

170

Toxicological issues

- Extreme lethal potency, but not uniform across species:
 guinea pig LD₅₀ = 1–2 µg/kg; hamster ~5000 µg/kg
 ↖ most sensitive species
 monkey ~ 70 µg/kg
 frog ~ 1000 µg/kg
- Many other toxic endpoints are observed besides lethality

malformation in fetus

- chloracne in human, rabbit
- teratogenicity in mouse
- carcinogenicity in rat, possibly human
- porphyria and immune suppression in many species

Poisoning of Viktor Yushchenko (2004), Ukrainian presidential candidate.

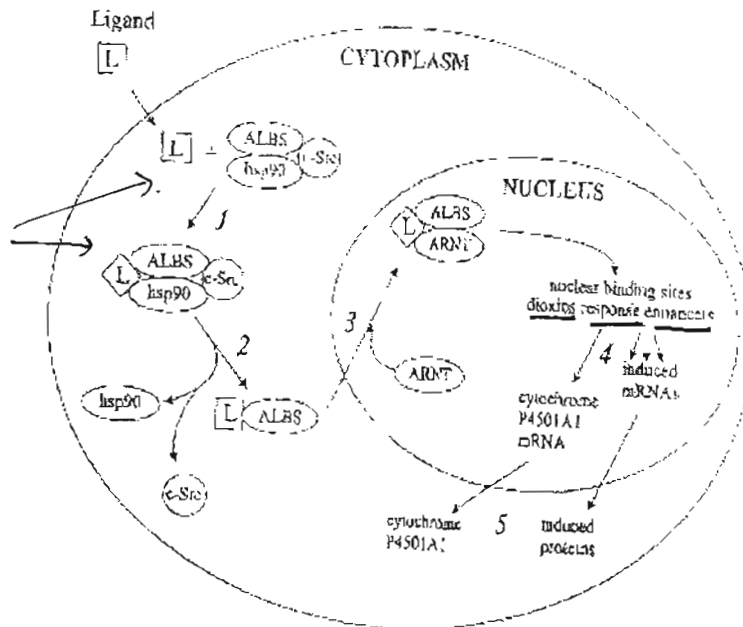
abnormalities in the production of heme ⇒ various disorders

- Induction of cytochrome P-450 monooxygenase enzymes (xenobiotic oxidizing enzymes) is a universal response, but is not an overtly toxic response

- Mechanism of action involves binding to the Ah receptor protein, with $K_{ass} \sim 10^{11} \text{ L mol}^{-1}$: a hydrophobic interaction
 ↖ an intracellular protein
 ↖ i.e. very strong binding

present in all vertebrates

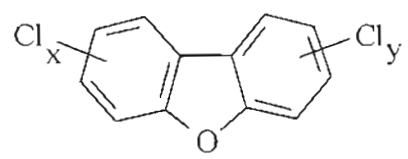
ALBS = Ah receptor binding subunit



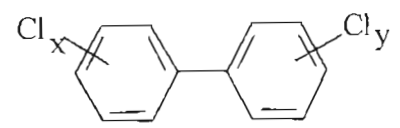
see Fig 9.9. txt p 318 for clearer figure.

171

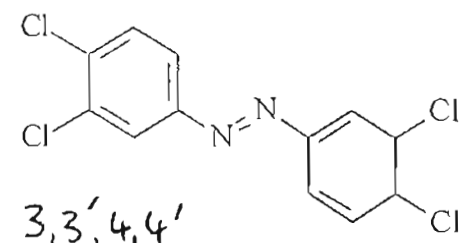
PCDDs are not the only "dioxin-like" substances



furans (PCDFs)



biphenyls (PCBs)

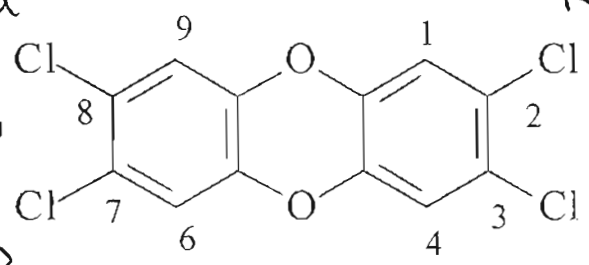


3,3',4,4'-tetrachloro-azobenzene (TCAB).

• Concept of "toxic equivalency factors" (TEFs)

The toxicity of different compounds (congeners of dioxins, furans, PCBs) are compared to the amount of TCDD that would have equal toxicity

$$\text{Toxic Equivalence (TEQ)} = \sum(c_i \times \text{TEF}_i)$$



TEFs are listed differently for mammals, fish and birds (cos of species variation)

• Examples of TEFs (PCDDs only):

< four 2,3,7,8-substituents	= 0	
2,3,7,8-Cl ₄ (TCDD)	= 1 ← (defined reference)	0.1
1,2,3,7,8-Cl ₅	= 0.5	0.05
1,2,3,4,7,8- / 1,2,3,6,7,8-Cl ₆	= 0.1	0.1
1,2,3,4,6,7,8-Cl ₇	= 0.01	0.01
1,2,3,4,6,7,8,9-Cl ₈	= 0.001	0.001

Furans
PCDFs ↘

(PCBs have been tabulated).

