSci 89, 4-30, 2006) as a starting point. Previous decisions of the 1997 expert consultation were reviewed in light of new data and of the distribution of REP values. For each congener, the decision scheme was applied and the 2005 TEF value derived and expressed as half-log increments. The decision taken for each congener is described in detail which significantly increases the transparency of the TEF derivation and allows for easier refinement should new data become available.

As a result, a number of TEF values have been changed, notably for PCBs, octachlorinated congeners and pentachlorinated furans.

In addition the expert group commented in detail on the application of the TEF concept and the possible inclusion of new compounds into this concept. Recommendations are given for future developments in this area.

The outcome of this expert consultation has been published as peer-reviewed article in the journal Toxicological Sciences:

The 2005 World Health Organization Re-evaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-like Compounds

Martin van den Berg, Linda S. Birnbaum, Michael Denison, Mike De Vito, William Farland, Mark Feeley, Heidelore Fiedler, Helen Hakansson, Annika Hanberg, Laurie Haws, Martin Rose, Stephen Safe, Dieter Schrenk, Chiharu Tohyama, Angelika Tritscher, Jouko Tuomisto, Mats Tysklind, Nigel Walker, and Richard E. Peterson

ToxSci Advance Access published 7 July 2006
pdf, 307kb
English

The final conclusion regarding the TEF values is summarized in the table below.

WHO advises that the new WHO 2005 TEF values are used from now as they replace the previous 1998 values.

Compound	WHO 1998 TEF	WHO 2005 TEF*
chlorinated dibenzo-p-dioxins		
2,3,7,8-TCDD	1	1
1,2,3,7,8-PeCDD	1	1
1,2,3,4,7,8-HxCDD	0.1	0.1
1,2,3,6,7,8-HxCDD	0.1	0.1
1,2,3,7,8,9-HxCDD	0.1	0.1
1,2,3,4,6,7,8-HpCDD	0.01	0.01
OCDD	0.0001	0.0003
chlorinated dibenzofurans		
2,3,7,8-TCDF	0.1	0.1
1,2,3,7,8-PeCDF	0.05	0.03
2,3,4,7,8-PeCDF	0.5	0.3
1,2,3,4,7,8-HxCDF	0.1	0.1
1,2,3,6,7,8-HxCDF	0.1	0.1
1,2,3,7,8,9-HxCDF	0.1	0.1

Compound	WHO 1998 TEF	WHO 2005 TEF*
2,3,4,6,7,8-HxCDF	0.1	0.1
1,2,3,4,6,7,8-HpCDF	0.01	0.01
1,2,3,4,7,8,9-HpCDF	0.01	0.01
OCDF	0.0001	0.0003
non-ortho substituted PCBs		
PCB 77	0.0001	0.0001
PCB 81	0.0001	0.0003
PCB 126	0.1	0.1
PCB 169	0.01	0.03
mono-ortho substituted PCBs		
105	0.0001	0.00003
114	0.0005	0.00003
118	0.0001	0.00003
123	0.0001	0.00003
156	0.0005	0.00003
157	0.0005	0.00003
167	0.00001	0.00003
189	0.0001	0.00003

Numbers in bold indicate a change in TEF value.

A PDF version of the above table is available below.

TEF values
pdf, 55kb

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May 2010

Key Facts

- Dioxins are a group of chemically-related compounds that are persistent environmental pollutants.
- Dioxins are found throughout the world in the environment and they accumulate in the food chain, mainly in the fatty tissue of animals.
- More than 90% of human exposure is through food, mainly meat and dairy products, fish and shellfish. Many national authorities have programmes in place to monitor the food supply.
- Dioxins are highly toxic and can cause reproductive and developmental problems, damage the immune system, interfere with hormones and also cause cancer.
- Due to the omnipresence of dioxins, all people have background exposure, which is not expected to affect human health. However, due to the highly toxic potential of this class of compounds, efforts need to be undertaken to reduce current background exposure.
- Prevention or reduction of human exposure is best done via source-directed measures, i.e. strict control of industrial processes to reduce formation of dioxins as much as possible.

Background

Dioxins are environmental pollutants. They have the dubious distinction of belonging to the "dirty dozen" - a group of dangerous chemicals known as persistent organic pollutants. Dioxins are of concern because of their highly toxic potential. Experiments have shown they affect a number of organs and systems. Once dioxins have entered the body, they endure a long time because of their chemical stability and their ability to be absorbed by fat tissue, where they are then stored in the body. Their half-life in the body is estimated to be seven to eleven years. In the environment, dioxins tend to accumulate in the food chain. The higher in the animal food chain one goes, the higher the concentration of dioxins.

The chemical name for dioxin is: *2,3,7,8- tetrachlorodibenzo para dioxin (TCDD).* The name "dioxins" is often used for the family of structurally and chemically related *polychlorinated dibenzo para dioxins (PCDDs)* and *polychlorinated dibenzofurans (PCDFs).* Certain dioxin-like polychlorinated

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Technical report: Evaluation of certain food additives and contaminants [pdf 911 kb]

biphenyls (PCBs) with similar toxic properties are also included under the term "dioxins". Some 419 types of dioxin-related compounds have been identified but only about 30 of these are considered to have significant toxicity, with TCDD being the most toxic.

Sources of dioxin contamination

Dioxins are mainly by products of industrial processes but can also result from natural processes, such as volcanic eruptions and forest fires. Dioxins are unwanted by products of a wide range of manufacturing processes including smelting, chlorine bleaching of paper pulp and the manufacturing of some herbicides and pesticides. In terms of dioxin release into the environment, uncontrolled waste incinerators (solid waste and hospital waste) are often the worst culprits, due to incomplete burning. Technology is available that allows for controlled waste incineration with low emissions.

Although formation of dioxins is local, environmental distribution is global. Dioxins are found throughout the world in the environment. The highest levels of these compounds are found in some soils, sediments and food, especially dairy products, meat, fish and shellfish. Very low levels are found in plants, water and air.

Extensive stores of PCB-based waste industrial oils, many with high levels of PCDFs, exist throughout the world. Long-term storage and improper disposal of this material may result in dioxin release into the environment and the contamination of human and animal food supplies. PCB-based waste is not easily disposed of without contamination of the environment and human populations. Such material needs to be treated as hazardous waste and is best destroyed by high temperature incineration.

Dioxin contamination incidents

Many countries monitor their food supply for dioxins. This has led to early detection of contamination and has often prevented impact on a larger scale. One example is the detection of increased dioxin levels in milk in 2004 in the Netherlands, traced to a clay used in the production of the animal feed. In another incident, elevated dioxin levels were detected in animal feed in the Netherlands in 2006 and the source was identified as contaminated fat used in the production of the feed.

