

# TOXICOLOGY

## Nuclear Receptor-Mediated Toxicity

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# LEARNING OBJECTIVES

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**After this lecture you will be able to:**

- explain why nuclear receptors mediate toxicity without genotoxicity
- describe the domain structure and activation mechanism of nuclear receptors
- name the principal xenobiotic receptors (AhR, PXR, CAR) and endocrine receptors (ER, AR, PPAR, RAR/RXR)
- give examples of NR-mediated toxicity: TCDD, xenoestrogens, antiandrogens, peroxisome proliferators, retinoids
- explain species differences, receptor cross-talk and their impact on risk assessment

### Evidence for Nuclear Receptor-Mediated Toxicity:

1. Tissue specific effect
2. Predictable effect
3. Transactivation of specific genes is increased
4. Rapid transcriptional response
5. Reversible binding of compound to intracellular molecules
6. Stereospecific effects

### Molecular Properties of Nuclear Receptors:

1. Soluble (intra-cellular) receptor that binds a ligand, migrates to cell nucleus and interacts with specific genomic response elements
2. No second messengers in NR signalling
3. Effector is DNA

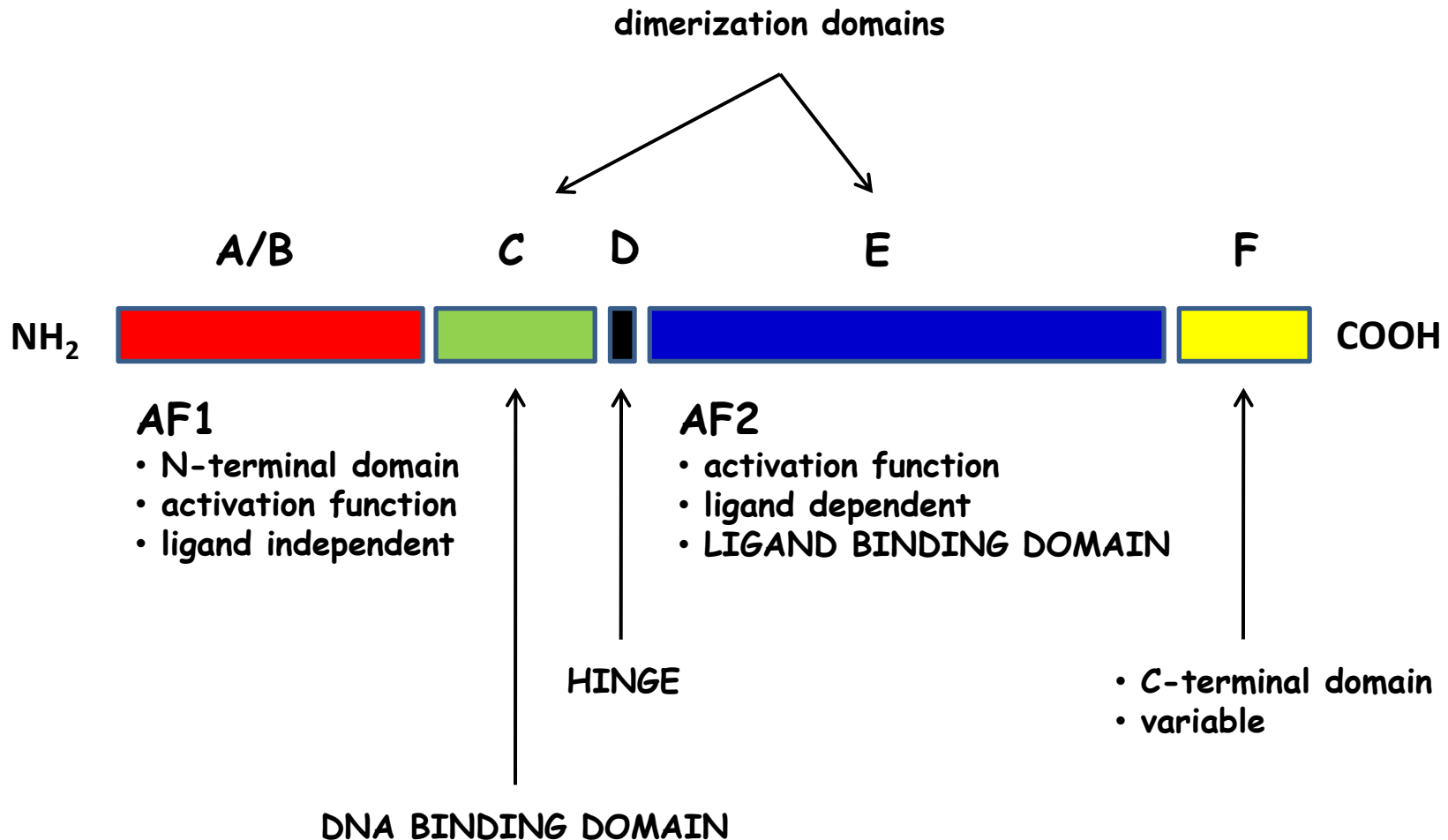
#### **STEROID/THYROID/RETINOID FAMILY**

- Steroid receptors (ER, PR, AR, GR, MR)
- Vitamin D Receptor (VDR)
- Retinoid Receptors (RARs, RXRs)
- Thyroid hormone receptor (TR)
- Peroxisome proliferator-activated r. (PPARs)

#### **PAS (Per/ARNT/Sim) FAMILY**

- AhR = Aryl Hydrocarbon Receptor
- ARNT = AhR Nuclear Translocator
- HIF1 $\alpha$  = Hypoxia-Inducible Factor

# STRUCTURE OF NUCLEAR RECEPTORS



# ARYL HYDROCARBON RECEPTOR

- dioxin receptor
- ubiquitously expressed (lung, thymus, placenta, liver, kidney, heart, spleen)
- ligand-(in)dependent activation
- ligands/activators:

NATURAL (flavonoids, isoflavones, stilbenes, anthocyanins)

DRUGS (omeprazole, lansoprazole, primaquine, ketoconazole)

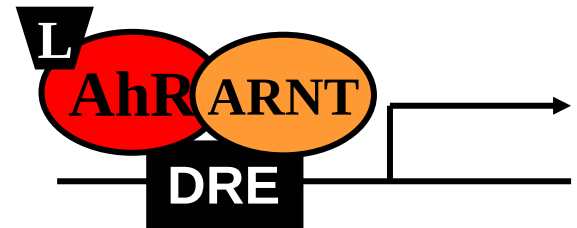
CHEMICALS (SP600125, U0126)

ENDOGENOUS (indoles)

**ENVIRONMENTAL POLLUTANTS (PCBs, PAHs....)**

- target genes - CYP1A1, CYP1A2, CYP1B1, phase II enzymes
- AHRR = AhR repressor - forms AHRR/ARNT heterodimer, which binds to XRE but does not trigger gene expression
- AHRR is up-regulated by AhR = negative regulatory feed-back

