

# Suspected effects of hazardous chemicals on wildlife

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# Topics

- Mass mortalities repeated
- Effects of chemicals on health of organisms

General information on mechanisms of toxicities

**EDCs**(endocrine-disrupting chemicals)

= Biological Effects mediated **nuclear receptor**

e.g. to neural system, immune system(thyroid function) & reproductive system

# Mass mortalities at Peru, Spring of 2012



**Feb.**, Stranding of dolphins

→ > 900 individuals

...have no known cause



**Apr.**, Sea birds (Pelicans, gannets etc.)

→ >5,000 individuals

**May** (Chile, neighboring country) Pelicans → 2,300

Rising water temperatures  
→ migration of fishes  
(diets) → starvation

# From 2011~(case of late)

## 2011

- Feb. New Zealand: Pilot whale →  $n=107$
- Mar. Japan (Ibaraki): Melon-headed whale →  $n=52$
- Australia (Tasmania): Pilot whale →  $n=32$
- May Scotland: Pilot whale →  $n=100$
- Nov. Australia: Sperm whale • Pilot whale →  $n=20+61$

## 2012

- Winter Japan (Saga): Pen shell
- Jan. Norway: Marine fishes →  $n=20t$
- USA: Terrestrial birds →  $n=$  several hundred
- Apr. China: Finless porpoise →  $n=20+15/300, 800$
- Japan (Wakayama) Eel • carp →  $n=65$
- Thailand: Storks →  $n=$  several thousand
- May Japan (Tottori): Carp →  $n=2,000$  (Mie) eel etc. → 1,000
- Germany: Fresh water fishes →  $n=500$



# Mass mortalities of seals came back at North Sea

May(2002): outbreak “mass death” of harbor seals (*Phoca vitulina*)

At first, large number of seal’s bodies were found on eastern part of Denmark.

Same phenomenon were expanded to wide area of European countries (Sweden, Holland and UK)

Estimated number of bodies: ca. 20,000 (ca. 2,000 individuals were found at only coastal area of Holland as 50 % of population of this area)

Apr. (1988) One student found a body of fetus of harbor seal.

Only three weeks from this, 40 bodies of fetus and pup were stranded

→Sweden (May) →Holland (Jun) →W. Germany → UK (Sep.)

17,936 bodies were found until on end of Oct.

(Number of seals reached to 18,000 until 1989)



From Baltic Sea, Gulf of Bosnia to Irish Sea

# Mass death of seabirds

Shearwaters, auks, etc. → in a cycle ?

1922 Streaked Shearwater (Japan Sea)

1993 Common Murre  $n \Rightarrow 100,000$  (Alaska)

1996 Pelican  $n=9667$  (California) ▪ Short-tailed Shearwater (Japan)

1997 Short-tailed Shearwater (Alaska ~ California)

Seabirds  $n=1300$  (Japan Sea ← the Nakhodka Accident)

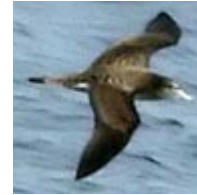
1999 Rhinoceros Auklet  $>10,000$  (Hokkaido) ▪ Cormorant (Saitama)

2000 Sooty Shearwater (Hokkaido)

2001 Streaked Shearwater (Japan Sea) ▪ Murres (Aomori)

2005 Brandt's Cormorant (West USA) ▪ Mallard  $n=215$  (Chile)

2006 Brünnich's Guillemot, Crested Auklet  $>5,000$  (Hokkaido)



Streaked Shearwater



Common Murre



Short-tailed Shearwater

**”The sea plays a final sink of all chemicals discharged by man”**

# Mass death of fishes

2002 Japan (Japanese trout ▪ crucian)

2003 Japan (Epidemic “koi herpes virus”)

2004 Japan (Great amberjack)

2005 Japan (Carp ▪ crucian)

2006 China ▪ Japan (Crucian etc.)

2007 Thailand ▪ Japan (Crucian)

.....

China

2005 : Jilin, 08 : Shandong、09 : Henan、11 : Fujian、12 : Shandong Province etc. ←Explosion, leakage and pollution by chemical plants



# Cause of Mass death of birds



Bohemian Waxwing



▪ Small scale  
Type "terrestrial"



Climate (direct/indirect)

Depletion of diets

Bacteria (produced toxin)

Infection

Pollution (toxic chemicals)

Accident (oil spil)

Dereliction of fish nets

Crime (pesticide, agents)

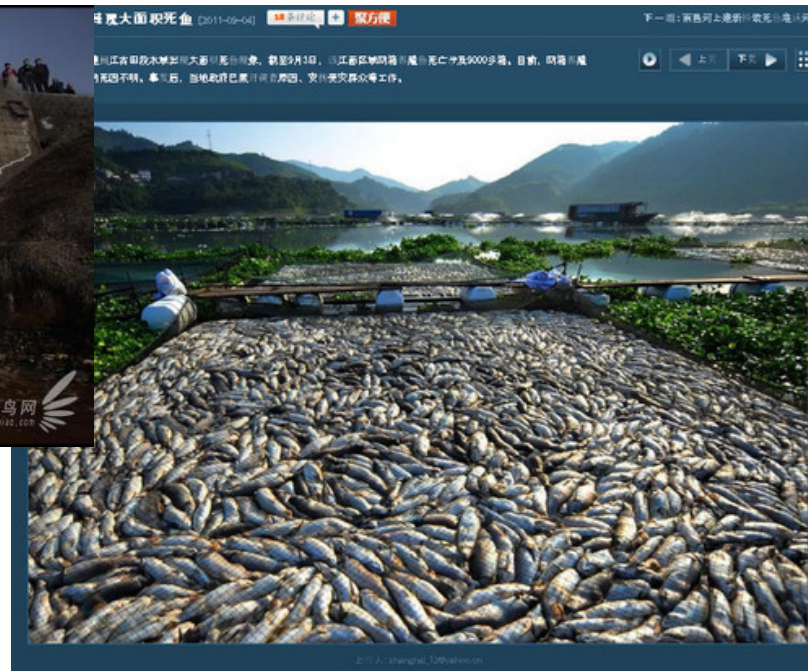
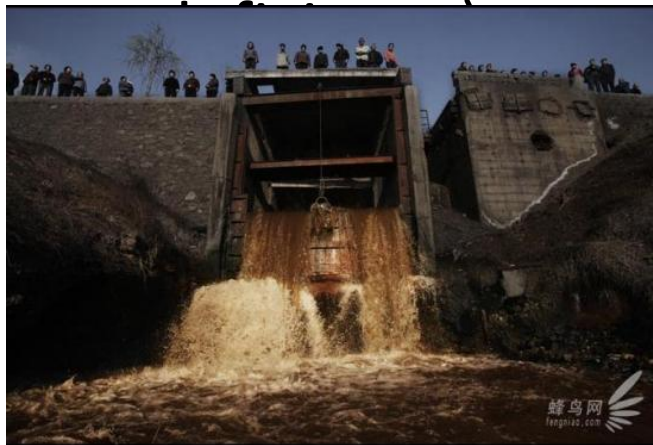
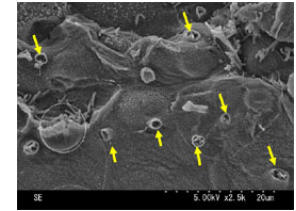
Natural