Some dioxin contamination events have been more significant, with broader implications in many countries.

In late 2008, Ireland recalled many tons of pork meat and pork products when up to 200 times more dioxins than the safe limit were detected in samples of pork. This finding led to one of the largest food recalls related to a chemical contamination. Risk assessments performed by Ireland indicated no public health concern. The contamination was traced back to contaminated feed.

In July 2007, the European Commission issued a health warning to its Member States after high levels of dioxins were detected in a food additive - guar gum - used as thickener in small quantities in meat, dairy, dessert or

delicatessen products. The source was traced to guar gum from India that was contaminated with pentachlorophenol (PCP), a pesticide no longer in use. PCP contains dioxins as contamination.

In 1999, high levels of dioxins were found in poultry and eggs from Belgium. Subsequently, dioxin-contaminated animal-based food (poultry, eggs, pork), were detected in several other countries. The cause was traced to animal feed contaminated with illegally disposed PCB-based waste industrial oil.

In March 1998, high levels of dioxins in milk sold in Germany were traced to citrus pulp pellets used as animal feed exported from Brazil. The investigation resulted in a ban on all citrus pulp imports to the EU from Brazil.

Another case of dioxin contamination of food occurred in the United States of America in 1997. Chickens, eggs, and catfish were contaminated with dioxins when a tainted ingredient (bentonite clay, sometimes called "ball clay") was used in the manufacture of animal feed. The contaminated clay was traced to a bentonite mine. As there was no evidence that hazardous waste was buried at the mine, investigators speculate that the source of dioxins may be natural, perhaps due to a prehistoric forest fire.

Large amounts of dioxins were released in a serious accident at a chemical factory in Seveso, Italy, in 1976. A cloud of toxic chemicals, including 2,3,7,8-Tetrachlorodibenzo-p-dioxin, or TCDD, was released into the air and eventually contaminated an area of 15 square kilometres where 37 000 people lived. Extensive studies in the affected population are continuing to determine the long-term human health effects from this incident. These investigations, however, are hampered by the lack of appropriate exposure assessments. A minor increase in certain cancers and effects on reproduction have been detected and are being further investigated. Possible effects on the children of exposed people are currently being studied.

TCDD has also been extensively studied for health effects linked to its presence as a contaminant in some batches of the herbicide Agent Orange, which was used as a defoliant during the Vietnam War. A link to certain types of cancers and also to diabetes is still being investigated.

Earlier incidents of food contamination have been reported in other parts of the world. Although all countries can be affected, most contamination cases have been reported in industrialized countries where adequate food contamination monitoring, greater awareness of the hazard and better regulatory controls are available for the detection of dioxin problems.

A few cases of intentional human poisoning have also been reported. The most notable incident is the 2004 case of Viktor Yushchenko, President of the Ukraine, whose face was disfigured by chloracne.

Effects of dioxins on human health

Short-term exposure of humans to high levels of dioxins may result in skin lesions, such as chloracne and patchy darkening of the skin, and altered liver function. Long-term exposure is linked to impairment of the immune system, the developing nervous system, the endocrine system and reproductive functions. Chronic exposure of animals to dioxins has resulted in several types of cancer. TCDD was evaluated by the WHO's International Agency for Research on Cancer (IARC) in 1997. Based on animal data and on human epidemiology data, TCDD was classified by IARC as a "known human carcinogen". However, TCDD does not affect genetic material and there is a level of exposure below which cancer risk would be negligible.

Due to the omnipresence of dioxins, all people have background exposure and a certain level of dioxins in the body, leading to the so-called body burden. Current normal background exposure is not expected to affect human health on average. However, due to the high toxic potential of this class of compounds, efforts need to be undertaken to reduce current background exposure.

Sensitive subgroups

The developing fetus is most sensitive to dioxin exposure. The newborn, with rapidly developing organ systems, may also be more vulnerable to certain effects. Some individuals or groups of individuals may be exposed to higher levels of dioxins because of their diets (e.g., high consumers of fish in certain parts of the world) or their occupations (e.g., workers in the pulp and paper industry, in incineration plants and at hazardous waste sites, to name just a few).

Prevention and control of dioxin exposure

Proper incineration of contaminated material is the best available method of preventing and controlling exposure to dioxins. It can also destroy PCB-based waste oils. The incineration process requires high temperatures, over 850°C. For the destruction of large amounts of contaminated material, even higher temperatures - 1000°C or more - are required.

Prevention or reduction of human exposure is best done via source-directed measures, i.e. strict control of industrial processes to reduce formation of dioxins as much as possible. This is the responsibility of national governments, but in recognition of the importance of this approach, the Codex Alimentarius Commission adopted in 2001 a Code of Practice for Source Directed Measures to Reduce Contamination of Foods with Chemicals (CAC/RCP 49-2001), and in 2006 a Code of Practice for the Prevention and Reduction of Dioxin and Dioxin-like PCB Contamination in Food and Feeds (CAC/RCP 62-2006).

More than 90% of human exposure to dioxins is through the food supply, mainly meat and dairy products, fish and shellfish. Consequently, protecting the food supply is critical. One approach includes, as mentioned above, source-directed measures to reduce dioxin emissions. Secondary

contamination of the food supply needs to be avoided throughout the food-chain. Good controls and practices during primary production, processing, distribution and sale are all essential to the production of safe food.

Food contamination monitoring systems must be in place to ensure that tolerance levels are not exceeded. It is the role of national governments to monitor the safety of food supply and to take action to protect public health. When incidents of contamination are suspected, countries should have contingency plans to identify, detain and dispose of contaminated feed and food. The exposed population should be examined in terms of exposure (e.g. measuring the contaminants in blood or human milk) and effects (e.g. clinical surveillance to detect signs of ill health).

What should consumers do to reduce their risk of exposure?

Trimming fat from meat and consuming low fat dairy products may decrease the exposure to dioxin compounds. Also, a balanced diet (including adequate amounts of fruits, vegetables and cereals) will help to avoid excessive exposure from a single source. This is a long-term strategy to reduce body burdens and is probably most relevant for girls and young women to reduce exposure of the developing fetus and when breastfeeding infants later on in life. However, the possibility for consumers to reduce their own exposure is somewhat limited.

What does it take to identify and measure dioxins in the environment and food?

The quantitative chemical analysis of dioxins requires sophisticated methods that are available only in a limited number of laboratories around the world. These are mostly in industrialized countries. The analysis costs are very high and vary according to the type of sample, but range from over US$ 1700 for the analysis of a single biological sample to several thousand US dollars for the comprehensive assessment of release from a waste incinerator.