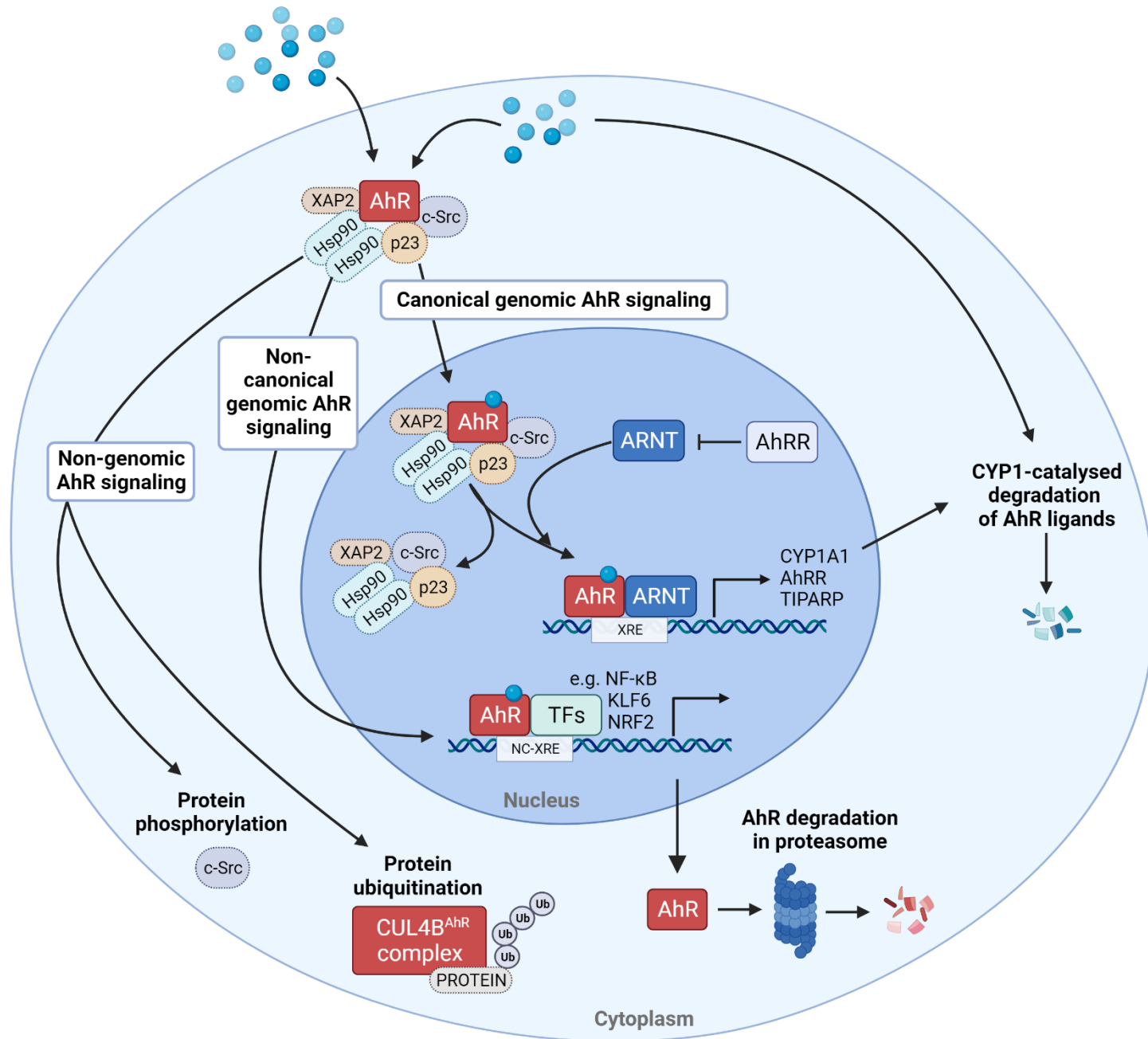
DRE = dioxin-responsive element  
XRE = xenobiotic-responsive element  
AHRE = AhR responsive element



core sequence  
consensus sequence

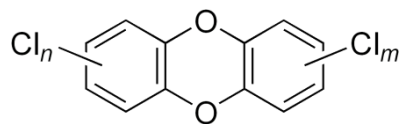
5'-GCGTG-3'

5'-T/GNGCGTGA/CG/CA-3'

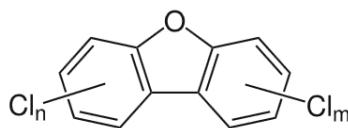


# AHR-MEDIATED TOXICITY

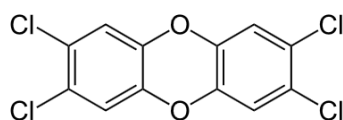
- AhR binds many polychlorinated aromatic compounds with differing affinity
- **pleiotropic toxicological effects**; multitude transcriptional and phenotypic effects
- PCDDs, PCDFs, PCBs = the **most toxic** environmental chemicals
- highly **lipophilic persistent** compounds = **long biological  $t_{1/2}$**  (7 - 11 years!)
- different degree of chlorination = **many congeners**; variable toxic potential
- often **mixtures** → **relative measure of toxicity = TOXICITY EQUIVALENTS (T.E.)**
- T.E.s calculated for the **most potent congener TCDD**; T.E. = 1.0
- relative toxic potential of PCBs, PCDDs and PCDFs correlates with their affinity to AhR
- binding to AhR is optimal when ligand is coplanar



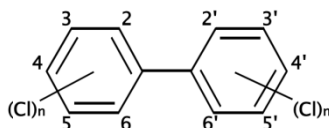
polychlorinated dibenzodioxins  
PCDDs (75 congeners)



polychlorinated dibenzofurans  
PCDFs (75 congeners)

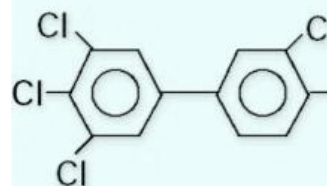


2,3,7,8-tetrachloro-*p*-dibenzodioxin  
TCDD



polychlorinated biphenyls  
PCBs (209 congeners)

**PCBs are structurally distinct and have more than one mechanism of action**

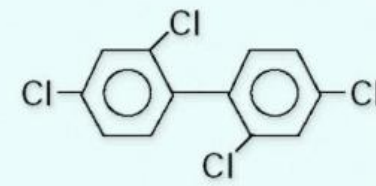


Coplanar PCBs

*meta, para* substituted

Bind with high affinity to the Ah receptor

Mediate many effects through changes in gene transcription



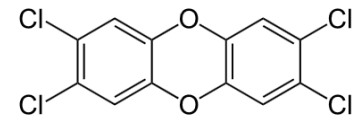
Noncoplanar PCBs

*ortho* substituted

Are not good ligands for the Ah receptor

Mechanisms of action are unknown but initiated by changes in cell signaling

# AHR-MEDIATED TOXICITY - TCDD



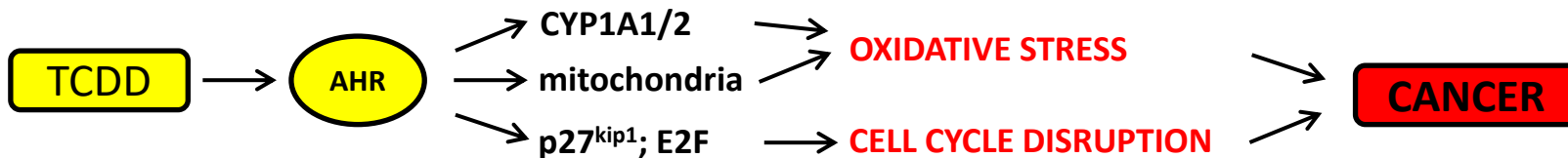
- environmental pollutant with a very high toxic potential featuring pleiotropic activity
- immunotoxicity, endocrine toxicity, embryotoxicity, teratogenesis (in animals)
- human **carcinogen** Class 1 via non-genomic mechanisms
- acute toxicity = maximal effects after 2-4 weeks after single exposure
- **species-specific sensitivity**; e.g. guinea pigs ( $LD_{50}$  500 ng/kg) vs hamster ( $LD_{50}$  5 mg/kg)
- in humans - **chloracne** = persistent disturbance of epithelial cells differentiation in skin
- high affinity of TCDD to AhR ( $K_d = 10^{-11}$  M) - species-specific(!)
- TCDD-activated AhR triggers transcriptional response of many genes, but one single „toxicity gene“ dysregulated by AHR is unlikely

