DIOXIN (TCDD)

Identity

Name (parent)	2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)
UN number	-
CAS number	1746-01-6
Intervention value (AGW in mg/m^3)	-
Structure	$C_{12}H_4Cl_4O_2$

Occurrence

Chemical state (at 20°C)	Solid
Physical appearances	Colorless to white needle like crystals
Industrial products	Byproduct of several industrial activities; used in research

Physicochemical properties

Molecular weight	321.96
Vapor pressure (mbar at 25 °C)	Negligible
Octanol/water partition coefficient (log Ko/w)	6.64
Water solubility (in mg/L at 25 °C)	$9.9 * 10^{-6}$

Toxicokinetics (parent)

Uptake by inhalation	Evaporation is negligible at 20°C (low vapor pressure). Airborne particle can contribute to the uptake of TCDD: relative pulmonary availability of TCDD of respirable soil particles is 100% [1].
Uptake by skin absorption	40.9% ± 1.8% of the dose applied to the skin of male rats was absorbed after 120 hours (rate constant 0.005 hr^{-1}) [2]. Note: rat skin is more permeable than human skin to TCDD. In vitro experiments with human skin showed that the vehicle of application influences skin absorption of TCDD: absorption after dry application is ten times faster than after oily application. Absorption rate dry application: 6 – 170 pg/h; absorption after oily application: 1.4 – 18 pg/h [3].
Uptake via gastrointestinal tract	Almost complete absorption after ingestion (absorption was >87% in a human volunteer ingesting a single radio-labeled dose of 0.00114 µg 2,3,7,8-TCDD/kg in corn oil [4]
Distribution	Storage in adipose tissue and liver
Metabolism	P450 CYP1A1, CYP1A2
Excretion via lungs	Negligible due to low vapor pressure.
Excretion via urine	In a self-dosing human experiment with ^{3}H-TCDD, radiolabeled equivalent of TCDD was not found in urine [5].
Excretion via feces	Main excretion route: in a self-dosing human experiment with ^{3}H-TCDD, radiolabeled equivalent of TCDD was found only in feces, not in urine [5].

Toxicodynamics

Toxicity	Genotoxicity, reproductive toxicity, immunotoxicity (TCDD is an immunosuppressant) [6]
Classifications for carcinogenicity	IARC class I; carcinogenic to humans [7]
Classifications for reprotoxicity	Reproductive and developmental toxicant. TCDD has a permanent disrupting effect on the male reproduction system, especially prepuberal men are very sensitive [8]. Parental exposure to TCDD is associated with birth defects [9, 10]
Classifications for sensitizing properties	Not classified

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Biological monitoring

Biomarkers	**TCDD in whole blood**	**TCDD in adipose tissue**	**TCDD in breast milk**
Molecular weight	321.96	321.96	321.96
Involved enzymatic metabolism	-	-	-
Biological material	Venous blood	Adipose tissue	Breast milk
Type of sample	Serum	Adipose tissue	Breast milk
Sampling strategy	Collection after fastening over-night Blood collection every few years	Collection after fastening over-night 10–20 g of anterior wall / abdominal / breast adipose tissue	Sampling of breast milk 30 days after giving birth
Excretion pattern	Excretion half-life increases with age: - estimated half-life in infants: 0.40 y (0.36 y – 0.43 y; estimated in 2 infants, 49 – 50 weeks of age) [11] - estimated half-life in adults: 7.78 y (mean of 6 studies in adult men; range of mean half-life: 5.8 – 9.7) [12] In a study of children and adolescent living in Seveso (TCDD measured in blood) [13]: - average half-life in children < 18 years: 1.6 years (determined in Seveso children). - average half-life in adolescent ≥ 18 years: 3.2 years (determined in Seveso adolescent). $t_{1/2} = 0.35 + 0.12 * \text{Age}$		
Materials	Heparanized vacutainers, hexane rinsed glass vials (serum dioxin), cryovials (serum lipids) Chemically clean containers,	Surgical removal of adipose tissue into chemically clean glass containers	Decontaminated glass collection vials, breast pumps [14].
Transportation	Frozen	Frozen	Within 1 day at 4°C [14]
Storage	-20°C	- 70°C — - 20°C	< 1 day at 4°C -20°C [14]
Stability	> 4 years at -20°C (DFG, volume 8)		
Measurement principle	1) Separation of the lipid fraction: It involves the separation of a spiked blood-water mixture on a Chem-Elut (modified silicagel) column and the subsequent elution with hexane/isopropanoi (3 : 2) and gravimetric determination. 2) Clean-up of the lipid-extract 3) High-resolution gas chromatography / High resolution mass spectroscopy (HR-GC/HR-MS) [15]	See whole blood	See whole blood