Increasingly, biological (cell- or antibody) -based screening methods are being developed. The use of such methods for food samples is not yet sufficiently validated. Nevertheless, such screening methods will allow more analyses at lower cost. In case of a positive screening test, confirmation of results must be carried out via more complex chemical analysis.

WHO activities related to dioxins

Reducing dioxin exposure is an important public health goal for disease reduction, also with respect to sustainable development. In order to give guidance on acceptable levels of exposure, WHO has held a series of expert meetings to determine a tolerable intake of dioxins to which a human can be exposed throughout life without harm.

In the latest of such expert meetings held in 2001, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) performed an updated comprehensive risk assessment of PCDDs, PCDFs, and "dioxin-like"

PCBs. The experts concluded that a tolerable intake could be established for dioxins on the basis of the assumption that there is a threshold for all effects, including cancer. The long half-lives of PCDDs, PCDFs and "dioxin-like" PCBs mean that each daily ingestion has a small or even a negligible effect on overall intake. In order to assess long- or short-term risks to health due to these substances, total or average intake should be assessed over months, and the tolerable intake should be assessed over a period of at least one month. The experts established a provisional tolerable monthly intake (PTMI) of 70 picogram/kg per month. This level is the amount of dioxins that can be ingested over lifetime without detectable health effects.

WHO, in collaboration with the Food and Agriculture Organization (FAO), through the joint FAO/WHO Codex Alimentarius Commission, has established a 'Code of Practice for the Prevention and Reduction of Dioxin and Dioxin-like PCB Contamination in Foods and Feed'. This document gives guidance to national and regional authorities on preventive measures. The establishment of Codex guideline levels for dioxins in foods is under consideration.

Since 1976, WHO has been responsible for the Global Environment Monitoring System's Food Contamination Monitoring and Assessment Programme. Commonly known as GEMS/Food, the programme provides information on levels and trends of contaminants in food through its network of participating laboratories in over 70 countries around the world. Dioxins are included in this monitoring programme.

Since 1987, WHO has conducted periodic studies on levels of dioxins in human milk, mainly in European countries. These studies provide an assessment of human exposure to dioxins from all sources. Recent exposure data indicate that measures introduced to control dioxin release in a number of countries have resulted in a substantial reduction in exposure to these compounds over the past two decades.

WHO is now working with the United Nations Environmental Programme (UNEP) on the implementation of the 'Stockholm Convention', an international agreement to reduce emissions of certain persistent organic pollutants (POPs), including dioxins. A number of actions are being considered internationally to reduce the production of dioxins during incineration and manufacturing processes. In responding to the needs of the Stockholm Convention on POPs, the WHO GEMS/Food has developed a new protocol for a Global Survey of Human Milk for POPs in order to meet the health, food safety and environmental objectives of WHO, UNEP and their member countries. This protocol will assist national and regional authorities to collect and analyse representative samples in order to assess the current state of background exposure and in the future to assess the effectiveness of measures taken to reduce exposure.

Dioxins occur as a complex mixture in the environment and in food. In order to assess the potential risk of the whole mixture, the concept of toxic equivalence has been applied to this group of contaminants. TCDD, the most toxic member of the family, is used as reference compound, and all

other dioxins are assigned a toxic potency relative to TCDD, based on experimental studies. During the last 15 years, WHO, through the International Programme on Chemical Safety (IPCS), has established and regularly re-evaluated toxic equivalency factors (TEFs) for dioxins and related compounds through expert consultations. WHO-TEF values have been established which apply to humans, mammals, birds and fish. The last such consultation was held in 2005 to update human and mammalian TEFs. These international TEFs have been developed for application in risk assessment and management, and have been adopted formally by a number of countries and regional bodies, including Canada, Japan, the United States and the European Union.

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World Health Organization

PREVENTING DISEASE THROUGH HEALTHY ENVIRONMENTS

EXPOSURE TO DIOXINS AND DIOXIN-LIKE SUBSTANCES: A MAJOR PUBLIC HEALTH CONCERN

Human exposure to dioxins and dioxin-like substances has been associated with a range of toxic effects, including immunotoxicity, developmental and neurodevelopmental effects, and changes in thyroid and steroid hormones and reproductive function. Developmental effects are the most sensitive health end-point, making children, particularly breastfed infants, the population most at risk.[1,2] Dioxins and dioxin-like substances are persistent organic pollutants (POPs) covered by the Stockholm Convention on Persistent Organic Pollutants; they can travel long distances from the emission source and can bioaccumulate in food-chains.[3] Human exposure occurs mainly through consumption of contaminated food.[1,4] Public health and regulatory actions are needed to reduce emissions of these substances, as required by the Stockholm Convention, and to reduce human exposure, particularly for children.

What are dioxins and dioxin-like substances?

The term "dioxins and dioxin-like substances" commonly refers to polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs). They are two- or three-ring structures that can be chlorinated to varying degrees. PCBs can have up to 10 chlorine atoms substituting for hydrogen atoms, and PCDDs and PCDFs can have up to 8. The compounds often have similar toxicity profiles and common mechanisms of action and are generally considered together as a group to set guidelines.[1,4]

Sources of exposure to dioxins and dioxin-like substances[1,4,5]

PCDDs and PCDFs are widely present in the environment, occurring naturally and as by-products of combustion and of various industrial processes. PCDFs were major contaminants of PCBs, but neither PCDDs nor PCDFs have ever been manufactured deliberately. They have no known uses.

PCBs are not natural substances but were globally manufactured and used in the past. Although PCB manufacture is prohibited under the Stockholm Convention on Persistent Organic Pollutants, their release into the environment still occurs from the disposal of large-scale electrical equipment and waste.

Mixtures of the substances with different numbers and positions of chlorine substitution are found in the environment. The degree of chlorination of dioxin mixtures released to the environment through incineration is determined by the source material and the amount of chlorine available.

Remedial actions have led to reductions in exposure in the developed world, with a fall to around 10% of levels seen in the 1970s. Countries with rapidly expanding development are experiencing increasing exposure, particularly to PCDDs and PCDFs, but levels are still below those developed countries in the 1970s.

Industrial processes and natural events

PCDDs and PCDFs are by-products of industrial processes, including the manufacture of chlorophenols and phenoxy herbicides, chlorine bleaching of paper pulp and smelting. They can also be generated by natural events, such as volcanic eruptions and forest fires. PCBs were previously manufactured for use as dielectric fluids (with low electrical conductivity) in larger-scale electrical products such as transformers and capacitors, in heat transfer and hydraulic systems and in industrial oils and lubricants. PCDFs were common contaminants of commercial PCB mixtures.