Anthro  
pogenic



# Cause of Mass death of fishes

1. Pollution (Hazardous chemical, wastewater,
2. Infection (Herpes virus etc.)
3. Climate condition (Temperature, oxygen



# Three major reasons

- Infection
- Climate condition
- Pollutant



# As a warning sign of crisis

- Mineral poison by Ashio copper mine

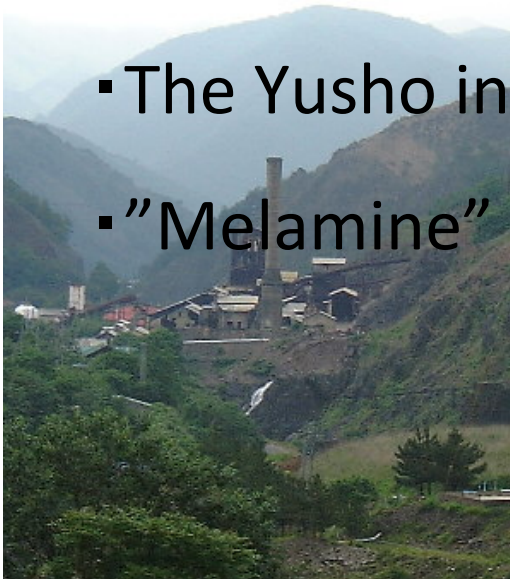
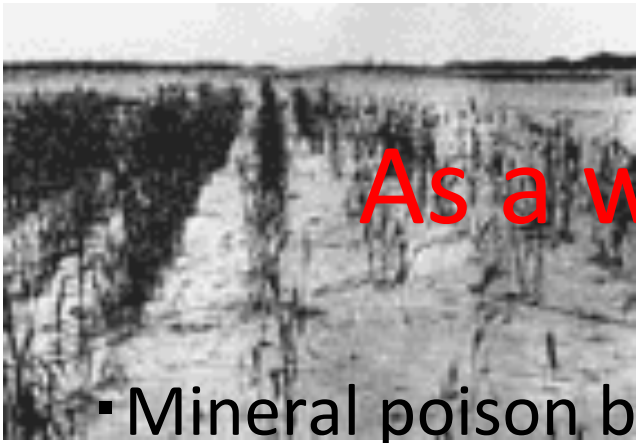
- Freshwater fishes (Ayu: Japanese trout)

- Itai-itai disease → Freshwater fishes (Ayu)

- Minamata disease → Fishes → birds → cats

- The Yusho incident → Chickens

- "Melamine" (China) → Pet animals



# Biological (toxicological) effect of hazardous chemicals

- General information of disposition (ADME) of chemicals
- Basic mechanisms of toxicities
- Introduction of case of EDCs as toxic effects

mediated nuclear receptor (NR)



# Disposition (Absorption, Distribution, Metabolism & Excretion) of chemicals

## Step4: Repair and & repair deficiency

Repair of  
**molecule**

Repair of  
**cell**

Repair of  
**tissue**

Repair deficiency

Toxicities from repair deficiency

**Tumor**

**Toxicity**

## Step3: Cellular dysfunction, injury

Damage of **cell regulation** (signaling)

