

## **NATUREZA DA TOXICIDADE**

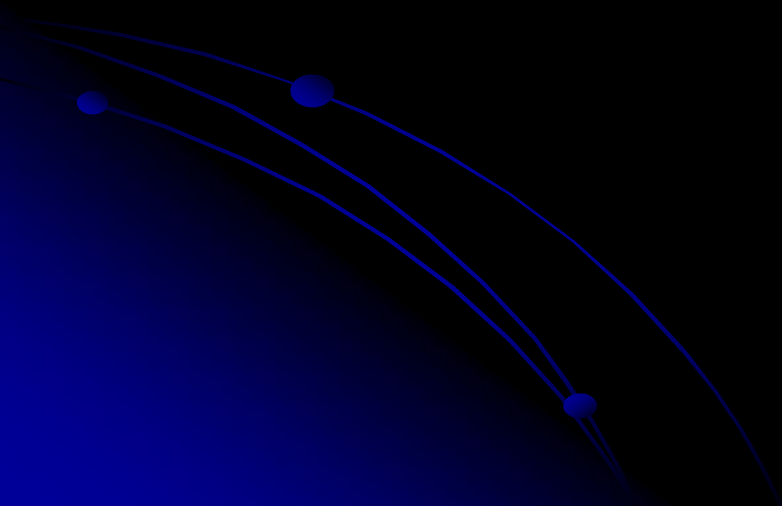
### **I - DESREGULAÇÃO DA FUNÇÃO CELULAR**

- a – desregulação da expressão gênica
- b – desregulação de células excitáveis eletricamente

### **II – DANOS ESTRUTURAIS**

- a - oxidação de macromoléculas
- b - inibição do metabolismo energético
- c - quebra da homeostase intracelular do cálcio
- d - reações imunológicas (idiossincrasia)

**DESREGULAÇÃO DA EXPRESSÃO  
GÊNICA INDUZIDA PELO TOXICANTE**



# A – DESREGULAÇÃO DA EXPRESSÃO GÊNICA

processo em que a informação codificada por um determinado gene é decodificada em uma proteína.