Food, water and air

Generally, levels of PCBs, PCDDs and PCDFs in air are very low, except in the vicinity of inefficient incinerators. Concentrations of these compounds in drinking-water and surface water are also very low, because they are poorly soluble in water. Releases to air from inadequate incineration and releases from waste sites contaminate soil and aquatic sediments, leading to bioaccumulation and bioconcentration through food-chains. The higher chlorinated components and components with specific positions of chlorination persist longer in the environment and show greater bioaccumulation. The substances have high fat solubility, which may lead to higher concentrations in fatty foods, such as dairy products, some fish, meat and shellfish. Most human exposure is through ingestion of contaminated food. These compounds persist in fatty tissue, with typical half-lives in humans in excess of 7 years.

Waste disposal

Any source of organic materials in the presence of chlorine or other halogens will generate dioxins and furans during combustion. PCDDs and PCDFs are generated through the incineration of waste (domestic, industrial and hospital) at low to moderate temperatures; guidance has been developed to identify and quantify releases from various incineration processes. The use of modern incineration technology destroys dioxins and furans, whereas inadequate incineration creates them.[6]

Disposal of electrical equipment may release PCBs (and PCDF contaminants); guidance is available on equipment likely to contain PCBs.[7,8] Stockpiles of old industrial lubricants containing PCBs are also a potential source of emissions.

Derivation of toxic equivalency factors (TEFs)

Some individual compounds with particular levels of chlorination and/or positions of the chlorine substitutions are much more toxic than others. Toxic equivalency factors (TEFs) have been established to compare the toxicities of individual PCDDs, PCDFs and PCBs relative to the most toxic of these compounds: 2,3,7,8-tetrachlorodibenzodioxin (TCDD), which is used as a reference and given a TEF of 1.[9,10] The common mechanism of action for these substances means that their effects are additive, and TEFs for individual compounds can be summed to establish a TEF for mixtures. This approach has proved robust as a method for establishing the relative toxicities of these compounds.

World Health Organization

World Health Organization (WHO) dioxin guidelines

Provisional tolerable monthly intake

In 2002, the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) established a provisional tolerable intake of 70 pg/kg body weight per month for PCDDs, PCDFs and coplanar PCBs expressed as TEFs, based on reproductive end-points.[1] The value is expressed "per month" to reflect that exposure is cumulative and chronic rather than acute.

Drinking-water

No water quality guidelines have been set for these substances because of their low water solubility.

Air

An air quality guideline for PCBs was not established, because direct inhalation exposures constitute only a small proportion of the total exposure, in the order of 1–2% of the daily intake from food. Although this air concentration is only a minor contributor to direct human exposure, it is a major contributor to contamination of the food-chain.[11]

Health effects

- Short-term exposure to high levels of dioxins and dioxin-like substances in occupational settings or following industrial accidents may cause skin lesions known as chloracne, which is persistent.[1]

- Longer-term environmental exposure causes a range of toxicity, including immunotoxicity, developmental and neurodevelopmental effects, and effects on thyroid and steroid hormones and reproductive function. The most sensitive life stage is considered to be the fetus or neonate. Guidance values have been based on reproductive and developmental effects.[1,4,5]

- Experimental animal studies indicate carcinogenicity in a range of species with multiple sites of tumours. Epidemiological studies in occupational settings also indicate human carcinogenicity at multiple sites. The International Agency for Research on Cancer (IARC) classified TCDD in Group 1 (*carcinogenic to humans*) and some other dioxins in Group 3 (*not classifiable as to their carcinogenicity to humans*).[12,13] PCBs as a group are classified in Group 2A (*probably carcinogenic to humans*).[14] In addition, IARC recently classified 2,3,4,7,8-pentachlorodibenzofuran and 3,3′,4,4′,5-pentachlorobiphenyl in Group 1.[13]

- These substances are not genotoxic carcinogens. It is considered that the mechanism of carcinogenesis, involving the aryl hydrocarbon receptor, means that there is a threshold for carcinogenicity. Tolerable intake guidance based on non-cancer end-points is considered protective for carcinogenicity.[1]

Risk mitigation recommendations

Inventory and reduce emissions

- Inventory emissions of dioxins and dioxin-like substances, guidance on inventory development and analysis of current inventories regionally and globally is available.[15]

Countries should develop local inventories based on guidance for the identification and quantification of dioxin and furan releases.[6]

- Reduce emissions of dioxins and dioxin-like substances as required under the Stockholm Convention on Persistent Organic Pollutants.[3]

- Incineration at high temperatures with long residence times and adequate mixing is required to reduce emissions of dioxins and dioxin-like substances. An inventory of suitable incineration facilities globally has been prepared.[16]

Disposal

- Follow global guidelines for the identification of PCBs in materials and equipment to inform local actions.[7,8]
- Clean up and safely dispose of industrial waste containing PCBs and PCDFs (or likely to generate PCDDs). Routine rehabilitation of contaminated sediments is not recommended. The necessity for environmental cleanup should be decided through risk assessment on a case-by-case basis.
- Guidance is available on the disposal of health-care waste.[17]
- Further develop international programmes for disposal to aid countries without suitable waste management facilities.

Reduce contamination in food

- Apply strategies developed by WHO/FAO to reduce contamination in food and feed. Countries should develop and implement local strategies.[2]

Monitoring

- Monitor PCDDs, PCDFs and PCBs in food items and human milk. WHO has been involved in such monitoring since 1976, and this is properly done at the international level.[18] More cost-effective bioassays should precede costly chemical analysis in individual developing countries.

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World Health Organization

Printed by the WHO Document Production Services, Geneva, Switzerland

Public Health and Environment

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International Agency for Research on Cancer (IARC) - Summaries & Evaluations

POLYCHLORINATED DIBENZO-*para*-DIOXINS

2,3,7,8-Tetrachlorodibenzo-*para*-dioxin
(Group 1)

Polychlorinated dibenzo-*para*-dioxins
(other than 2,3,7,8-tetrachlorodibenzodioxin):
2,7-DCDD
1,2,3,7,8-PeCDD
1,2,3,6,7,8-/1,2,3,7,8,9-HxCDD
1,2,3,4,6,7,8-HpCDD
(Group 3)

Dibenzo-*para*-dioxin
(Group 3)

For definition of Groups, see Preamble Evaluation

VOL.: 69 (1997) (p. 33)

CAS No.: 1746-01-6
Chem. Abstr. Name: 2,3,7,8-Tetrachlorodibenzo[*b*,*e*][1,4]dioxin

CAS No.: 33857-26-0
Chem. Abstr. Name: 2,7-Dichlorodibenzo[*b*,*e*][1,4]dioxin

CAS No.: 40321-76-4
Chem. Abstr. Name: 1,2,3,7,8-Pentachlorodibenzo[*b*,*e*][1,4]dioxin