For example:

Dining on 30pg of TCDD, 60 pg of 1,2,3,7,8 PCDF and 200 pg of octachloro (Cl₈) PCDD, would have a toxicity equivalent to,

$$\frac{(30 \text{ pg} \times 1.0)}{30} + \frac{(60 \text{ pg} \times 0.05)}{3} + \frac{(200 \text{ pg} \times 0.001)}{0.2}$$

i.e. 33.2 pg of 2,3,7,8 TCDD. ... yummy!

N.B. PCBs are far more prevalent

Confusion over the term “dioxin”: Hamilton plastics fire (1999)

- specifically 2,3,7,8-TCDD?
- all PCDDs: weight basis? TEQ basis?
- all PCDD-like compounds? TEQ basis

- Environmental sources of PCDDs
 - Historical: 2,4,5-T usage; chlorine-bleaching of wood pulp; principally 2,3,7,8-TCDD: see later

 - Incineration/combustion: municipal waste; hospital waste; residential garbage; principally Cl₇ and Cl₈ dioxins and furans → low TEQ

 - 2000: residential garbage burning contributes significantly to the environmental dioxin load

Potential human health effects of dioxin exposure

- Ontario population intake of dioxins in food (as TEQs).
 - adults 0.5-2 pg/kg BW/day
 - children 2-14 1.3-5
 - infants 0.5-2 3-11
 - neonates < 0.5 165

- major source = meat and dairy (breast milk for neonates)

- whole body half-life is very long 5-8 years in humans

- Background human body burden (US EPA data): 9 ng/kg

Levels at which adverse effects have been seen in humans:

- chloracne 45-3000 ng/kg
- decreased birth weight 1500
- cancer (estimated) 110-7000
- smaller testes 14
- altered glucose tolerance 15-110

- decreased sperm count (rat) 64
- endometriosis (monkey) 54

- induction of cytochrome P-450 2-10 nM (human cells in culture)
- estrogen receptor binding ~ 50 nM (in culture)

- reproductive/developmental effects likely more significant than cancer

- present controversy: does dioxin exposure act as a contributing factor to diabetes?

174

Endocrine system... controls glands that secrete hormones ("messengers") to target organs where the cells act on them.

* Endocrine disrupting compounds (not in book)

substances that interfere with hormone action e.g. disruption of hormones guiding growth, development, intelligence, reproduction

female sex hormone →
male version ↗

estrogen mimics the most widely studied to date: androgens and thyroid hormone mimics becoming a research focus

Both estrogens and androgens are usually steroid hormones

and can be passed on to the next generation

concerns about:

- sewage works effluents
- pulp and paper effluents
- industrial spills
- natural compounds

endocrine disrupters interfere with normal hormone action: they can either

selectively bind to a specific receptor and trigger a response i.e. mimics hormones

- act as hormone agonists, or
- antagonize (block) normal hormone action

a key issue is that hormones act at minuscule concentrations: nM and less. Even weak hormone mimics can show biological activity at μM and less

* Endocrine disrupting compound (or chemicals), EDCs.

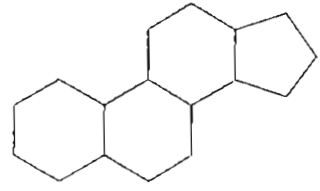
In the context of estrogens, they are also known as "environmental estrogens" or "xenoestrogens"

175

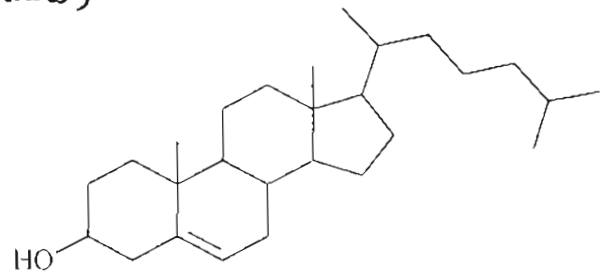
steroid
Mammalian hormones
5 groups, including
- progestagens
- androgens
- estrogens

Steroid hormones

- biosynthesized in vertebrates from cholesterol (in the gonads and adrenal glands)

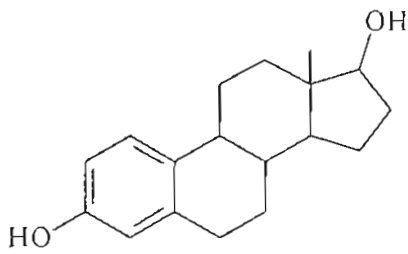


steroid skeleton

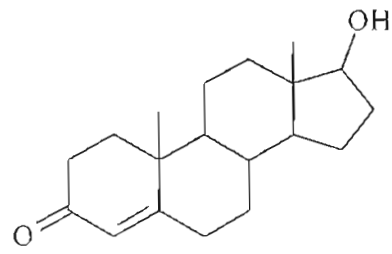


cholesterol

- the most important sex hormones



estradiol



testosterone

- testosterone is an intermediate in the formation of estradiol (aromatase) enzyme that catalyses test. → est.
- both males and females produce both estrogens and androgens
- these hormones have important roles in development, including fetal development
- "used" steroid hormones are metabolized by cytochrome P-450 enzymes: estradiol → 17 ketone (estrone), to 16-hydroxylation (estriol), and 2- and 4-hydroxylation

ie. can undergo hydroxylation, reduction or aromatisation.