**DNA**

TAC CGG TTC GAA

transcrição

**RNA<sub>m</sub>**

AUG GCC AAG CUU

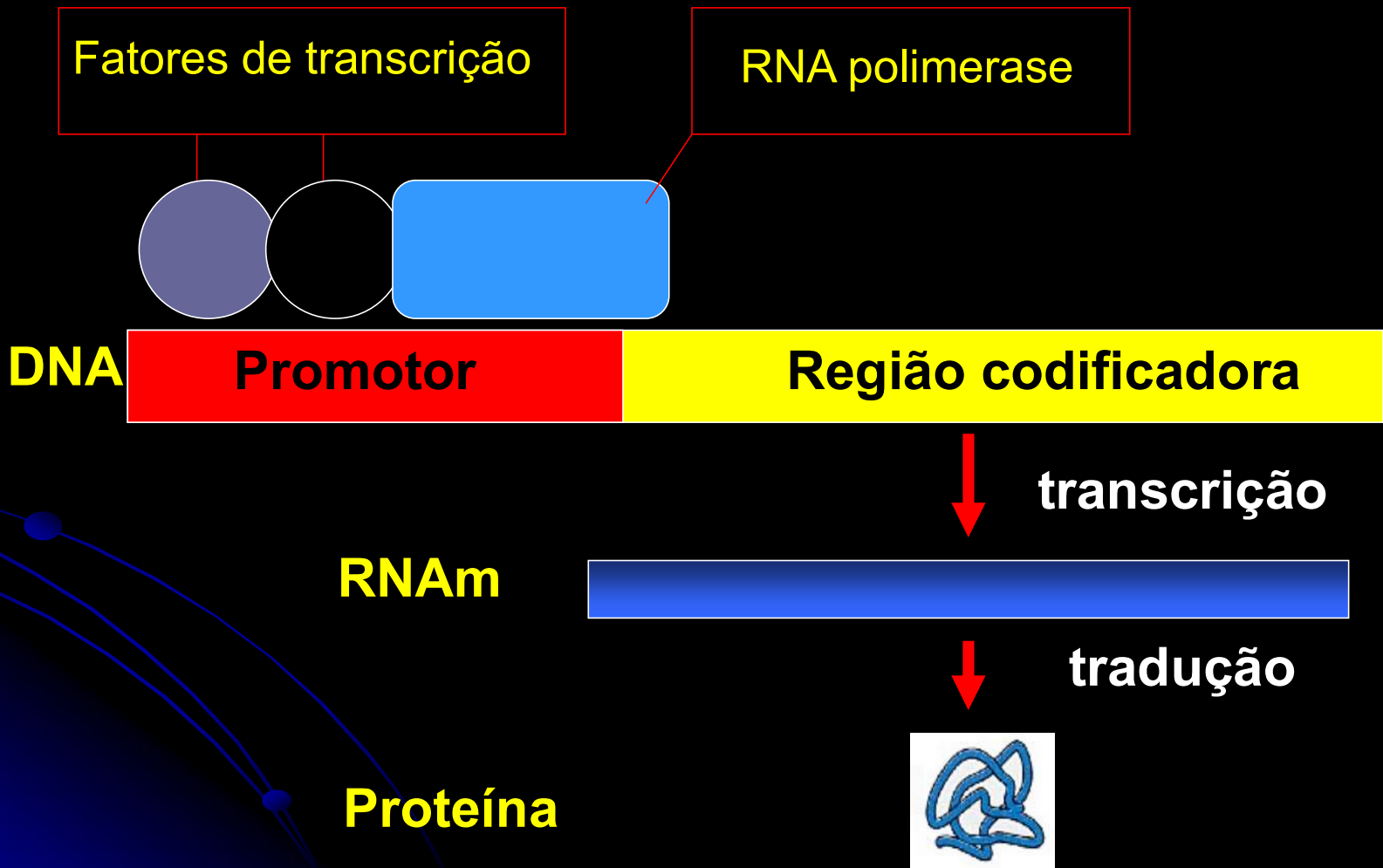
tradução

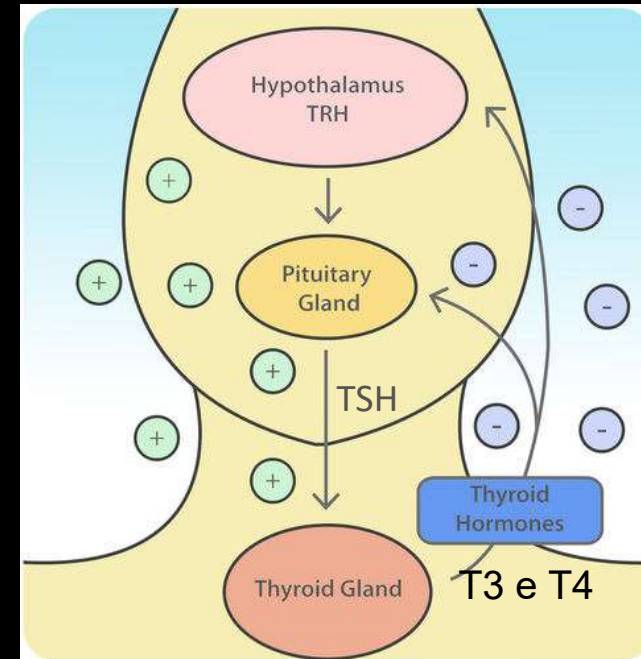
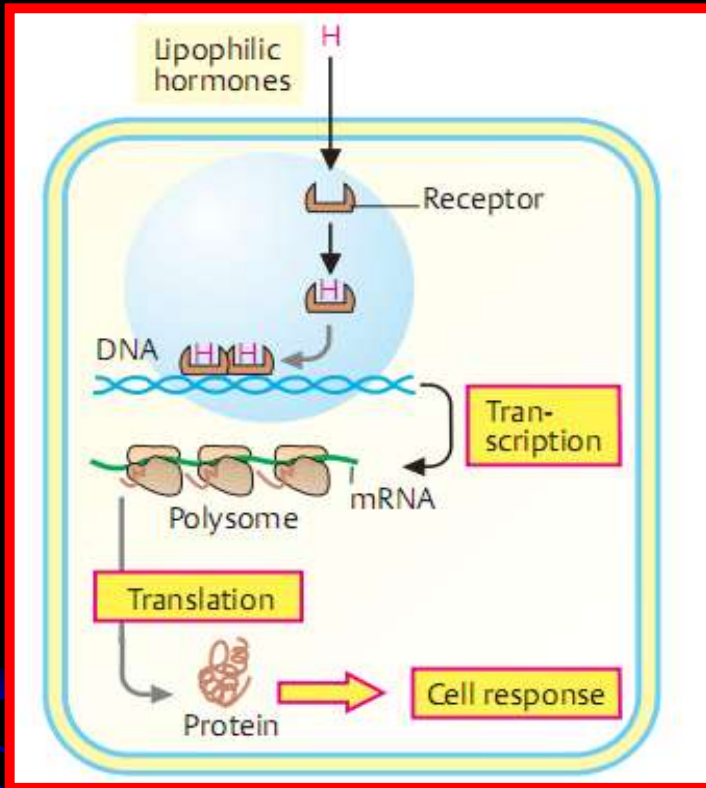
**proteína**

MET ALA LIS LEU

**FUNÇÃO BIOLÓGICA**

o toxicante provoca a ativação de fatores de transcrição





## Feedback negativo

[https://www.ck12.org/book/cbse\\_biology\\_book\\_class\\_xi/section/23.3/](https://www.ck12.org/book/cbse_biology_book_class_xi/section/23.3/)