CAS No.: 57653-85-7
Chem. Abstr. Name: 1,2,3,6,7,8-Hexachlorodibenzo[*b*,*e*][1,4]dioxin

CAS No.: 19408-74-3
Chem. Abstr. Name: 1,2,3,7,8,9-Hexachlorodibenzo[*b*,*e*][1,4]dioxin

CAS No.: 35822-46-9
Chem. Abstr. Name: 1,2,3,4,6,7,8-Heptachlorodibenzo[*b*,*e*][1,4]dioxin

CAS No.: 262-12-4
Chem. Abstr. Name: Dibenzo[*b*,*e*][1,4]dioxin

CAS No.: 39227-28-6

Chem. Abstr. Name: 1,2,3,4,7,8-Hexachlorodibenzo[*b*,*e*][1,4]dioxin

CAS No.: 3268-87-9
Chem. Abstr. Name: Octachlorodibenzo[*b*,*e*][1,4]dioxin

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Polychlorinated dibenzo-*para*-dioxins (PCDDs) are formed as inadvertent by-products, sometimes in combination with polychlorinated dibenzofurans (PCDFs), during the production of chlorophenols and chlorophenoxy herbicides, and have been detected as contaminants in these products. PCDDs and PCDFs also may be produced in thermal processes such as incineration and metal-processing and in the bleaching of paper pulp with free chlorine. The relative amounts of PCDD and PCDF congeners produced depend on the production or incineration process and vary widely.

PCDDs are ubiquitous in soil, sediments and air. Excluding occupational or accidental exposures, most human exposure to PCDDs occurs as a result of eating meat, milk, eggs, fish and related products, as PCDDs are persistent in the environment and accumulate in animal fat. Occupational exposures to PCDDs at higher levels have occurred since the 1940s as a result of production and use of chlorophenols and chlorophenoxy herbicides. Even higher exposures have occurred sporadically in relation to accidents in these industries.

Mean background levels of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (2,3,7,8-TCDD) in human tissues today are in the range of 2-3 ng/kg fat. Available data suggest that these levels have decreased by a factor of 3 to 5 since the late 1970s, when the development of gas chromatography/mass spectrometry methodology first permitted these extremely low levels of PCDDs in tissues and the environment to be measured accurately. Similarly, since the mid-1980s, mean tissue levels of total PCDDs and PCDFs (measured as international toxic equivalents (I-TEQs)) in the general population have decreased by two- to three-fold. Human exposures related to occupation or accidents have led to tissue levels of 2,3,7,8-TCDD up to several orders of magnitude higher than background levels.

5.2 Human carcinogenicity data

In the evaluation of the evidence of carcinogenicity of 2,3,7,8-TCDD, more weight has been given to studies with direct 2,3,7,8-TCDD measurements and to studies involving heavy exposure to herbicides likely to be contaminated with 2,3,7,8-TCDD. The effects of 2,3,7,8-TCDD and those of the products in which it was found cannot be separated in most of the epidemiological studies; however, the focus here is on the contaminant.

The most important studies for the evaluation of the carcinogenicity of 2,3,7,8-TCDD are four cohort studies of herbicide producers (one each in the United States and the Netherlands, two in Germany), and one cohort of residents in a contaminated area from Seveso, Italy. These studies involve the highest exposures to 2,3,7,8-TCDD among all epidemiological studies, although the exposures at Seveso were lower and the follow-up shorter than those in the industrial settings. In addition, the multi-country cohort study from IARC is of special interest because it includes three of four high-exposure cohorts and other industrial cohorts, many of them not reported in separate publications, as well as some professional applicators. Most of the four industrial cohorts include analyses of sub-cohorts considered to have the highest exposure and/or longest latency. These cohorts, and their respective high-exposure sub-cohorts, are the focus of the summary here. Additional studies of herbicide applicators, both cohort and case-

control studies, who have considerably lower exposures to 2,3,7,8-TCDD, are not considered critical for the evaluation.

An increased risk for all cancers combined is seen in the cohort studies cited above. The magnitude of the increase is generally low; it is higher in sub-cohorts considered to have the heaviest 2,3,7,8-TCDD exposure within the cohorts listed above. Furthermore, statistically significant positive dose-response trends for all cancers combined were present in the largest and most heavily exposed German cohort. A positive trend ($p = 0.05$) was also seen in the smaller German cohort where an accident occurred with release of large amounts of 2,3,7,8-TCDD; the positive trend in this cohort was limited to smokers. Cumulative dose in both these trend analyses was estimated by combining data from blood 2,3,7,8-TCDD levels and knowledge of job categories, work processes and calendar time of exposure. Increased risks for all cancers combined were also seen in the longer-duration longer-latency sub-cohort of the United States study. These positive trends with increased exposure tend to reinforce the overall positive association between all cancers combined and exposure, making it less likely that the increase is explained by confounding, either by smoking or by other carcinogenic exposures in the industrial setting.

An increased risk for lung cancer is also present in the most informative cohort studies, again especially in the more highly exposed sub-cohorts. The relative risk for lung cancer in the combined highly exposed sub-cohorts was estimated to be 1.4 (statistically significant). It is possible that lung cancer relative risks of this order could result from confounding by smoking, but only if there were a pronounced difference in smoking habits between the exposed population and the referent populations, a difference which seems unlikely. It therefore seems unlikely that confounding by smoking can explain all the excess lung cancer risk, although it could explain part of it. It is also possible that other occupational carcinogens, many of which would affect the lung, are causing some confounding.

An excess risk for soft-tissue sarcoma, based on a small number of deaths, has been reported. Incidence data for soft-tissue sarcoma were generally not available. A case-control study nested in the IARC international cohort found a dose-response relationship with estimated 2,3,7,8-TCDD exposure; however, strong positive trends were also found with estimated exposure to 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). A similar increase in soft-tissue sarcoma was present in the Seveso population, but only in the zone which overall had the lowest exposure. No such increase is present in the German or Dutch cohort studies. Soft-tissue sarcomas are subject to serious misclassification on death certificates; although it is unlikely that this occurs differentially in the exposed and the referent populations, reclassification of a few cases would have important consequences on results based on small numbers.

An increased risk for non-Hodgkin lymphoma was found in most of the populations studied in the four industrial cohort studies and in the Seveso population, although the relative risks were mostly nonsignificant and below 2. A case-control study nested in the IARC international cohort provided weak evidence of a dose-response relationship with estimated 2,3,7,8-TCDD exposure. Although it is plausible that other chemicals cause non-Hodgkin lymphoma, strong potential confounding factors are not known. The lack of complete consistency among the studies and the weak effect detected in most of the positive ones, however, caution against a causal interpretation of the findings.