## Evidence for AHR-mediated toxicity of TCDD:

- Responsiveness to TCDD positively correlates and segregates with  $Ah^{b-l}$  allele
- The  $K_d$  for TCDD of nonsensitive mouse strains is 10-20 x higher than of sensitive ones
- AhR-null mice are resistant against toxic effects of TCDD

# AHR-MEDIATED TOXICITY - TCDD&CANCER

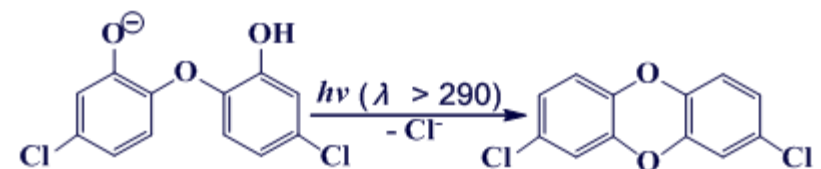
- mechanism is probably combined, involving **disruption of cell cycle and oxidative stress**
- TCDD alters transcription factors (E2F) and cyclin-dependent kinases inhibitors (p27<sup>kip1</sup>), resulting in **CELL CYCLE DISRUPTION**
- TCDD induces extensive **OXIDATIVE STRESS** by induction of CYP1A1/2 and in mitochondria by interfering with electron transport chain (oxidation of SH- groups, increase of Ca<sup>2+</sup>, ROS production, DNA damage)
- ROS production in mitochondria is low in AhR-knock-out mice = mitochondrial oxidant stress depends rather on AhR than on CYP1A1/2



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## TRICLOSAN

- antifungal, antibacterial
- tooth pastes, soaps, deodorants
- gets to environment where it undergoes photochemical degradation to 2,8-DCDD



# AHR-MEDIATED TOXICITY - TCDD

## AhR-mediated toxicity: historical TCDD exposures

all caused by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) — the most potent AhR ligand among environmental pollutants

### Agent Orange, Vietnam 1962–1971



- mass defoliation herbicide, contaminated with TCDD as a by-product of synthesis
- ~80 million liters sprayed
- dioxin hotspots (Da Nang, Bien Hoa) persist for decades
- **health effects** in veterans and subsequent generations

### Seveso, Italy 1976



- ICMESSA plant explosion — TCDD cloud over populated area
- the highest-known residential TCDD exposure in history
- **chloracne** in ~190 children
- zones A, B, R evacuated; soil decontamination took years

### Yushchenko, Ukraine 2004



- presidential candidate poisoned with pure TCDD
- blood level ~100,000 pg/g lipid — among the highest ever recorded in a human
- **severe chloracne** on the face; recovery took years
- criminal poisoning case — TCDD identified by mass spectrometry

### Germany 2010–11: dioxin in eggs



- industrial fatty acids (biodiesel residue) diverted into animal feed
- dioxin up to 77× the legal limit in feed fat
- ~4,700 farms closed, eggs recalled across the food chain
- led to stricter EU feed-monitoring rules

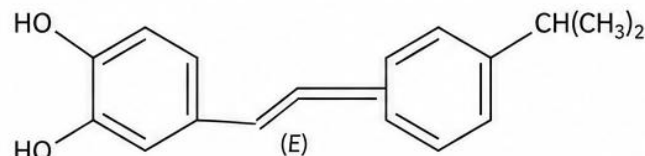
*Common thread: chloracne is the hallmark of TCDD toxicity — and dioxin monitoring of the food chain remains a permanent task*

# AHR-THERAPEUTIC TARGET

## AhR: from toxicology to pharmacology

the same receptor that mediates dioxin toxicity is now a validated drug target — translation took ~30 years

### Tapinarof (VTAMA) — first AhR agonist drug



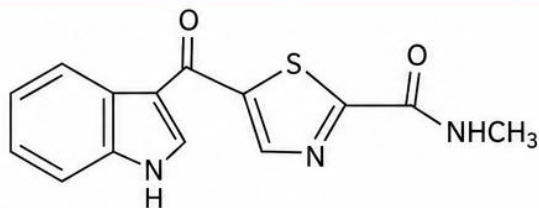
**tapinarof** — bacterial stilbene derivative

FDA approved for plaque psoriasis (2022)

FDA approved for atopic dermatitis (2024)

mechanism: ↓ IL-17A/IL-13 signaling, ↑ skin barrier proteins, Nrf2 activation

### AhR ligands in inflammatory bowel disease



**ITE-CONHCH<sub>3</sub>** — indole-thiazole bioisostere of ITE

EC<sub>50</sub> = 1.6 nM, 10× more stable than ITE

alleviates DSS-induced colitis in mice

Dvořák et al. 2026, *Front. Pharmacol.* 17:1931941 — *in vitro* profiling supports preclinical development

### Clinical pipeline — both directions

#### AGONISTS



**EQ504 (Equillum)** — phase I, ulcerative colitis, colon-targeted oral

**AT-177 (Azora/Adial)** — oral colon-targeted indirubin prodrug, ulcerative colitis

**AT-193 (Azora/Adial)** — topical indirubin, hidradenitis suppurativa, nail psoriasis

**ATB102 (Alliantnera/Falk)** — phase I, gut-enriched, ulcerative colitis

**AQ312 (Aqilion), DMVT-506** — phase I–II dermatology

**indigo naturalis (qing-dai)** — indirubin, UC trials; limited by **hypertension** and **hepatotoxicity**

#### ANTAGONISTS



**BAY 2416964 (Bayer)** — phase I ± pembrolizumab, solid tumors

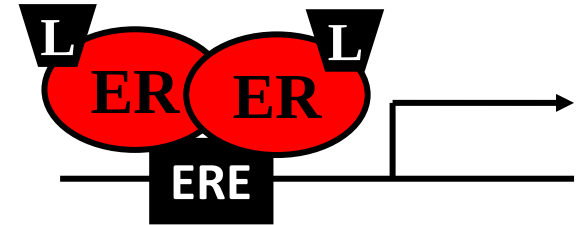
**IK-175 (Ikena)** — phase I + nivolumab, FDA Fast Track, urothelial carcinoma

agonism for barrier-tissue inflammation (skin, gut) — antagonism to restore tumor immunosurveillance; direction depends on tissue and disease context.

Lesson: 30 years ago AhR was the 'dioxin receptor' — today it is a drug target in dermatology, gastroenterology and oncology.

# ESTROGEN RECEPTOR - ER

- exists in two forms ER $\alpha$  and ER $\beta$  - distinct proteins differing in transcriptional activity
- tissue-specific expression
- forms homodimers ER $\alpha$ /ER $\alpha$  and ER $\beta$ /ER $\beta$
- ER $\alpha$  form preferentially heterodimer ER $\alpha$ /ER $\beta$
- ER binds large variety of chemically unrelated compounds = „promiscuity“



Estrogen Response Element - ERE

**XENOESTROGENS** = environmental estrogens

- xenobiotics that can elicit agonistic (enhancing) response mediated by ER
- responsible for hormonally-controlled cancers (mammary, testicular, prostate)
- interfere with normal reproduction in wildlife
- DDT, hydroxy-PCBc, alkylphenols, bisphenol A, diethylstilbestrol (anti-abortion)

## complicated risk assessment

A) xenoestrogens are usually **weak ER agonists**, i.e. they have **low relative estrogenic potency** as compared to endogenous estrogens = rather high concentrations of xenoestrogens are required to elicit adverse effect