Toxic changes at **cell maintenance**

## Step2: Interaction with target molecule

Effects to target molecule

or

Alteration of biological environment

Attributes of target

Reaction types

## Step1: Delivery (Exposure site to target site)

**Absorption**

Whole body

→Elimination

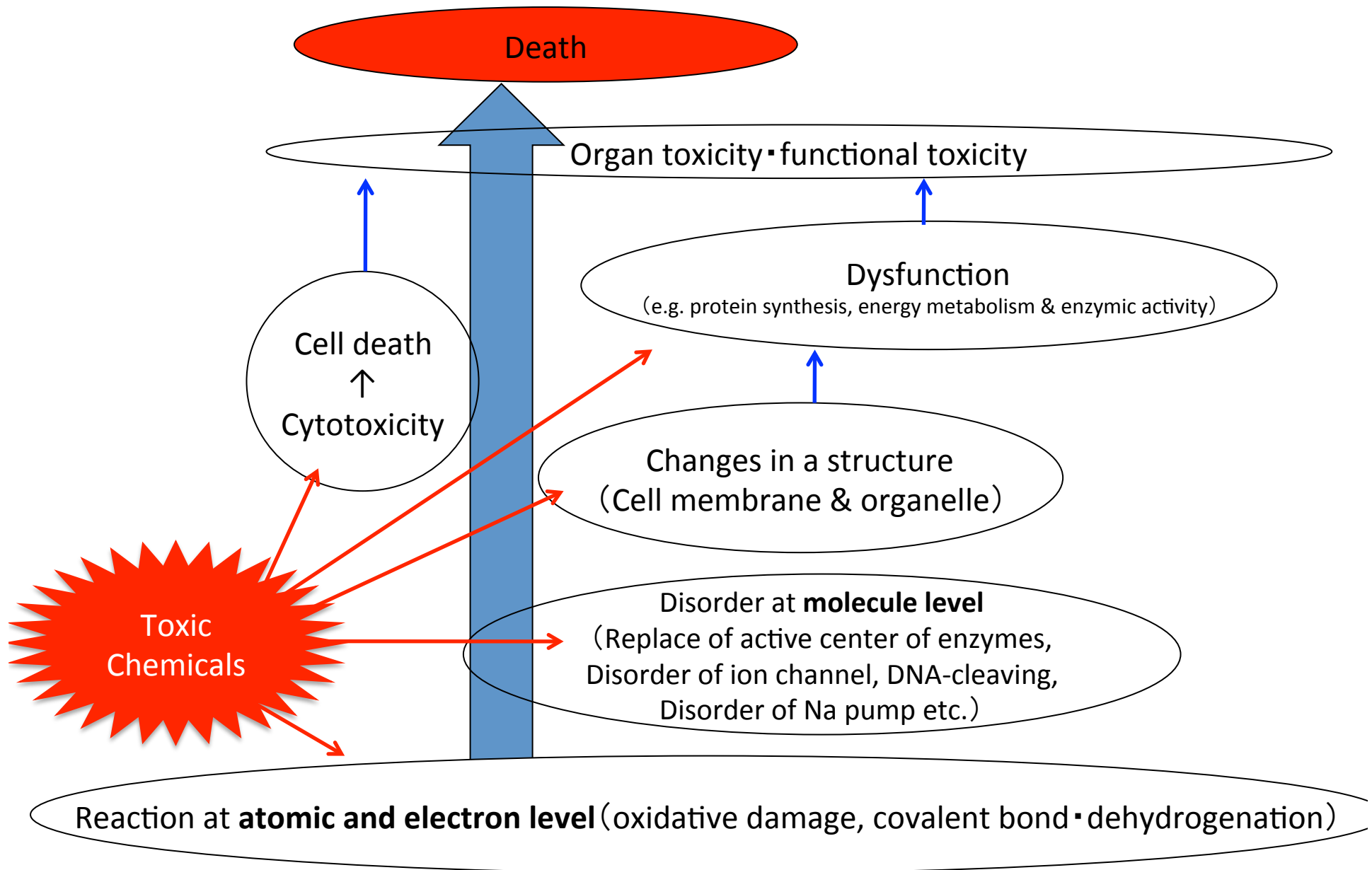
Target tissue

→Elimination

Excretion •  
reabsorption

Toxication or  
•detoxication

# Conceptual diagram of toxic mechanism using layered structure of animal body

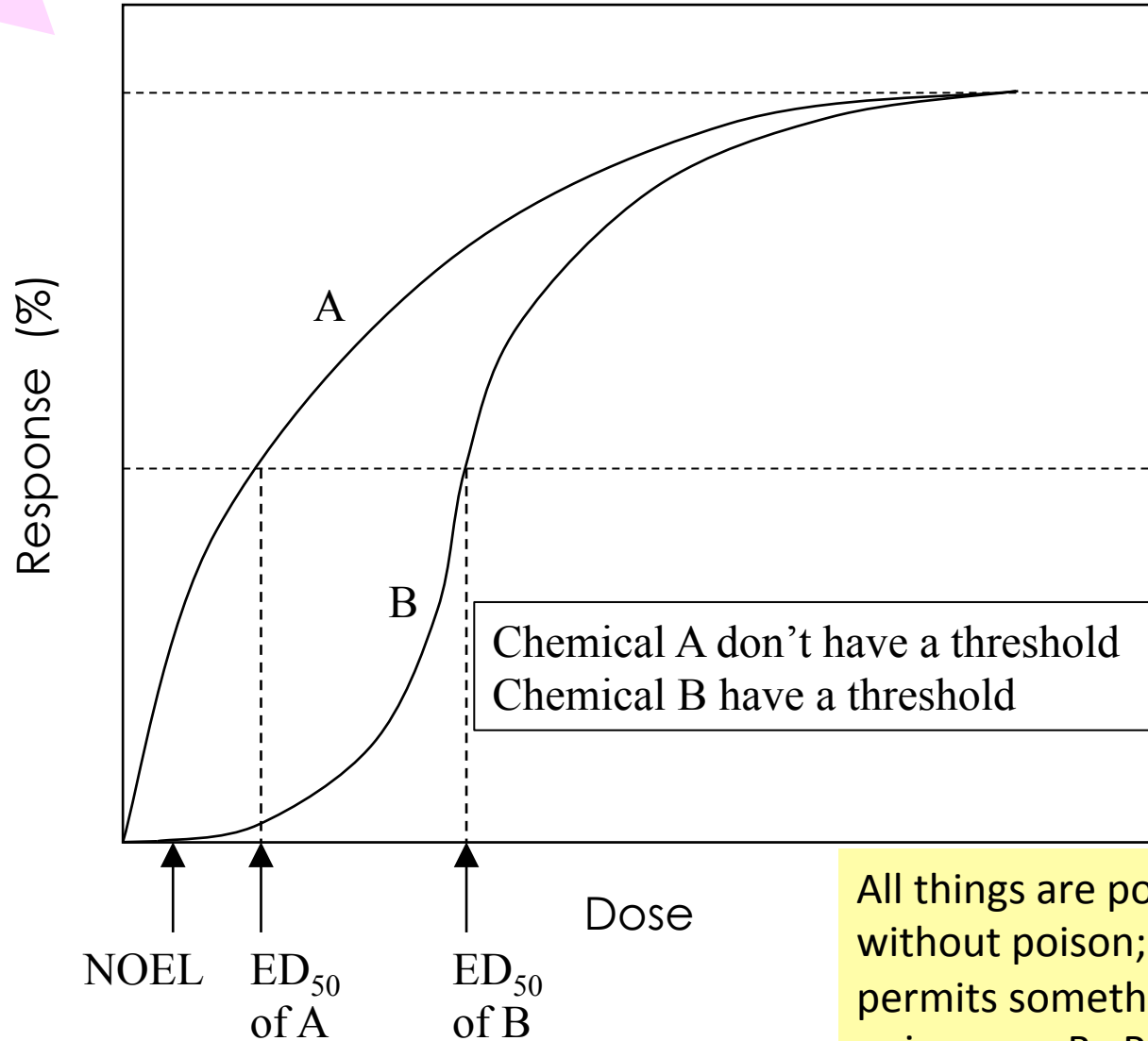


Basic concept  
of toxicology

## Dose-response relationship

of chemicals A & B

(Chemical B has a NOEL that is no-observed effect level)



All things are poison, and nothing is without poison; only the dose permits something not to be poisonous. By Paracelsus

## What are Endocrine disruptor compounds ?

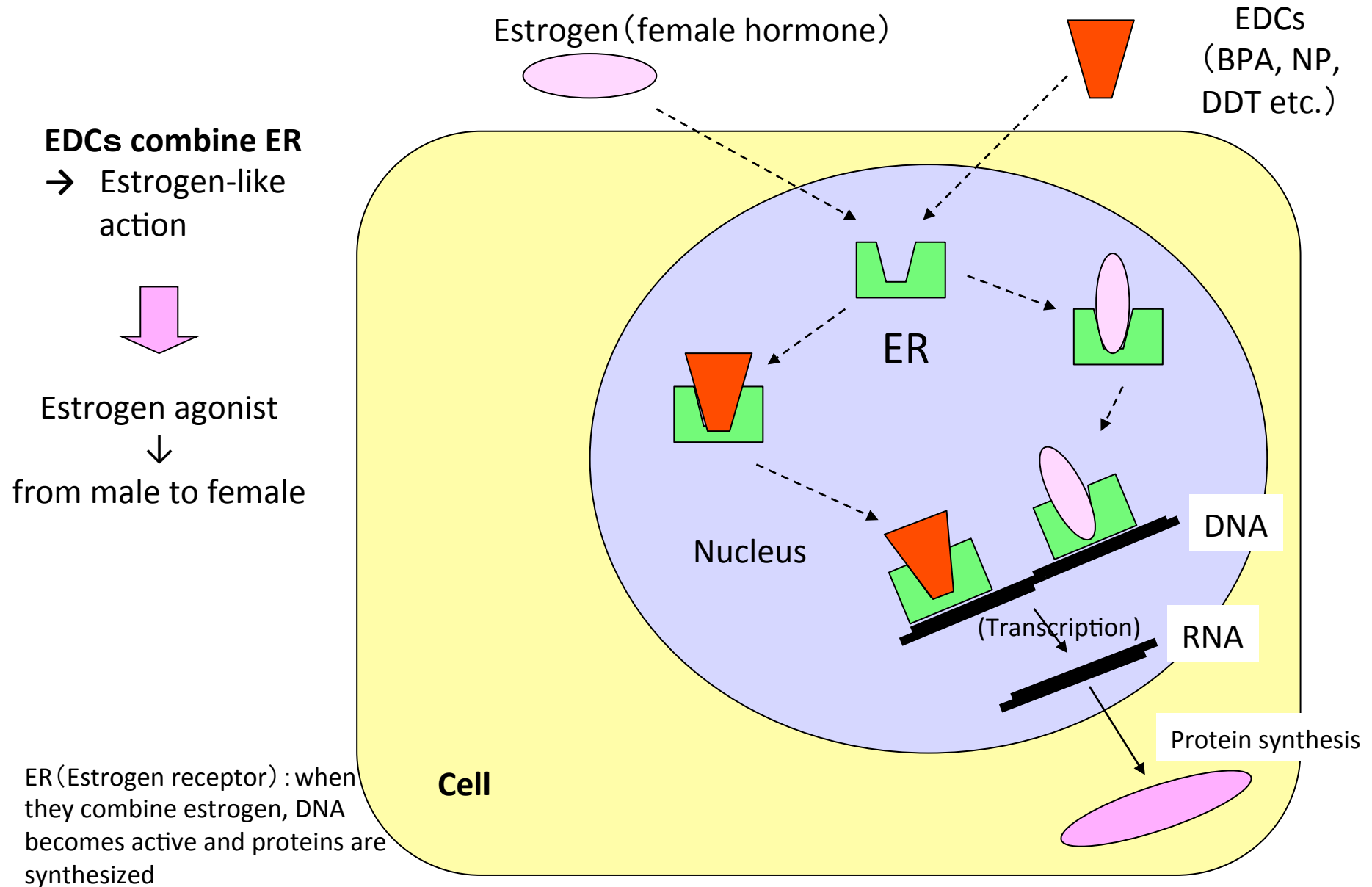
- They are chemicals that interfere with endocrine (or hormone system) in animals, including humans.
- They are known to cause learning disabilities, severe attention deficit disorder, cognitive and brain development problems, deformations of the body (including limbs); sexual development problems, feminizing of males or masculine effects on females, etc.
- Endocrine disruptors are substances that "interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for development, behavior, fertility, and maintenance of homeostasis (Crisp *et al.*, 1998)."