Increased risks for several other malignant neoplasms have been sporadically reported among workers exposed to 2,3,7,8-TCDD, and at Seveso, perhaps most notable being for digestive system cancers and multiple myeloma. The available results are not fully consistent, and several studies have not reported the results for each individual cancer site.

Overall, the strongest evidence for the carcinogenicity of 2,3,7,8-TCDD is for all cancers combined,

rather than for any specific site. The relative risk for all cancers combined in the most highly exposed and longer-latency sub-cohorts is 1.4. While this relative risk does not appear likely to be explained by confounding, this possibility cannot be excluded. There are few examples of agents which cause an increase in cancers at many sites; examples are smoking and ionizing radiation in the atomic bombing survivors (for which, however, there are clearly elevated risks for certain specific cancer sites). This lack of precedent for a multi-site carcinogen without particular sites predominating means that the epidemiological findings must be treated with caution; on the other hand, the lack of precedent cannot preclude the possiblity that in fact 2,3,7,8-TCDD, at high doses, does act as a multi-site carcinogen. It should be borne in mind that

the general population is exposed to levels far lower than those experienced by the industrial populations.

5.3 Animal carcinogenicity data

2,3,7,8-TCDD was tested for carcinogenicity by oral administration in three experiments in mice and in three experiments in rats. It was also tested by exposure of immature mice and by intraperitoneal or subcutaneous injection in one study in hamsters, and by skin application in mice.

In three experiments in two strains of mice, administration of 2,3,7,8-TCDD orally by gastric instillation increased the incidence of hepatocellular adenomas and carcinomas in both males and females. In one of these three experiments, 2,3,7,8-TCDD increased the incidence of follicular-cell adenomas of the thyroid, lymphomas and subcutaneous fibrosarcomas in female mice; a trend for an increased incidence of alveolar/bronchiolar adenomas or carcinomas in male mice was also observed.

Oral administration of 2,3,7,8-TCDD by gastric instillation or in the diet to rats increased the incidence of benign hepatocellular neoplasms (identified as adenomas, neoplastic nodules and hyperplastic nodules) in females in two strains and the incidence of hepatocellular carcinomas in one strain. An increased incidence of follicular-cell adenomas of the thyroid in male and female rats in the study with administration by gastric instillation was reported. In the feeding study, 2,3,7,8-TCDD increased the incidence of squamous-cell carcinomas of the tongue, hard palate, nasal turbinates and lung in both sexes of rats. In the feeding study, a high incidence of endocrine-related tumours (pituitary adenomas, phaeochromocytomas and pancreatic islet-cell tumours) was observed in control female rats. The incidence of these tumours was lower after treatment with 2,3,7,8-TCDD, associated with decreased body weight.

In one experiment involving oral administration to immature mice of two strains, 2,3,7,8-TCDD increased the incidence of hepatocellular adenomas and carcinomas in males and that of hepatocellular adenomas in females of one strain. Treatment of immature mice increased the incidence of thymic lymphomas in male and female mice of both strains.

Application of 2,3,7,8-TCDD to the skin increased the incidence of dermal fibrosarcomas in female mice. Intraperitoneal or subcutaneous administration of 2,3,7,8-TCDD to small groups of hamsters increased the incidence of squamous-cell carcinomas of the skin.

In several studies in mice, administration of 2,3,7,8-TCDD following administration with known carcinogens enhanced the incidences of skin papillomas, lung adenomas, liver adenomas and hepatoblastomas. 2,3,7,8-TCDD enhanced the incidence of focal hepatic lesions in several strains of female rats following administration of various *N*-nitrosamines. In one study, 2,3,7,8-TCDD enhanced the incidence of lung carcinomas in ovariectomized compared with intact female rats following administration of *N*-nitrosodiethylamine.

In summary, 2,3,7,8-TCDD administered at low doses by different routes to rats and mice causes tumours at multiple sites. It also causes tumours in hamsters.

Dibenzo-*para*-dioxin was tested for carcinogenicity by oral administration in one experiment in mice and in one experiment in rats. No increased incidence of tumours at any site was observed in mice or rats of either sex.

2,7-Dichlorodibenzo-*para*-dioxin (2,7-DCDD) was tested for carcinogenicity by oral administration in one experiment in mice and in one experiment in rats. No increased incidence of tumours was seen at any site in rats of either sex. In male but not in female mice, an increased incidence of hepatocellular adenomas was observed, but the impurity of the chemical confounds an evaluation of its carcinogenicity. In one study, 2,7-DCDD did not enhance the incidence of skin papillomas in mice treated with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine.

A mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-*para*-dioxins was tested for carcinogenicity by oral administration in mice and in rats, and by administration to the skin in mice. The incidence of hepatocellular adenomas was increased in male and female mice and in female rats following oral administration. Impurities in the mixture were unlikely to have been responsible for the observed response. No significant increase in tumours at any site was observed following application to the skin in mice.

In other studies, administration of either 1,2,3,7,8-pentachlorodibenzo-*para*-dioxin or 1,2,3,4,6,7,8-heptachlorodibenzo-*para*-dioxin led to an increased incidence of hepatic focal lesions in female rats following treatment with nitrosamines.

Administration of a defined mixture of 49 PCDDs increased the incidence of hepatic focal lesions in female rats following treatment with *N*-nitrosomorpholine.

5.4 Other relevant data

5.4.1 *Kinetics*

In most vertebrate species, the 2,3,7,8-substituted PCDDs are the congeners which are predominantly retained. If chlorine atoms are present on all 2,3,7,8 positions, the biotransformation rate of PCDDs is strongly reduced, resulting in significant bioaccumulation. In most species the liver and adipose tissue are the major storage sites.

As Ah receptor-mediated effects are caused primarily by the parent compound, biotransformation to more polar metabolites should be considered to be a detoxification process. Although kinetics influence the biological and toxic effects, genetic factors seem to play a dominant role.

5.4.2 *Toxic effects*

Human exposure to 2,3,7,8-TCDD or other PCDD congeners due to industrial or accidental exposure has been associated with chloracne and alterations in liver enzyme levels in both children and adults. Changes in the immune system and glucose metabolism have also been observed in adults. Infants exposed to PCDDs and PCDFs through breast milk exhibit alterations in thyroid hormone levels and possible neurobehavioural and neurological deficits.

The extraordinary potency of 2,3,7,8-TCDD and related 2,3,7,8-substituted PCDDs has been

demonstrated in many animal species. The lethal dose of 2,3,7,8-TCDD, however, varies more than 5000-fold between the guinea-pig, the most sensitive, and the hamster, the least sensitive species. In all mammalian species tested so far, lethal doses of 2,3,7,8-TCDD result in delayed death preceded by excessive body weight loss ('wasting').