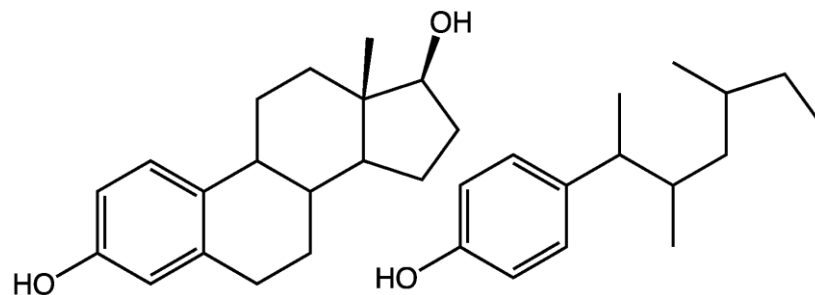
B) **environmental stability, bioaccumulation, high lipophilicity** = increased danger

# ER-MEDIATED TOXICITY: ALKYLPHENOLS

- **alkylphenol ethoxylates** - industrial and household use - detergents, emulsifiers
- massive commercial production - nonionic surfactants, stabilizers in plastics...
- bacterial degradation to alkylphenols
- **alkylphenols**
  - very low acute toxicity vs accumulation in organisms and sediments
  - **estrogenic activity !!!**
- the most known **p-nonylphenol (PNP)**
- PNP binds to and activates ER
- transactivation of estrogen-responsive genes

## Risk of PNP is low or high?

- PNP has 30,000× lower affinity to ER than E2
- PNP is inactivated by glucuronidation
- PNP does not cross placental barrier
- PNP accumulates in fat tissue
- **risk assessment must be very complex**

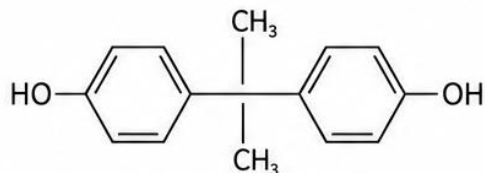


estradiol

p-nonylphenol

## ER-mediated toxicity – update: BPA and PFAS

## BPA: EFSA re-evaluation 2023



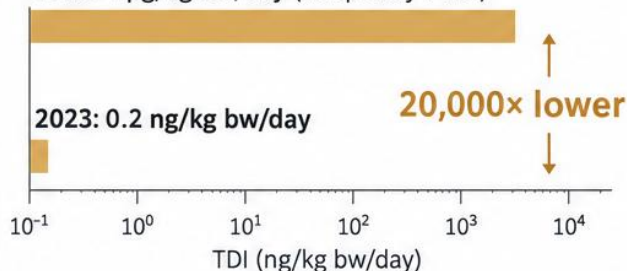
bisphenol A (BPA) — weak ER agonist

**Tolerable daily intake (TDI)**

**2015:** 4 µg/kg bw/day (temporary t-TDI)

2023: 0.2 ng/kg bw/day

20,000x lower



**critical effect:** increased Th17 cells  
(immune system)

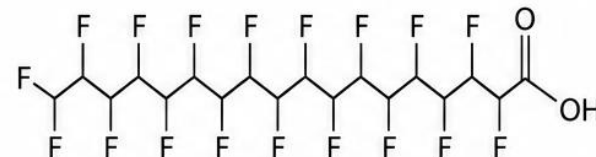
dietary exposure exceeds the TDI in ALL age groups by **2–3 orders of magnitude**

## EU ban 2024



## EU ban of BPA in food-contact materials (2024)

## PFAS — ‘forever chemicals’



perfluoroalkyl acids (e.g. PFOA)

**extreme persistence** (C-F bonds)

emerging **endocrine disruptors**

ER-mediated effects on **reproduction**  
and **development**

*Lesson: the xenoestrogen story moves from 'weak agonists, complex risk assessment' to regulatory action — potency is not the only variable that matters*

# ER-MEDIATED TOXICITY: ER&AHR

- cross-talk between nuclear receptors, e.g. ER vs AHR
- biphasic effects of TCDD on ER: positive and negative

Monostory K., Pascucci J.M., Kobori L., Dvorak Z. (2009) Hormonal regulation of CYP1A expression. *Drug Metab Rev* 41(4):547-572.

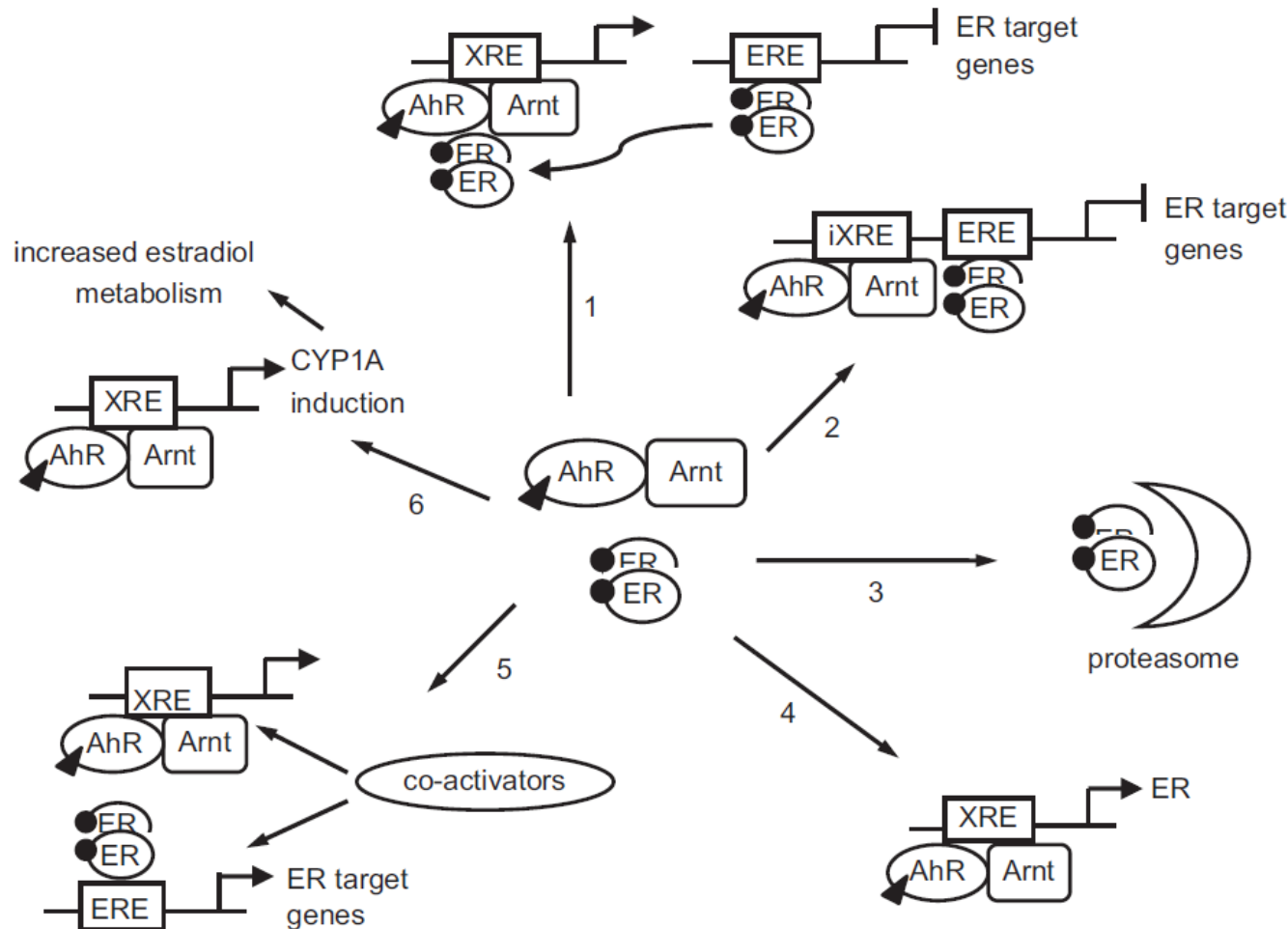
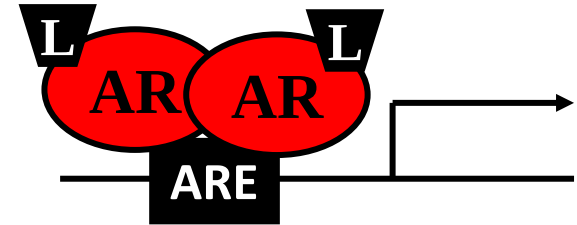