# In the first place, “What is Hormone ?”

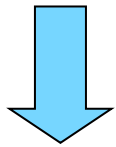
- Origin of a word : from Greek “Horman” means impetus
- This is a chemical released by a cell or a gland in one part of the body that sends out messages that affect cells in other parts of the organism.
- **Only a small amount** of hormone is required to alter cell metabolism. In essence, it is a chemical messenger that transports a signal from one cell to another.
- Cells respond to a hormone when they express a **specific receptor** for that hormone.
- The hormone binds to the receptor protein, resulting in the activation of a signal transduction mechanism that ultimately leads to cell type-specific responses.

# Mechanism of EDCs (Estrogen-like compounds)



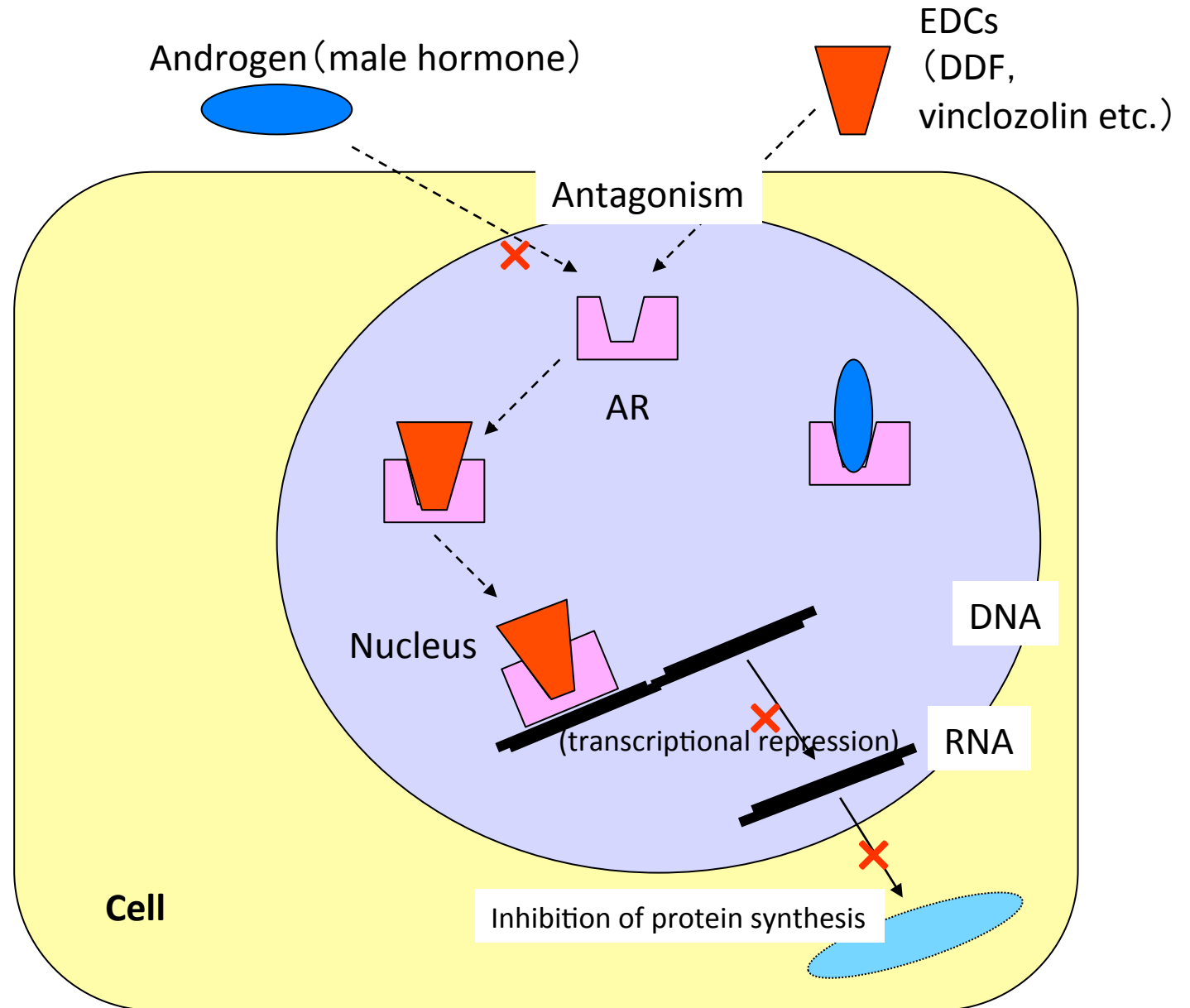
# Mechanism of EDCs (Androgen-like compounds)

EEDs combine AR,  
→ **block**  
combination of  
androgen with AR,  
as a result, they  
inhibit androgen's  
action.