Other signs of 2,3,7,8-TCDD intoxication include thymic atrophy, hypertrophy/hyperplasia of hepatic, gastrointestinal, urogenital and cutaneous epithelia, atrophy of the gonads, subcutaneous oedema and systemic haemorrhage.

In tissue culture, 2,3,7,8-TCDD affects growth and differentiation of keratinocytes, hepatocytes and cells derived from other target organs. Toxicity of 2,3,7,8-TCDD segregates with the Ah receptor, and relative toxicity of other PCDD congeners is associated with their ability to bind to this receptor.

PCDDs cause suppression of both cell-mediated and humoral immunity in several species at low doses.

PCDDs have the potential to suppress resistance to bacterial, viral and parasitic challenges in mice.

5.4.3 *Effects on reproduction*

Most studies on reproductive effects of PCDDs in humans concerned paternal exposure, usually long after high exposure had occurred. Most studies have a limited power to detect elevations in specific birth defects. The studies also showed discordant results concerning an increase in the risk of spontaneous abortions. Some studies have shown alterations in hormone levels and sperm characteristics after PCDD exposure.

2,3,7,8-TCDD is both a developmental and reproductive toxicant in experimental animals. The developing embryo/fetus appears to display enhanced sensitivity to the adverse effects of PCDDs. Perturbations of the reproductive system in adult animals require overtly toxic doses. In contrast, effects on the developing organism occur at doses > 100 times lower that those required in the mother. Sensitive targets include the developing reproductive, nervous and immune systems. Perturbation of multiple hormonal systems and their metabolism due to PCDD exposure may play a role in these events.

5.4.4 *Genetic effects*

In human studies after in-vivo exposure, there have been no unequivocal reports of effects of 2,3,7,8-TCDD or other PCDD congeners upon the frequencies of chromosomal aberrations.

In animal studies *in vivo* and in cultured human and animal cells *in vitro*, 2,3,7,8-TCDD gave conflicting results with regard to several genetic endpoints, such as DNA damage, gene mutations, sister chromatid exchange and cell transformation.

Experimental data indicate that 2,3,7,8-TCDD and probably other PCDDs and PCDFs are not direct-acting genotoxic agents.

5.4.5 *Mechanistic considerations*

The administration of 2,3,7,8-TCDD in rodent bioassays significantly increased the incidence of benign and/or malignant tumours in various tissues (liver, lung, lymphatic system, soft tissue, nasal turbinates, hard palate, thyroid and tongue) in both sexes. The number of tumours per animal (multiplicity) was small. Prior exposure to a known carcinogen and subsequent exposure to 2,3,7,8-TCDD enhanced

(promoted) tumour incidence and/or multiplicity and resulted in the appearance of tumours at earlier times. While 2,3,7,8-TCDD has been demonstrated to increase tumour incidence at different sites, the pattern of tumour sites is a function of species, sex and study.

2,3,7,8-TCDD is not directly genotoxic. A number of hypotheses addressing the mechanisms of 2,3,7,8-TCDD-mediated tumour promotion have been presented. These hypotheses include Ah receptor-mediated alteration in expression of networks of genes involved in cell growth and differentiation, DNA damage mediated by cytochrome P450-catalysed metabolic activation pathways, expansion of preneoplastic cell populations via inhibition of apoptosis, positive modulation of intra- or extracellular growth stimuli, or suppression of immune surveillance. For thyroid tumour induction, an indirect mechanism of 2,3,7,8-TCDD-induced carcinogenesis has also been proposed. In rodents, the induction of hepatic uridine diphosphate-glucuronosyl transferase resulted in enhanced elimination of thyroid hormones as glucuronides from the circulation, and subsequent enhanced stimulation of the thyroid gland via elevated levels of circulating thyroid-stimulating hormone.

(*a*) *Ah receptor*

The Ah receptor is a ubiquitous transcription factor found in both rodents and humans. PCDDs bind to human and rodent Ah receptors with very similar structure-activity relationships; 2,3,7,8-TCDD has the highest affinity of the PCDDs for both rodent and human receptors.

Both in humans and in mice, two forms of Ah receptor have been identified which exhibit a 5-10-fold difference in binding affinity for 2,3,7,8-TCDD. In humans, one form of the Ah receptor exhibits a K_d (a measure of binding affinity) for 2,3,7,8-TCDD of 0.4 nM, whereas the other form binds 2,3,7,8-TCDD with a K_d of about 2 nM.

In congenic mouse strains, expression of the lower or higher affinity forms of receptor has been extensively demonstrated to result in proportional differences in sensitivity to 2,3,7,8-TCDD with regard to biochemical changes and toxic effects. Thus, congenic mice expressing the lower-affinity form of receptor require higher doses of 2,3,7,8-TCDD to elicit these effects than strains expressing higher-affinity forms. A similar difference in sensitivity to PCDDs has also been demonstrated in tumour promotion studies in skin of congenic mouse strains. In these studies, PCDDs show the same rank order of potency in Ah receptor binding *in vitro* and tumour induction *in vivo*. Taken together, these data strongly support a receptor-mediated mechanism of mouse skin carcinogenesis.

(*b*) *Gene expression*

The best studied 2,3,7,8-TCDD-dependent gene expression response is the induction of *CYP1A1* and *CYP1A2*. In both rodent and human cells, this response is mediated by the Ah receptor. In rodent and human cells, PCDDs show very similar potencies in inducing *CYP1A1* and *CYP1A2* expression in rodent and human cells. The role, if any, of the induction of these genes in carcinogenesis by 2,3,7,8-TCDD is unclear. 2,3,7,8-TCDD-induced gene regulatory responses and biochemical effects documented in rodent tissues and/or cells have also been observed in human tissues or cells.

(*c*) *Comparison of tissue concentrations in humans and animals*

Four epidemiological studies of high-exposure industrial cohorts in Germany, the Netherlands and the United States found an increase in overall cancer mortality.