**Figure 3.** Crosstalk between the AhR- and ER-signaling pathways. 1: Liganded ER is recruited to AhR target genes; 2: AhR complex interacts with iXRE in the promoter of ER target genes; 3: AhR induces the proteasomal downregulation of ER; 4: AhR downregulates the expression of ER; 5: AhR signaling competes with ER signaling for the common coactivator pool; and 6: induction of CYP1A increases the metabolism of estrogen.

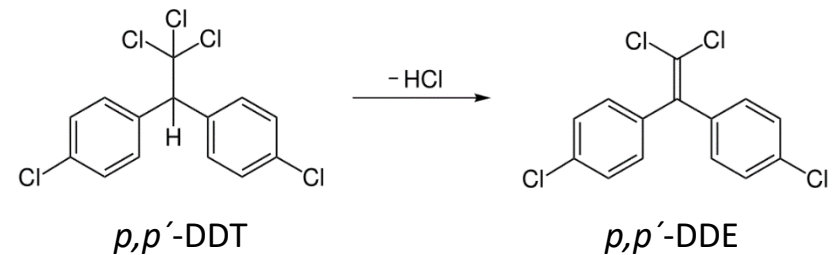
# ANDROGEN RECEPTOR - AR

- pivotal role in development of male gonadal tissues
- implicated in development of tumors (prostate cancer)
- present in most tissues; abundant in male reproductive organs; low levels in female reproductive organs
- endogenous ligands - testosterone, DHT
- xenobiotics causing endocrine-disruption through

AR = **ANTIANDROGENS** (e.g. Vinclozolin, DDT)



Androgen Response Element - ARE



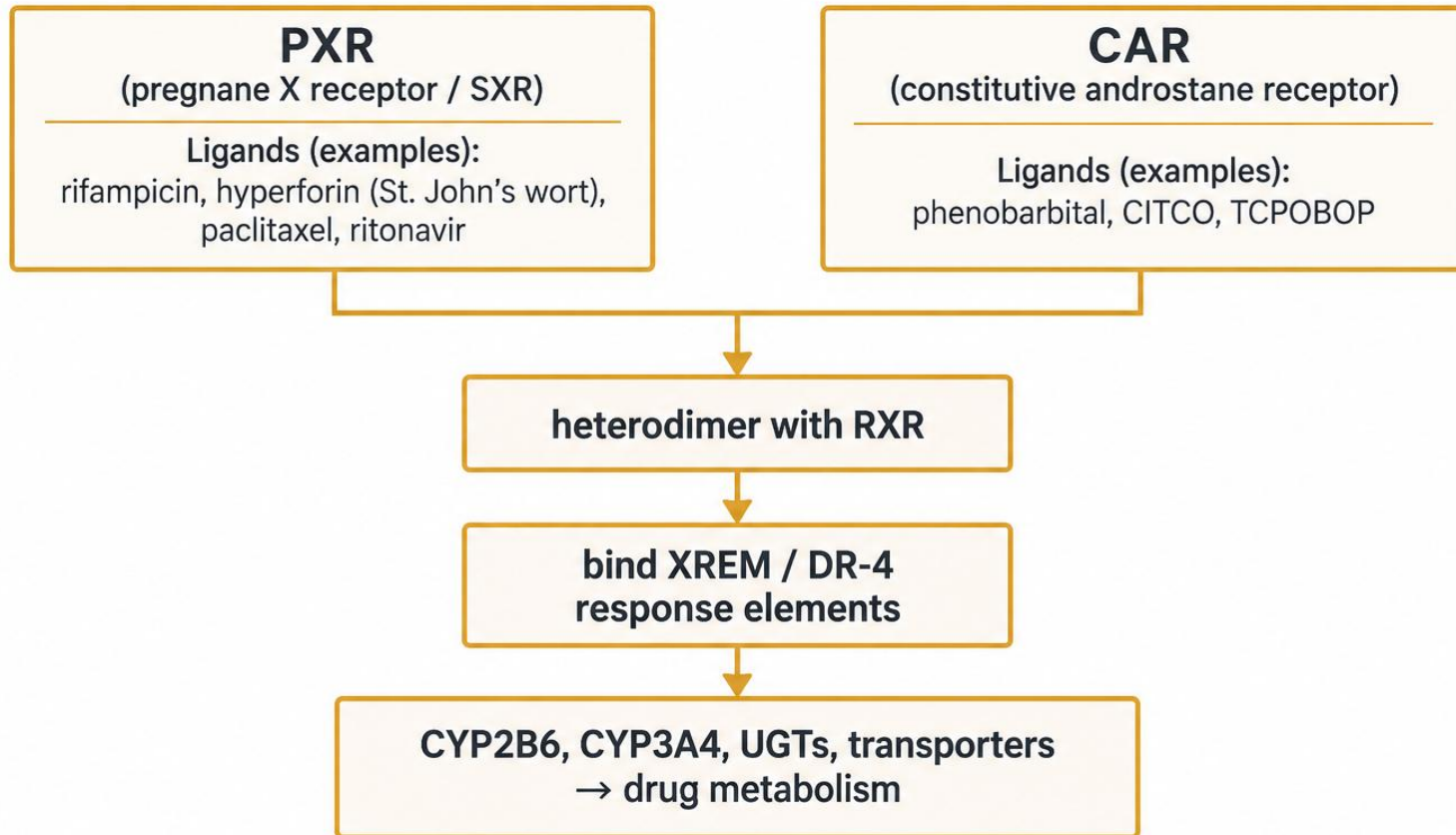
- DDT = massively used pesticide in the past; DDE = breakdown product of DDT
- DDE = **antiandrogen**, persistent, lipophilic, widespread in environment
- DDE blocks AR functions in multiple ways:
  - ↓ AR interaction with coactivators
  - ↓ androgen binding to AR
  - ↓ AR nuclear translocation → ↓ DNA binding

**Some xenobiotics are dual ECD: XENOESTROGENS and ANTIANDROGENS**

e.g. bisphenol A, p-nonylphenol

# PREGNANE X RECEPTOR & CONSTITUTIVE ANDROSTANE RECEPTOR

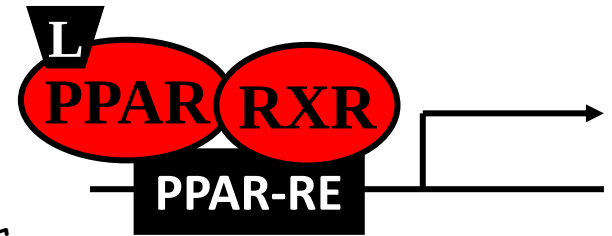
## PXR and CAR – the xenosensors



**Toxicological relevance:** drug–drug interactions, herbicide–drug interactions, altered endobolite metabolism, species-specific ligand recognition (human vs rodent PXR/CAR)