### hormônios como ativadores de fatores de transcrição

hormônio liberador da tireoide (TRH)  
hormônio estimulador da tireoide (TSH).

triiodotironina (T3) e tiroxina (T4)

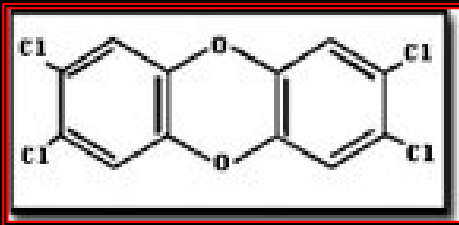
## Desreguladores Endócrinos

- ◇ são toxicantes naturais ou sintéticos que podem interferir com o sistema endócrino (síntese, secreção, transporte, ligação, ação e eliminação de hormônios)
- ◇ sistema endócrino = sistema do organismo responsável pelo desenvolvimento, crescimento, comportamento e reprodução
- ◇ controlado naturalmente pelas glândulas endócrinas: pituitária, tireóide, pâncreas, adrenal, ovários e testículos
- ◇ os efeitos são observáveis a concentrações extremamente baixas dos xenobióticos (partes por trilhão)

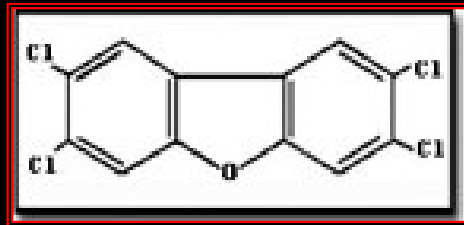
# Desreguladores Endócrinos

Category	Substances
Polychlorinated Compounds (from industrial production or by-products of mostly banned substances)	Polychlorinated dioxins, polychlorinated biphenyls
Organochlorine Pesticides (found in insecticides, many now phased out)	DDT, dieldrin, lindane
Pesticides currently in use	Atrazine, trifluralin, permethrin
Organotins (found in antifoulants used to paint the hulls of ships)	Tributyltin
Alkylphenols (Surfactants - certain kinds of detergents used for removing oil)	Nonylphenol
Phthalates (found in plasticizers)	Dibutyl phthalate, butylbenzyl phthalate
Hormones ( synthetic steroids, found in contraceptives)	Estradiol, estrone, and testosterone; ethynyl estradiol
Phytoestrogens (found in plant material)	Isoflavones, lignans