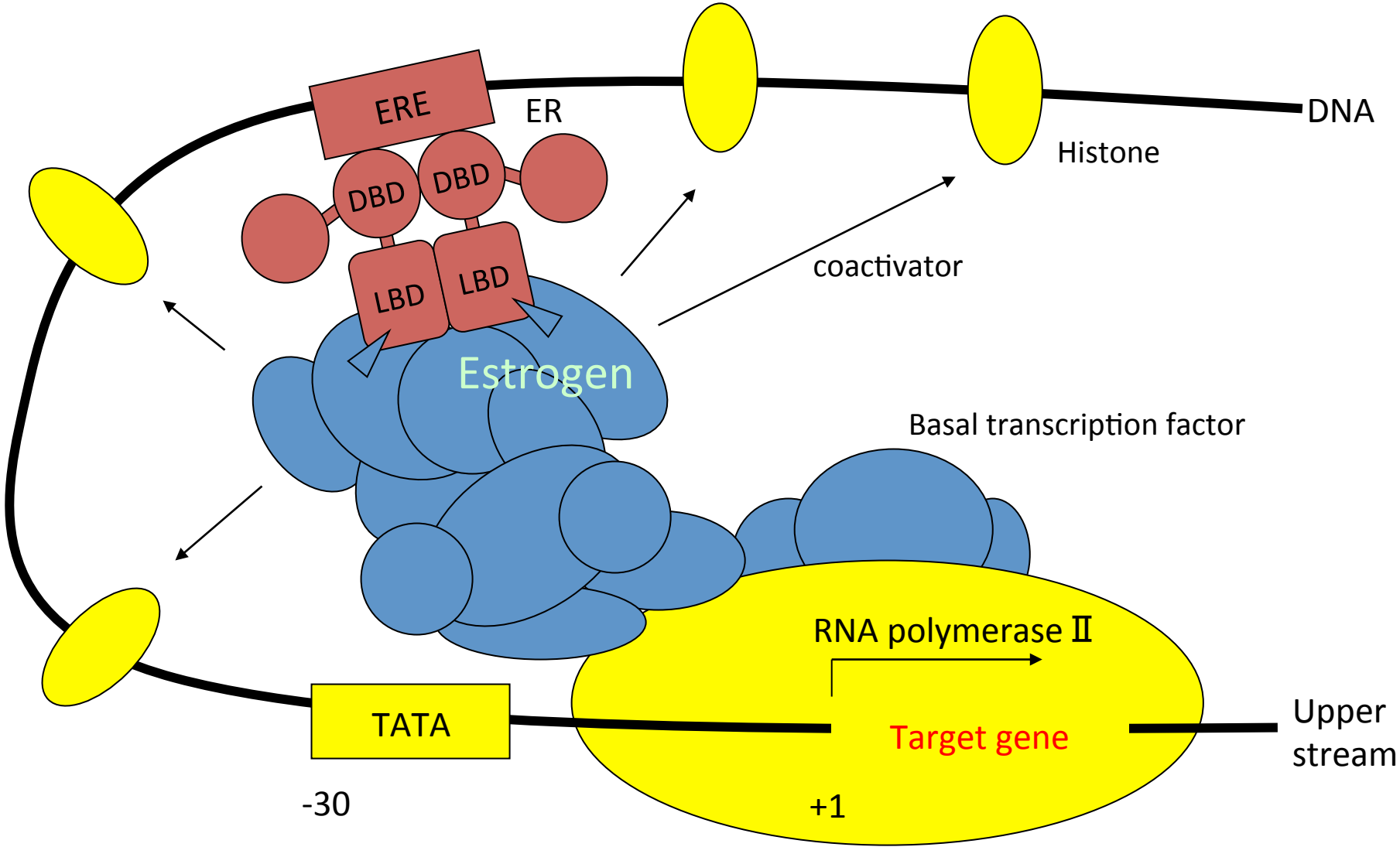


Androgen  
antagonist  
↓  
from male to female

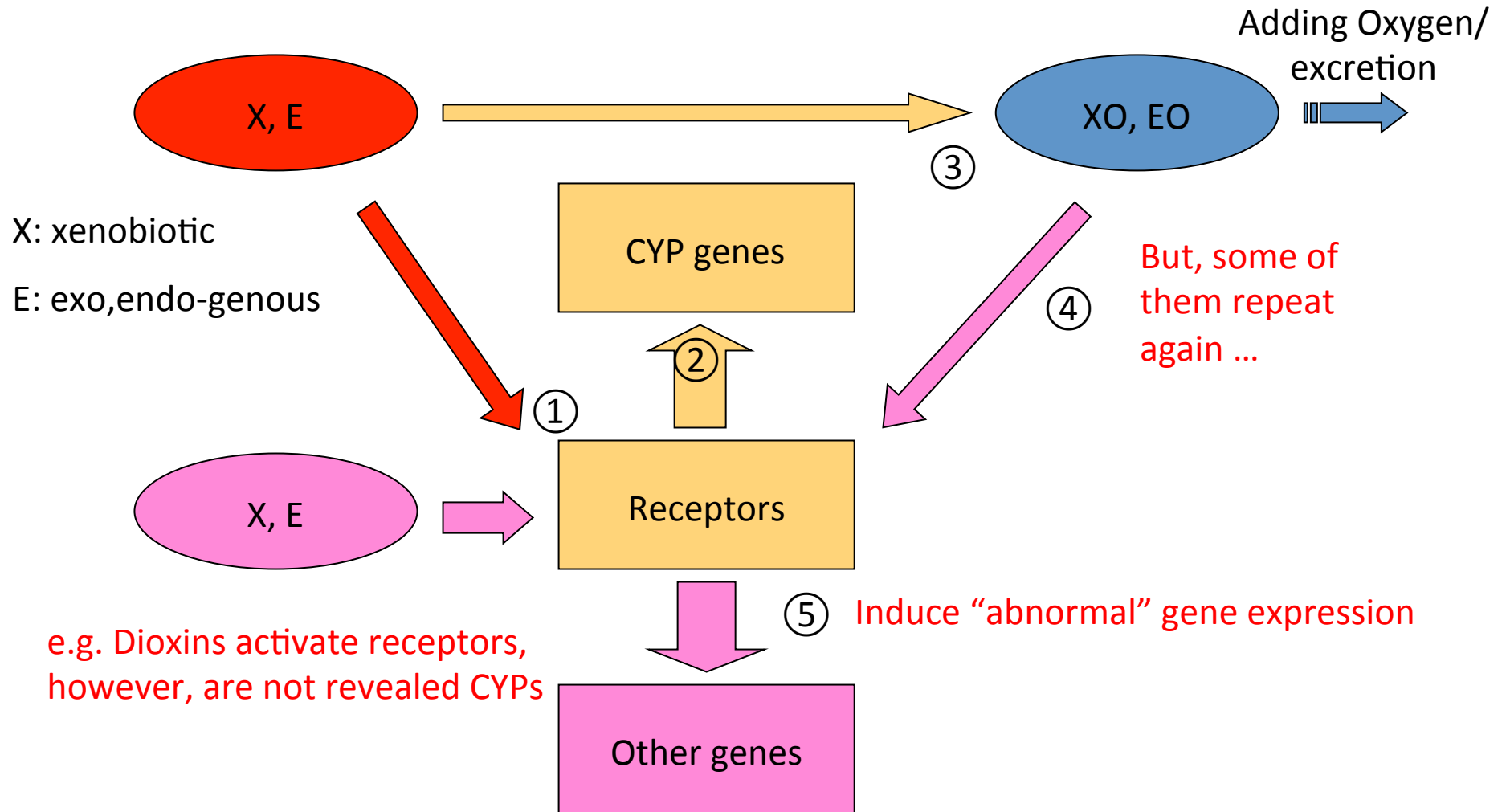
AR (Androgen receptor) :  
when they combine  
androgen, DNA becomes  
active