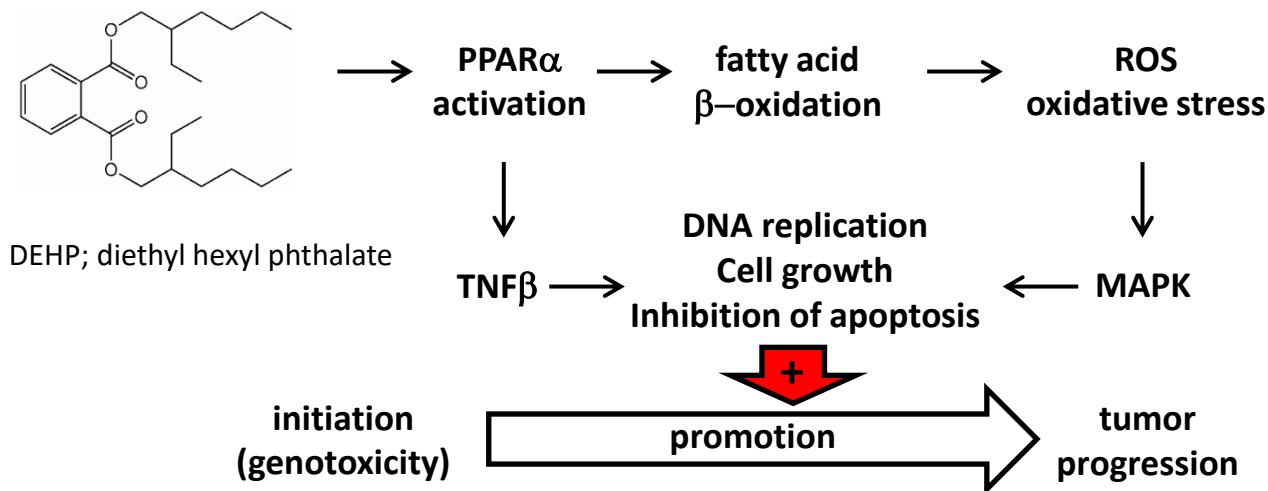
# PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR - PPAR

- PPARs - endogenous ligands: **fatty acids** and **eicosanoids+metabolites**
- subtypes: PPAR $\alpha$ , PPAR $\beta$  (= PPAR $\delta$ ), PPAR $\gamma$  → **different tissue distribution and function**
- name PPAR - historic reasons = ligands for PPAR caused proliferation of peroxisomes in rodents ; but in humans it is not true; better „*fatty acid-activated receptor*“
- **peroxisomes** = subcellular organelles that function as sites of fatty acyl- $\beta$ -oxidation, cholesterol metabolism glycerolipid synthesis and other lipids pathways
- **peroxisome proliferators** = chemically diverse compounds (clofibrate, ciprofibrate, gemfibrozil, nafenodipin, plasticizers - phtalates, solvents)
- PPs induce proliferation of peroxisomes and cause liver tumors in rodents
- the common for PPs is that they are ligands for PPARs = chicken&egg problem
- all subtypes of PPAR form heterodimer with RXR



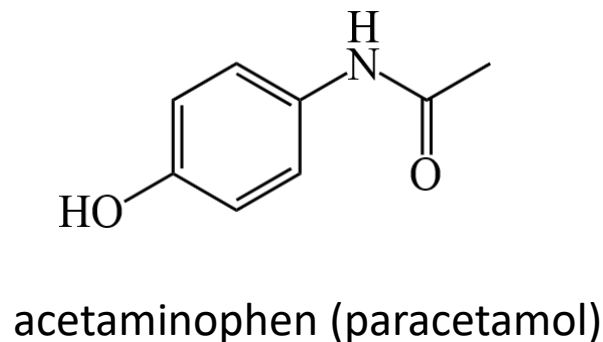
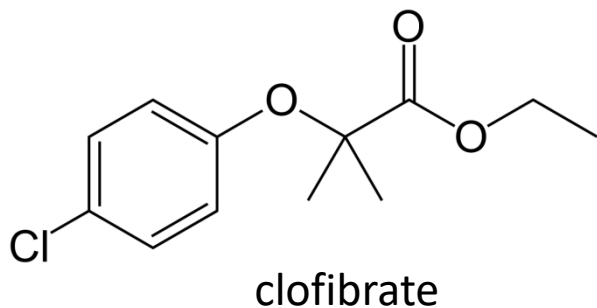
# PPAR $\alpha$ -MEDIATED TOXICITY

- PPAR $\alpha$  - ligands/activators cause hepatocarcinogenesis
- PPs stimulate replicative DNA synthesis and liver growth = **tumor-promoting characteristics**
- PPs inhibit hepatocyte apoptosis *in vivo* and *in vitro* → **tumor-promotion**
- involvement of tumor necrosis factor beta (**TNF $\beta$** ) → it suppresses apoptosis and stimulates DNA synthesis in hepatocytes
- role for mitogen-activated protein kinases (**MAPKs; p38**) → activated by oxidative stress
- PPs increase fatty acyl- $\beta$ -oxidation (in rodents not in man) → increased production of H<sub>2</sub>O<sub>2</sub> → **Reactive Oxygen Species = oxidative stress**
- sustained oxidative stress leads to nongenotoxic liver carcinogenesis
- demonstrated in rodents not in man = perhaps irrelevant mechanism in man?



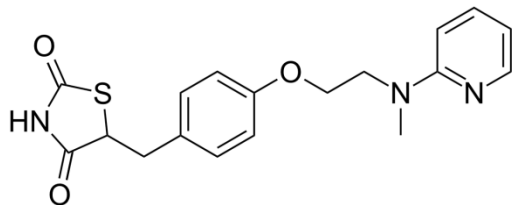
# PPAR $\alpha$ -MEDIATED TOXICITY

- PPAR $\alpha$  interestingly participates in **cytoprotection** against chemically different and mechanistically distinct hepatotoxics
- **clofibrate** (hypolipidemic drug - class „fibrates“) has hepatoprotective effect against liver injury induced by acetaminophen APAP, carbon tetrachloride, bromobenzene, chloroform
- **mechanism of protection is unrelated to mechanism of liver injury**
- PPAR $\alpha$ -null mice had lost the ability to be resistant against APAP when given clofibrate; they also showed impaired liver regeneration after partial hepatectomy
- PPAR $\alpha$  controls **growth regulatory genes** (c-Ha-ras, fos, jun, egr-1) that are involved in the progression of cell cycle ( $G_0 \rightarrow S$  transition)
- **the mechanism of PPAR $\alpha$ -mediated hepatoprotection may involve stimulation of mitogenic response  $\rightarrow$  increased hepatocellular proliferation  $\rightarrow$  regeneration**