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Aliquot for 1 analysis	100 mL, necessary for analysis: 40 mL	10 – 20 g anterior wall adipose tissue	50 mL – 100 mL [14]
Limit of quantification	1 – 2 pg/g fat 18.8 pg/g fat	1 pg/g fat (limit of detection) on a whole-weight basis	0.1 pg/g fat [14]
Recommended adjustments	Adjustment for lipid content of serum	Adjustment for lipid content adipose tissue	Adjustment for lipid content breast milk
Preferred units for expression of results	pg / g fat ppt	Pg/g fat	pg/g
Conversion factor	1 pg/g = 1 ppt	1 pg/g = 1 ppt	1 pg/g = 1 ppt
Biological exposure value US	-	-	-
Biological exposure value Germany	-	-	-
Background value	3-7 pg/g fat	Germany: am ± sd 7.0 ± 4.0 pg/g fat Median: 6.1 pg/g fat; 95th percentile: 16.6 pg/g fat; range: not detected – 202 ppt 1.5 – 18 pg/g fat (2 – 20); mean: 7.2 [16]	Belgium: median: 2.4 pg/g fat, range: 1.3 – 3.8 pg/g fat measured in 20 women living near an industrial area [14]
Possible confounders	Age, living in industrial areas	Age, living in industrial areas	Age, living in industrial areas
Remark	Content of dioxin is the highest in blood lipid, followed by adipose tissue lipid, and the mother milk lipid content		

References

1. Nessel CS, Amoruso MA, Umbreit TH, Meeker RJ, Gallo MA. Pulmonary bioavailability and fine particle enrichment of 2,3,7,8-tetrachlorodibenzo-p-dioxin in respirable soil particles. Fundam Appl Toxicol. 1992 Aug;19(2):279-85.
2. Banks YB, Birnbaum LS. Absorption of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) after low dose dermal exposure. Toxicol Appl Pharmacol. 1991 Feb;107(2):302-10.
3. Weber LW, Zesch A, Rozman K. Penetration, distribution and kinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in human skin in vitro. Arch Toxicol. 1991;65(5):421-8.
4. Maruyama W, Yoshida K, Tanaka T, Nakanishi J. Determination of tissue-blood partition coefficients for a physiological model for humans, and estimation of dioxin concentration in tissues. Chemosphere. 2002 Feb;46(7):975-85.
5. Wendling JM, Orth RG, Poiger H. Determination of [3H]-2,3,7,8-tetrachlorodibenzo-p-dioxin in human feces to ascertain its relative metabolism in man. Anal Chem. 1990 Apr 15;62(8):796-800.
6. Kerkvliet NI. Recent advances in understanding the mechanisms of TCDD immunotoxicity. Int Immunopharmacol. 2002 Feb;2(2-3):277-91.
7. (IARC) IAfroC. Agents reviewed by the IARC monographs, volumes 1-99. 2008 12-05 [cited; Available from:
8. Mocarelli P, Gerthoux PM, Patterson DG, Jr., Milani S, Limonta G, Bertona M, et al. Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. Environ Health Perspect. 2008 Jan;116(1):70-7.
9. Ngo AD, Taylor R, Roberts CL, Nguyen TV. Association between Agent Orange and birth defects: systematic review and meta-analysis. Int J Epidemiol. 2006 Oct;35(5):1220-30.
10. Goldstone HM, Stegeman JJ. Molecular mechanisms of 2,3,7,8-tetrachlorodibenzo-p-dioxin cardiovascular embryotoxicity. Drug Metab Rev. 2006;38(1-2):261-89.

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11. Leung HW, Kerger BD, Paustenbach DJ. Elimination half-lives of selected polychlorinated dibenzodioxins and dibenzofurans in breast-fed human infants. J Toxicol Environ Health A. 2006 Mar;69(6):437-43.
12. Geyer HJ, Schramm KW, Feicht EA, Behechti A, Steinberg C, Bruggemann R, et al. Half-lives of tetra-, penta-, hexa-, hepta-, and octachlorodibenzo-p-dioxin in rats, monkeys, and humans--a critical review. Chemosphere. 2002 Aug;48(6):631-44.
13. Kerger BD, Leung HW, Scott P, Paustenbach DJ, Needham LL, Patterson DG, Jr., et al. Age- and concentration-dependent elimination half-life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Seveso children. Environ Health Perspect. 2006 Oct;114(10):1596-602.
14. Focant JF, Pirard C, Thielen C, De Pauw E. Levels and profiles of PCDDs, PCDFs and cPCBs in Belgian breast milk. Estimation of infant intake. Chemosphere. 2002 Sep;48(8):763-70.
15. Päpke O, Ball M, Lis ZA, Scheunert K. Determinants of PCDD/PCDF in whole blood from persons involved in fire incidents. Chemosphere. 1990;20(7-9):959-66.
16. Beck H, Dross A, Mathar W. PCDD and PCDF exposure and levels in humans in Germany. Environ Health Perspect. 1994 Jan;102 Suppl 1:173-85.

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