# Target genes mediated by estrogenic activity & receptor



# Ligand-receptor-CYPs



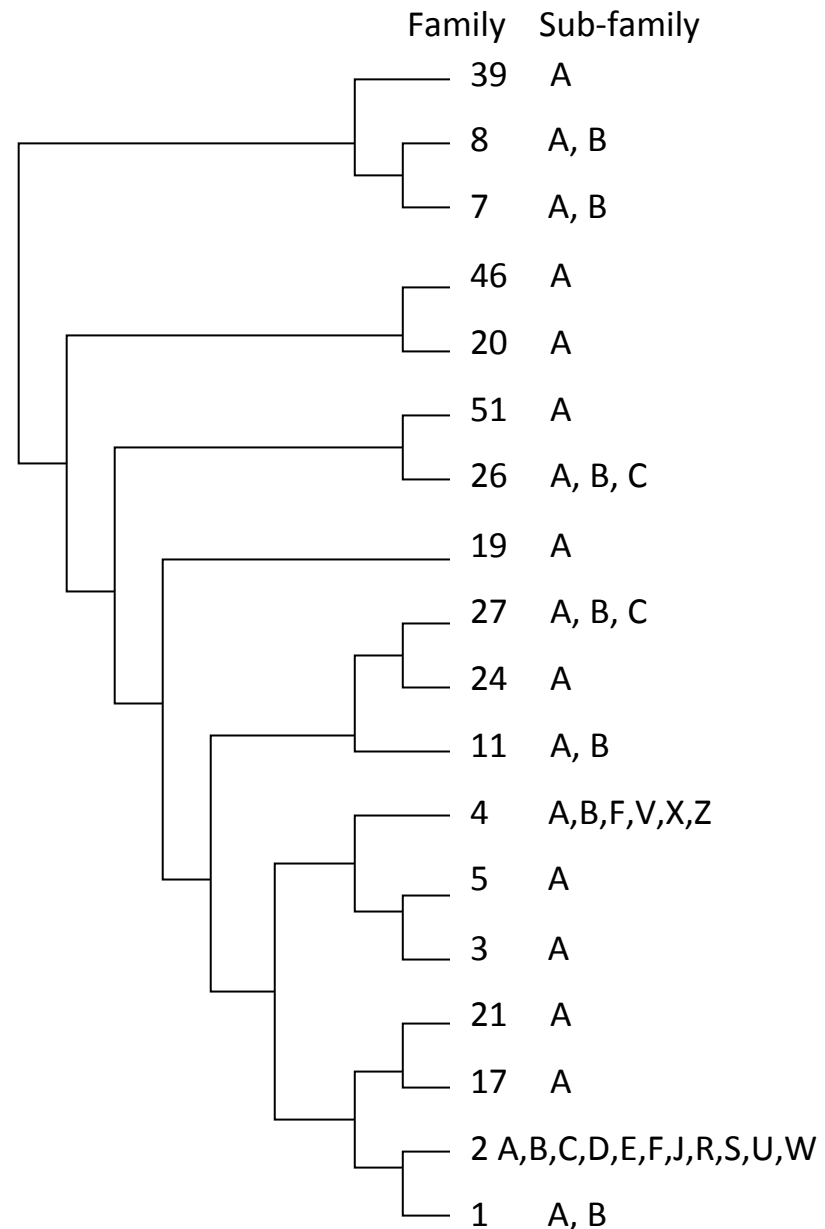
# CYP superfamily

- Monooxygenase (enzyme)

The function is to catalyze the oxidation of organic substances. The substrates of them include metabolic intermediates such as lipids and **steroidal hormones**, as well as **xenobiotic** substances such as **drugs, pollutants** and **carcinogen**.

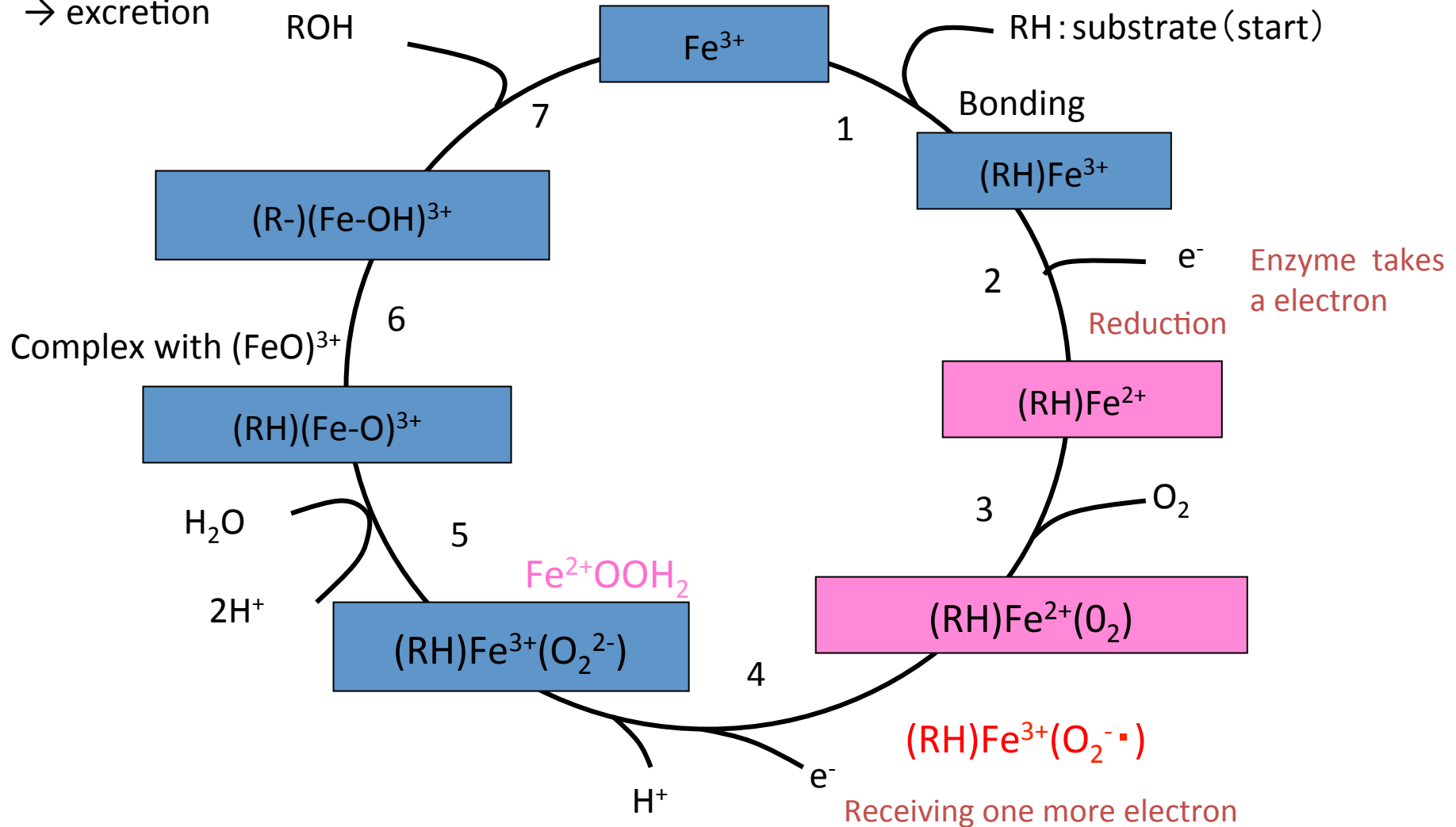
- They respond to endogenous/exogenous signal relating to changes of gene expression.