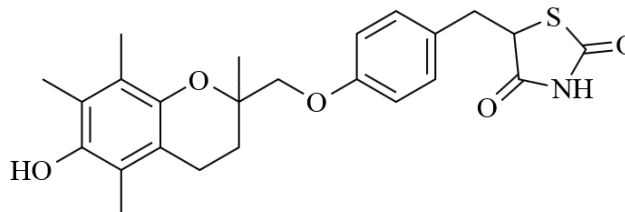


# PPAR $\gamma$ -MEDIATED TOXICITY

- PPAR $\gamma$  - “opposing receptor” = mediates biological functions opposite to those by PPAR $\alpha$
- antitumor effects, increase the storage of lipids
- PPAR $\gamma$  - encoded by single gene, highly conserved structure in mice, rats, humans
- alternative promotor use and alternative splicing = PPAR $\gamma$ 1, PPAR $\gamma$ 2
- two forms of proteins identified: PPAR $\gamma$ 1, PPAR $\gamma$ 2  $\rightarrow$  distinct tissue distribution
- extra-adipose tissues (PPAR $\gamma$ 1) vs adipose tissue (PPAR $\gamma$ 2; 10-100x more)
- expression of PPAR $\gamma$  is influenced epigenetically ( $\uparrow$ nutrition,  $\uparrow$ obesity,  $\uparrow$ type II diabetes)
- activation of PPAR $\gamma$  drastically differs under **normal and pathophysiological conditions!**
- several drugs (e.g. thiazolidinediones, TZD) are ligands for PPAR $\gamma$
- **TZD can induce fat accumulation in the bone marrow  $\rightarrow$  anemia**
- **TZD cause fatty changes in mice liver - enlargement of liver, microvesicular steatosis**
- **occured only in obese mice with type II diabetes!! - extrapolation to humans??**



rosiglitazone



troglitazone

# PPAR $\gamma$ -MEDIATED TOXICITY

- TZD → increased transcription of adipocyte-specific PPAR $\gamma$ -regulated genes in bone marrow stromal cells
- OBESE mice have highly up-regulated expression of PPAR $\gamma$  in liver
- TZD induced transcription of genes involved in lipid metabolism (fatty acid-binding protein, fatty acid translocase) in liver of **OBESE but not LEAN mice!!** → translation to humans??

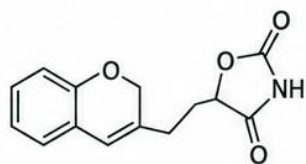
## FUNCTIONAL CHANGES BY TZD-PPAR $\gamma$ :

- Increased flux of non-esterified fatty acids NEFA from adipose tissue to liver in obese animals = continuous exposure of hepatocytes to fatty acids
- Increased *de novo* synthesis of fatty acids from glucose in liver (through PPAR $\gamma$ )
- Up-regulation of fatty acid transporters and binding proteins (PPAR $\gamma$ -regulated genes)
- Inhibition of fatty acids  $\beta$ -oxidation by TZD
  
- AhR-PPAR $\gamma$  cross-talk? TCDD down-regulates PPAR $\gamma$
- Relation between TCDD exposure and development of type II diabetes in humans

# PPAR $\gamma$ -MEDIATED TOXICITY

## PPAR $\gamma$ agonists (glitazones): two toxicity stories

### Troglitazone (Rezulin, Warner-Lambert/Pfizer)



Troglitazone

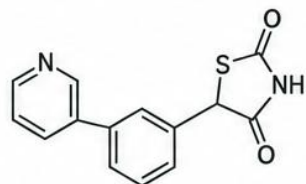
(thiazolidinedione, chromane ring)



Hepatotoxicity



### Rosiglitazone (Avandia, GSK)

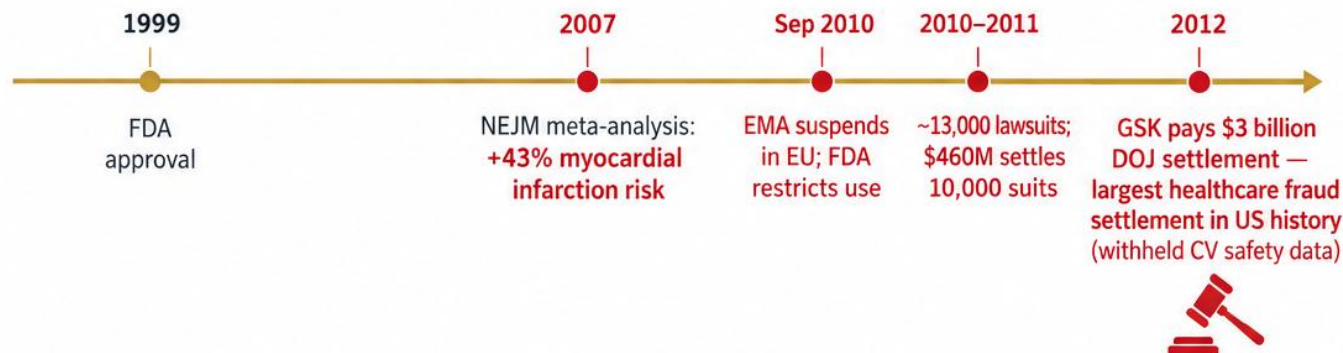


Rosiglitazone

(thiazolidinedione, pyridine ring)



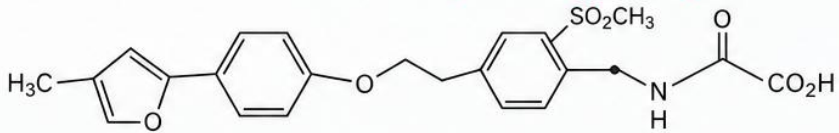
Cardiovascular toxicity

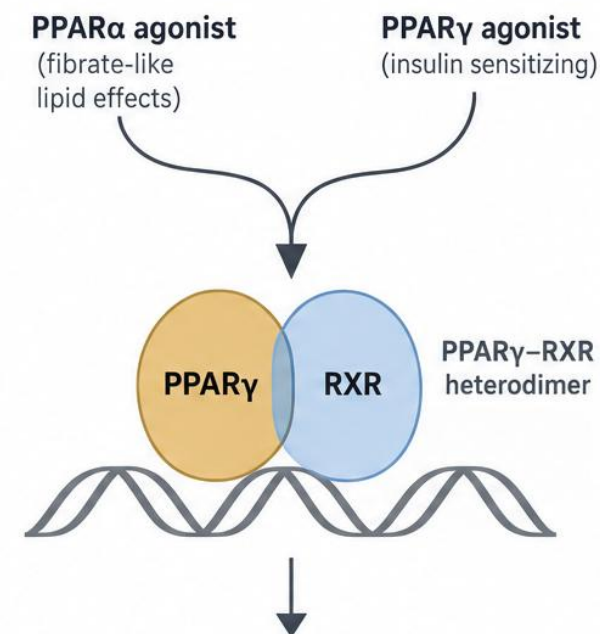


**Lesson:** receptor promiscuity + incomplete safety data = delayed detection of organ toxicity (liver vs heart).

# Dual and pan-PPAR agonists (glitazars): promiscuity cuts both ways

designed to combine PPAR $\alpha$  (fibrate-like lipid effects) + PPAR $\gamma$  (insulin sensitizing) — one receptor switch for glucose AND lipids

|           |                                                                                                    |                                                                                                                                                       |
|-----------|----------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2002      | <b>Ragaglitazar</b><br>Novo Nordisk / Dr Reddy's                                                   | <b>suspended:</b><br>urinary bladder tumors in rodents                                                                                                |
| 2003      | <b>Farglitazar</b><br>GSK                                                                          | <b>discontinued:</b><br>edema                                                                                                                         |
| 2005–2006 | <b>Muraglitazar</b><br>BMS/Merck, Pargluva                                                         | FDA advisory committee voted 8:1 for approval, but JAMA analysis (Nissen) showed 2.2 $\times$ death/MI/stroke;<br><b>development stopped May 2006</b> |
|           | <br>muraglitazar |                                                                                                                                                       |
| 2006      | <b>Tesaglitazar</b><br>AstraZeneca, Galida                                                         | <b>discontinued:</b><br>decreased glomerular filtration (kidney effects)                                                                              |
| 2013      | <b>Aleglitazar</b><br>Roche                                                                        | <b>abandoned in phase III:</b><br>safety signals                                                                                                      |