In these cohorts, the blood lipid 2,3,7,8-TCDD levels estimated to the last time of exposure were 2000

ng/kg (mean) (up to 32 000 ng/kg) in the United States cohort, 1434 ng/kg geometric mean (range, 301-3683 ng/kg) among accident workers in the Dutch cohort, 1008 ng/kg geometric mean in the group of workers with severe chloracne in the BASF accident cohort in Germany and measurements up to 2252 ng/kg in the Boehringer cohort in Germany. These calculated blood 2,3,7,8-TCDD levels in workers at time of exposure were in the same range as the estimated blood levels in a two-year rat carcinogenicity study. In rats exposed to 100 ng/kg bw 2,3,7,8-TCDD per day, hepatocellular carcinomas and squamous-cell carcinomas of the lung were observed. Estimated blood levels were 5000-10 000 ng/kg 2,3,7,8-TCDD. In the same study, in rats exposed to 10 ng/kg bw 2,3,7,8-TCDD per day, hepatocellular nodules and focal alveolar hyperplasia were observed. Estimated blood levels were 1500-2000 ng/kg 2,3,7,8-TCDD. These results indicate parallel tumorigenic responses to high exposure to 2,3,7,8-TCDD in both humans and rats.

In view of the results mentioned above, it should be noted that the present background levels of 2,3,7,8-TCDD in human populations (2-3 ng/kg) are 100 to 1000 times lower than those observed in this rat carcinogenicity study. Evaluation of the relationship between the magnitude of the exposure in experimental systems and the magnitude of the response (i.e., dose-response relationships) do not permit conclusions to be drawn on the human health risks from background exposures to 2,3,7,8-TCDD.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin.

There is *evidence suggesting lack of carcinogenicity* in experimental animals for dibenzo-*para*-dioxin.

There is *limited evidence* in experimental animals for the carcinogenicity of a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-*para*-dioxins.

There is *inadequate evidence* in experimental animals for the carcinogenicity of 2,7-dichlorodibenzo-*para*-dioxin.

There is *inadequate evidence* in experimental animals for the carcinogenicity of 1,2,3,7,8-pentachlorodibenzo-*para*-dioxin.

There is *inadequate evidence* in experimental animals for the carcinogenicity of 1,2,3,4,6,7,8-heptachlorodibenzo-*para*-dioxin.

Overall evaluation

2,3,7,8-Tetrachlorodibenzo-*para*-dioxin is *carcinogenic to humans (Group 1)*.

In making the overall evaluation, the Working Group took into consideration the following supporting evidence:

(i) 2,3,7,8-TCDD is a multi-site carcinogen in experimental animals that has been shown by several lines of evidence to act through a mechanism involving the Ah receptor;

(ii) this receptor is highly conserved in an evolutionary sense and functions the same way in humans as

in experimental animals;

(iii) tissue concentrations are similar both in heavily exposed human populations in which an increased overall cancer risk was observed and in rats exposed to carcinogenic dosage regimens in bioassays.

Other polychlorinated dibenzo-*para*-dioxins are *not classifiable as to their carcinogenicity to humans (Group 3)*.

Dibenzo-*para*-dioxin is *not classifiable as to its carcinogenicity to humans (Group 3)*.

Previous evaluations: Vol. 15 (1977) (p. 41); Suppl. 7 (1987) (pp. 59, 350)

For definition of the italicized terms, see Preamble Evaluation

Synonyms for 2,3,7,8-Tetrachlorodibenzo[*b*,*e*][1,4]dioxin:

- D48
- Dioxin
- TCDBD
- TCDD
- 2,3,7,8-TCDD
- 2,3,7,8-Tetrachlorodibenzo-1,4-dioxin
- 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin
- 2,3,7,8-TetraCDD

Synonyms for 2,7-Dichlorodibenzo[*b*,*e*][1,4]dioxin:

- 2,7-Dichlorodibenzo-*para*-dioxin
- 2,7-DCDD
- 2,7-Dichlorodibenzodioxins
- 2,7-DiCDD

Synonyms for 1,2,3,7,8-Pentachlorodibenzo[*b*,*e*][1,4]dioxin

- D54
- 1,2,3,7,8-PeCDD
- 1,2,3,7,8-PnCDD
- 1,2,3,7,8-Pentachlorodibenzo-*para*-dioxin
- 1,2,3,7,8-Pentachlorodibenzodioxin
- 2,3,4,7,8-Pentachlorodibenzo-*para*-dioxin
- 2,3,4,7,8-Pentachlorodibenzodioxin
- 1,2,3,7,8-PentaCDD

Synonyms for 1,2,3,6,7,8-Hexachlorodibenzo[*b*,*e*][1,4]dioxin

- D67
- 1,2,3,6,7,8-Hexachlorodibenzodioxin
- 1,2,3,6,7,8-Hexachlorodibenzo-*para*-dioxin
- 1,2,3,6,7,8-Hexachlorodibenzo[1,4]dioxin
- 1,2,3,6,7,8-HxCDD

- 1,2,3,6,7,8-HexaCDD

Synonyms for 1,2,3,7,8,9-Hexachlorodibenzo[*b*,*e*][1,4]dioxin

- D70
- 1,2,3,7,8,9-Hexachlorodibenzodioxin
- 1,2,3,7,8,9-Hexachlorodibenzo-*para*-dioxin
- 1,2,3,7,8,9-Hexachlorodibenzo[1,4]dioxin
- 1,2,3,7,8,9-HxCDD
- 1,2,3,7,8,9-HexaCDD

Synonyms for 1,2,3,4,6,7,8-Heptachlorodibenzo[*b*,*e*][1,4]dioxin

- D73
- 1,2,3,4,6,7,8-Heptachlorodibenzodioxin
- Heptachlorodibenzo-*para*-dioxin
- 1,2,3,4,6,7,8-Heptachlorodibenzo-*para*-dioxin
- 1,2,3,4,6,7,8-Heptachlorodibenzo[1,4]dioxin
- 1,2,3,4,6,7,8-HpCDD
- 1,2,3,4,6,7,8-HeptaCDD

Synonyms for Dibenzo[*b*,*e*][1,4]dioxin

- Dibenzodioxin
- Dibenzo[1,4]dioxin
- Dibenzo-*para*-dioxin
- Diphenylene dioxide
- Oxanthrene
- Phenodioxin
- DD

Synonyms for 1,2,3,4,7,8-Hexachlorodibenzo[*b*,*e*][1,4]dioxin

- D66
- 1,2,3,4,7,8-Hexachlorodibenzodioxin
- 1,2,3,4,7,8-Hexachlorodibenzo-*para*-dioxin
- 1,2,3,4,7,8-Hexachlorodibenzo[1,4]dioxin
- 1,2,3,4,7,8-HexaCDD
- 1,2,3,4,7,8-HxCDD

Synonyms for Octachlorodibenzo[*b*,*e*][1,4]dioxin

- D75
- OCDD
- Octachlorodibenzo-*para*-dioxin
- 1,2,3,4,6,7,8,9-Octachlorodibenzo-*para*-dioxin
- 1,2,3,4,6,7,8,9-Octachlorodibenzo[1,4]dioxin
- OctaCDD

Last updated 08/12/1997

See Also:
Toxicological Abbreviations