- Their transcription regulations are through ligand-dependent nuclear receptor.



# CYP catalytic cycle

(goal) Substrate gets a Oxygen:  
 Adding hydroxyl group → polarity ↑  
 → excretion



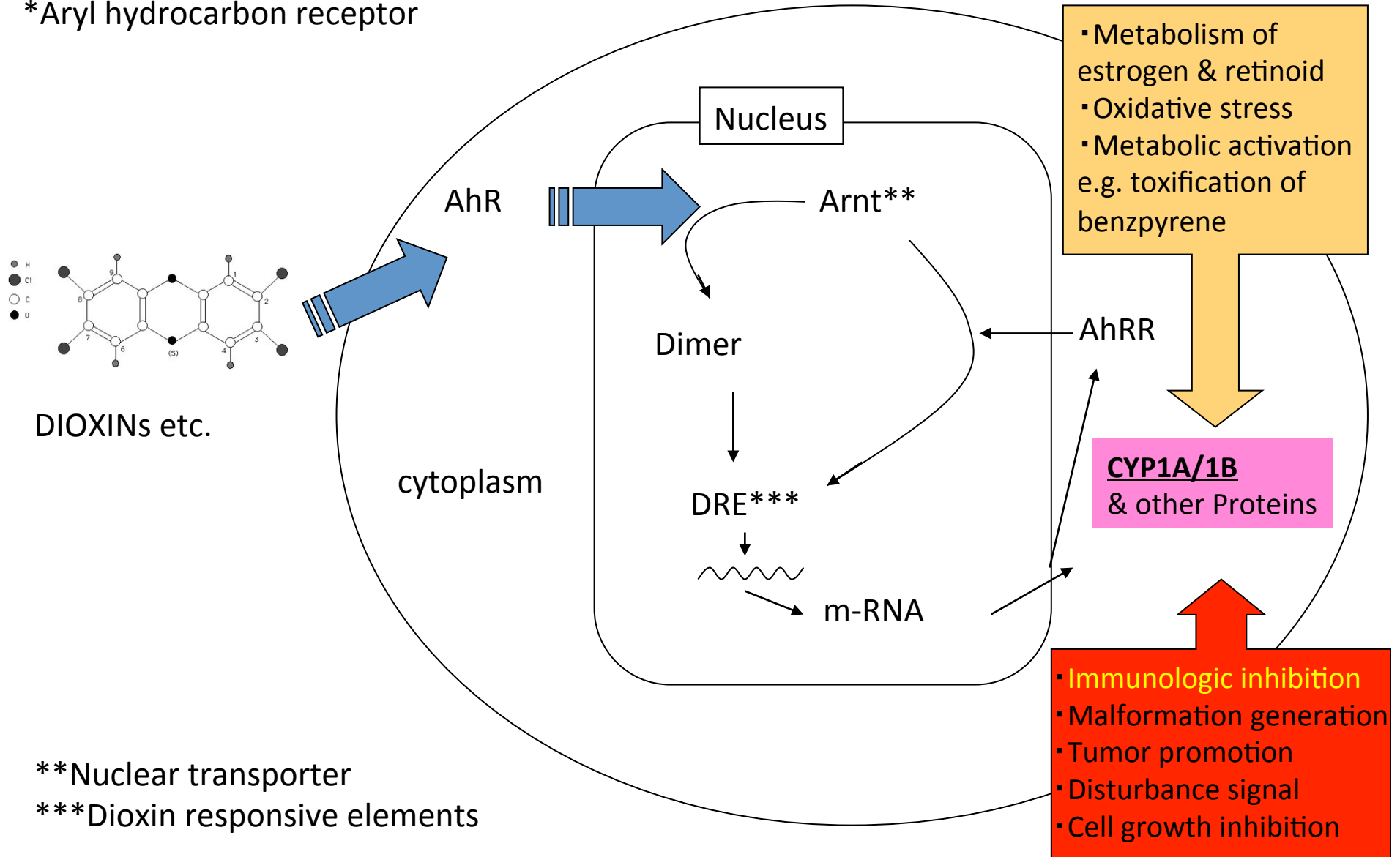
## Ligand, receptor and substance relating with CYP

CYP	Receptor	Exogenous ligand	Endogenous ligand	Endogenous substance
1A	AhR	Dioxin Coplanar PCB PAH	?	Estrogen Retinoid
2B	CAR	Non-coplanar PCB DDT Phenobarbital TCPOBOP	Androgen Estrogen Progesterone	Androgen Estrogen
3A	PXR (SXR)	Dexamethasone Rifampicin	Progesterone Carotenoid	Androgen Corticoid
4A	PPAR	Phthalate ester	Fatty acid Eicosanoid	Fatty acid