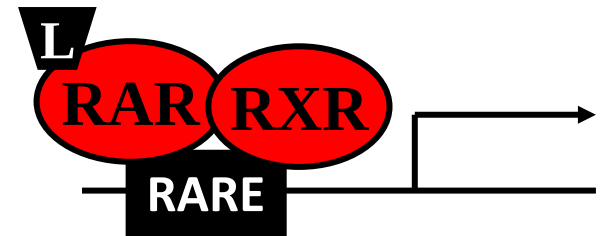


**dual activation = dual toxicity:**  
**edema, heart failure, CV events,**  
**rodent tumors**

**Lesson:** activating two nuclear receptors at once doubles the transcriptional side-effect surface — **none of the glitazars ever reached the market.**

# RETINOIC ACID RECEPTOR - RAR

- physiological ligands for RAR: **retinol**, *all-trans-retinoic acid*
- RAR - expressed abundantly in **liver**, also testes and epididymis (Sertoli cells)
- perturbation of RAR (agonist/antagonist) → **testicular toxicity and embryotoxicity**
- **BMS189453** - retinoid analogue (treatment of skin diseases; RAR $\beta$  agonist, RAR $\alpha/\gamma$  antagonist) induced testicular atrophy and hypospermia in rats - symptoms of vitamin A deficiency
- retinoids are important in embryonic development = xenobiotics that interfere with RAR during embryonic development cause developmental abnormalities
- **Isotretinoin (Accutane)** (13-cis-retinoic acid) - classic human teratogen; absolute contraindication in pregnancy

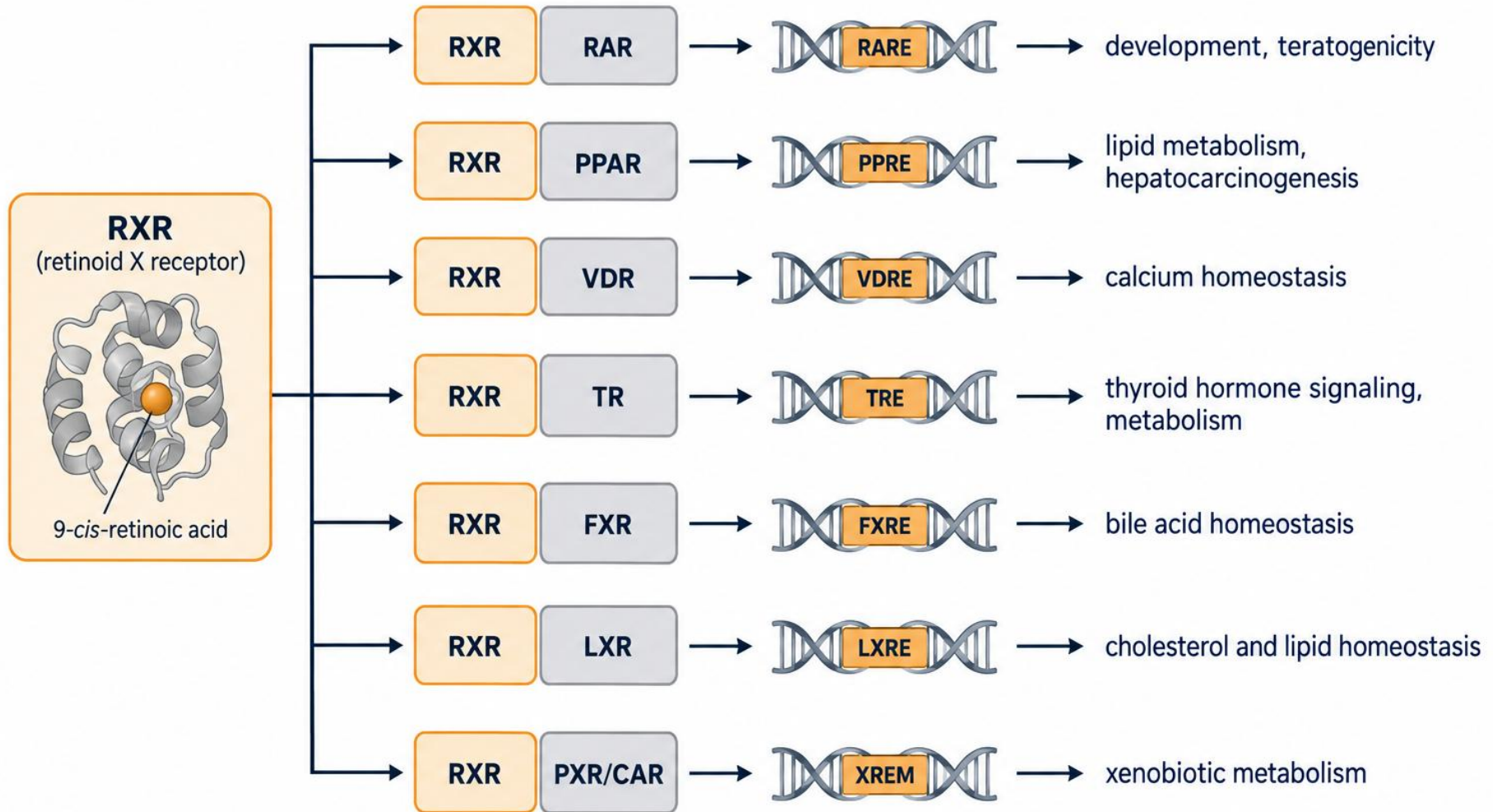


## PHENYTOIN:

- Anticonvulsant
- Causes embryopathy and teratogenic effects in animals and humans (craniofacial abnormalities, microcephaly)
- Up-regulates RAR $\alpha,\beta,\gamma$  in embryonic tissues

# RETINOID X RECEPTOR

## RXR — the universal heterodimerization partner



# Environmental obesogens: organotins hijack PPAR $\gamma$ /RXR

## Sources of exposure



tributyltin in ship antifouling paints, IMO ban 2008



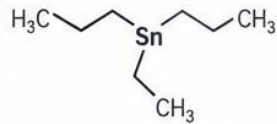
PVC stabilizers



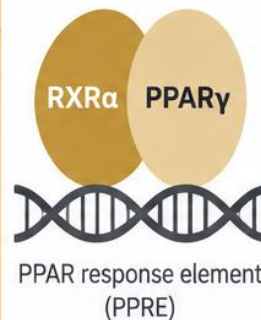
pesticides: triphenyltin

## Mechanism

**Organotins:**  
tributyltin (TBT),  
triphenyltin (TPT)



bind RXR $\alpha$  and  
PPAR $\gamma$  at nanomolar  
concentrations  
—  
RXR/PPAR $\gamma$   
heterodimer activated



↑ adipocyte  
differentiation and  
lipid accumulation  
(adipogenesis)



## Evidence

Newborn mice exposed to  
TBT → **increased adiposity**  
in adulthood, transmitted to  
F2–F3 generations  
(Grün et al. 2006)

Classic ecotoxicology:  
TBT causes **imposex**  
in marine snails at  
picomolar levels

Obesogen hypothesis:  
endocrine-disrupting  
chemicals promote obesity  
by redirecting precursor cells  
toward adipocyte fate

**Lesson:** the same receptor promiscuity that causes drug toxicity lets environmental chemicals hijack metabolic regulators — nuclear receptors as targets of pollution.

# TAKE-HOME MESSAGES

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- Nuclear receptors mediate toxicity by altering gene transcription - no genotoxicity required.
- Ligand promiscuity (AhR, ER, PXR) means many unrelated chemicals can trigger the same receptor.
- Species differences in receptor biology (PPARα, PXR, CAR, AhR affinity) make extrapolation the central problem of risk assessment.
- Receptors cross-talk - toxicity rarely comes from a single receptor in isolation.
- NR toxicology is clinically relevant (troglitazone, rosiglitazone, isotretinoin) and therapeutically exploitable (tapinarof, AhR ligands in IBD).