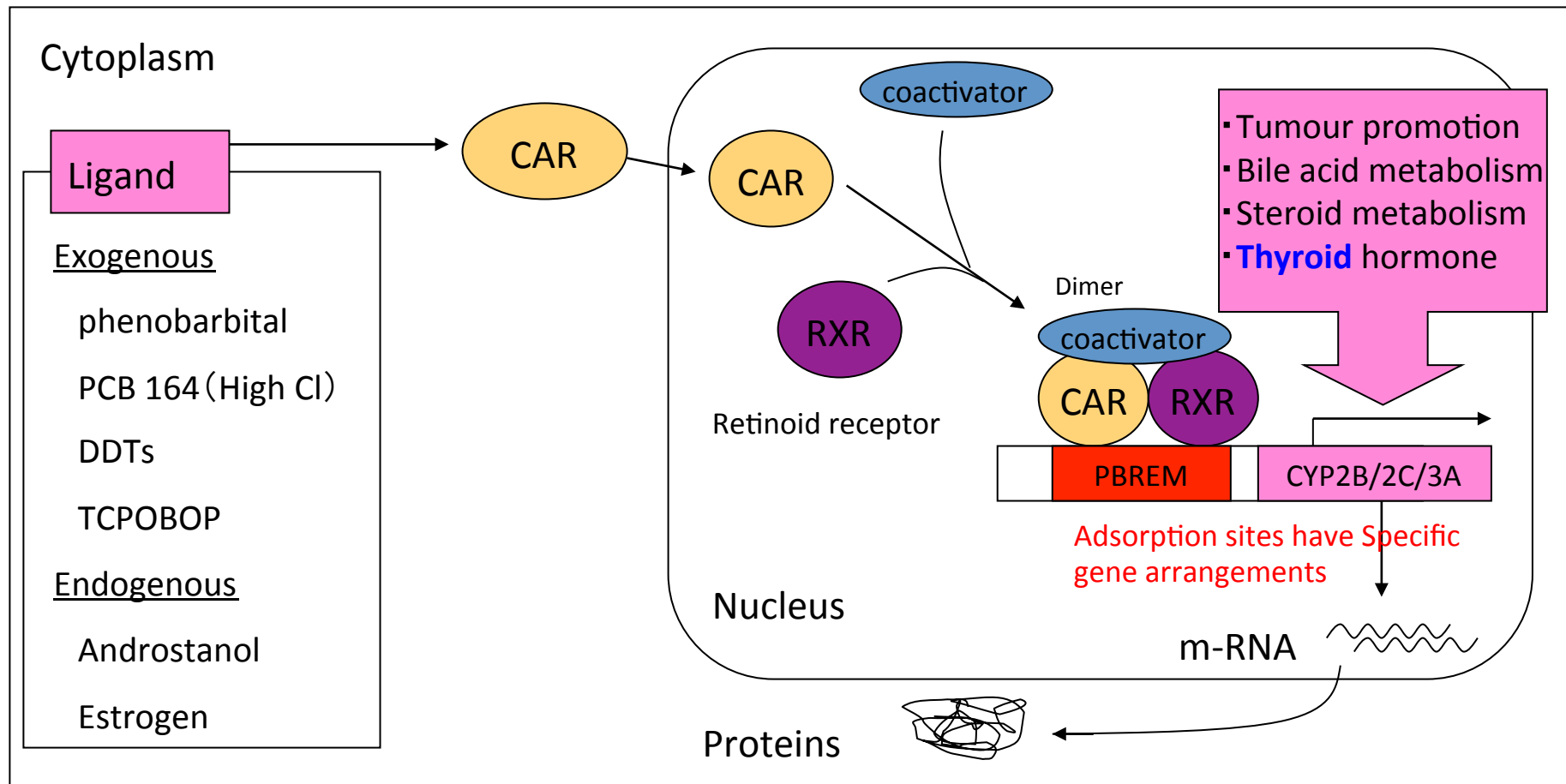
# Induction mediated by AhR\* → development of toxicity

\*Aryl hydrocarbon receptor



# Mechanism mediated by CAR\*

\*Constitutive Androstane /Active Receptor  
relating with CYP2B, 2C & 3A (DDTs & coplanar PCB)

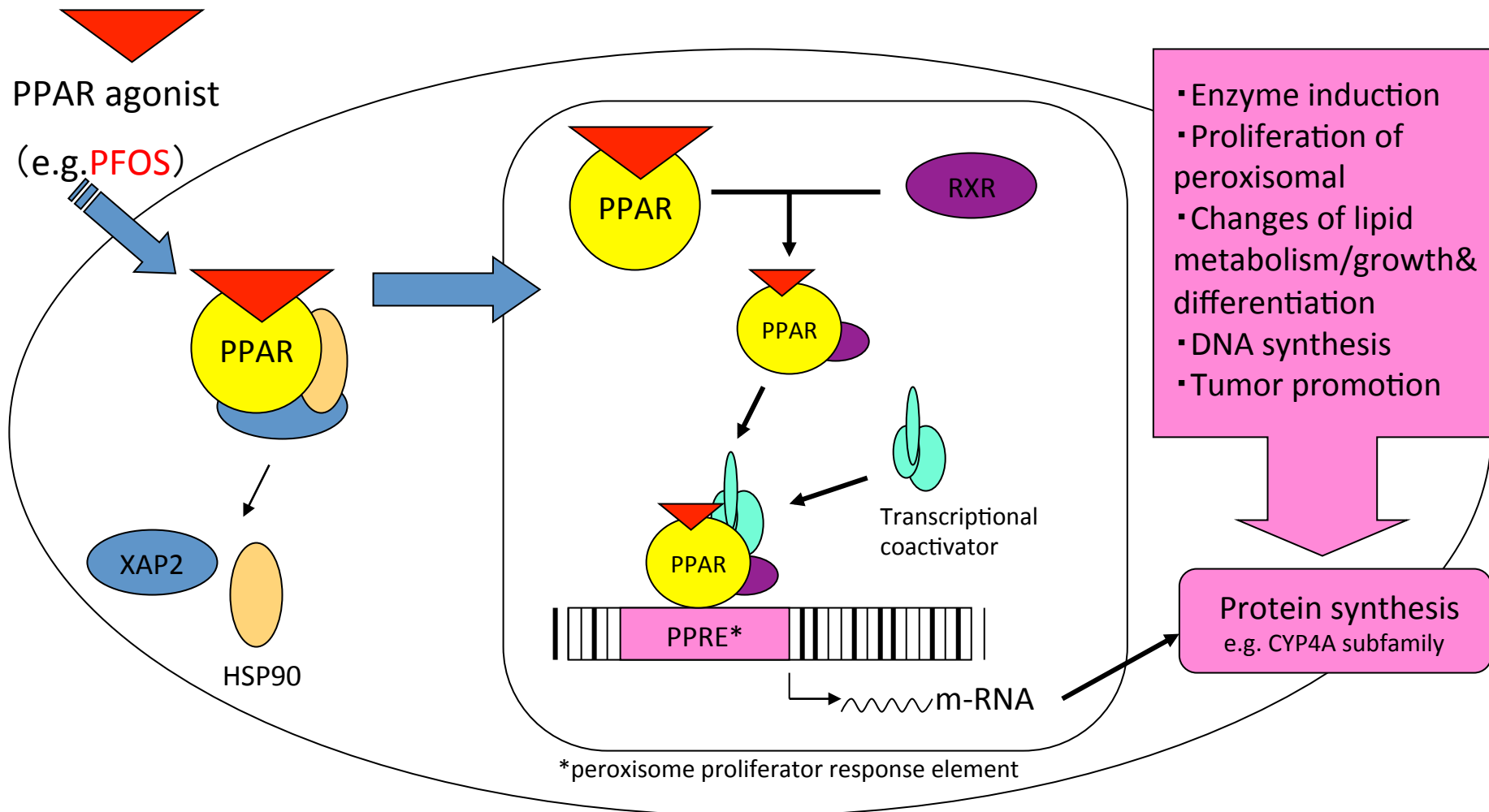


# Mechanism mediated by PPAR

Peroxisome proliferator-activated receptor:

nuclear receptor of ligand – induced transcriptional regulator

- Control manifestation of genes related with lipid metabolism → Cure of hyperlipidaemia



# Summaries

- Environmental contaminants are suspected that they contribute some toxic effects to wildlife health

- It is also suspected that hazardous chemicals give various disorders of organs and tissues mediated by biochemical

- It is require strongly to monitor and to remediate hazardous pollutants in all environments & wildlife