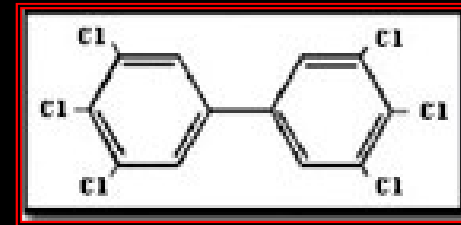
## DIOXINAS E COMPOSTOS RELACIONADOS



*2,3,7,8-Tetraclorodibenzo-p-dioxina  
(TCDD)*



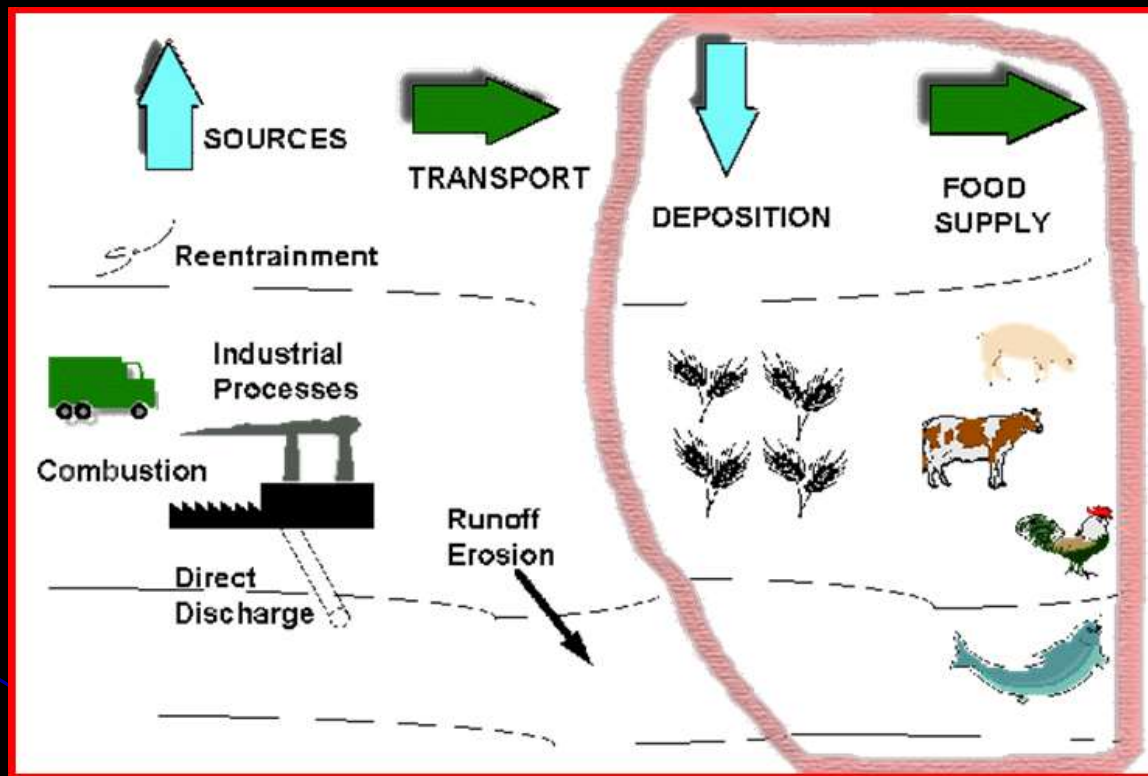
*2,3,7,8-Tetraclorodibenzofurano*



*3,3',4,4',5,5'-Hexaclorobifenila*

**Poluentes Orgânicos Persistentes  
(Persistent Organic Pollutants, POPs)**

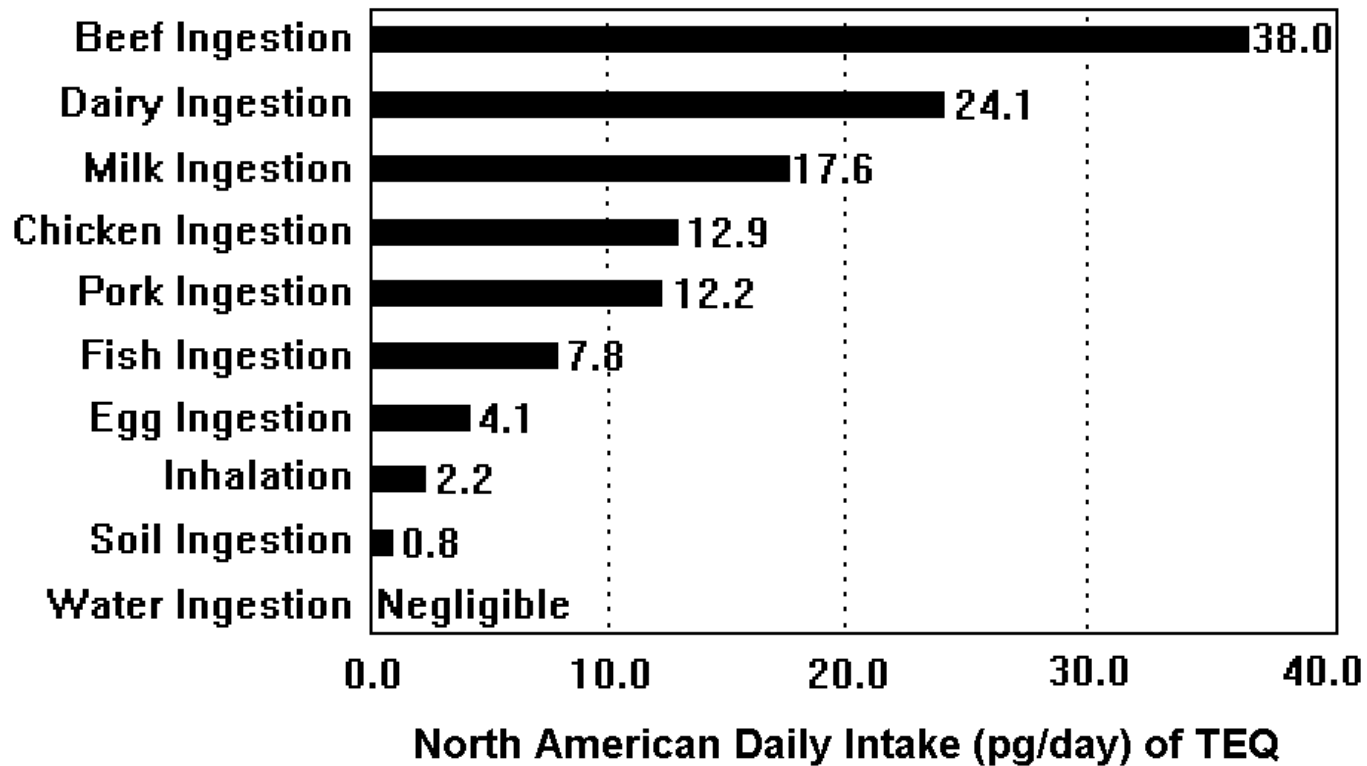




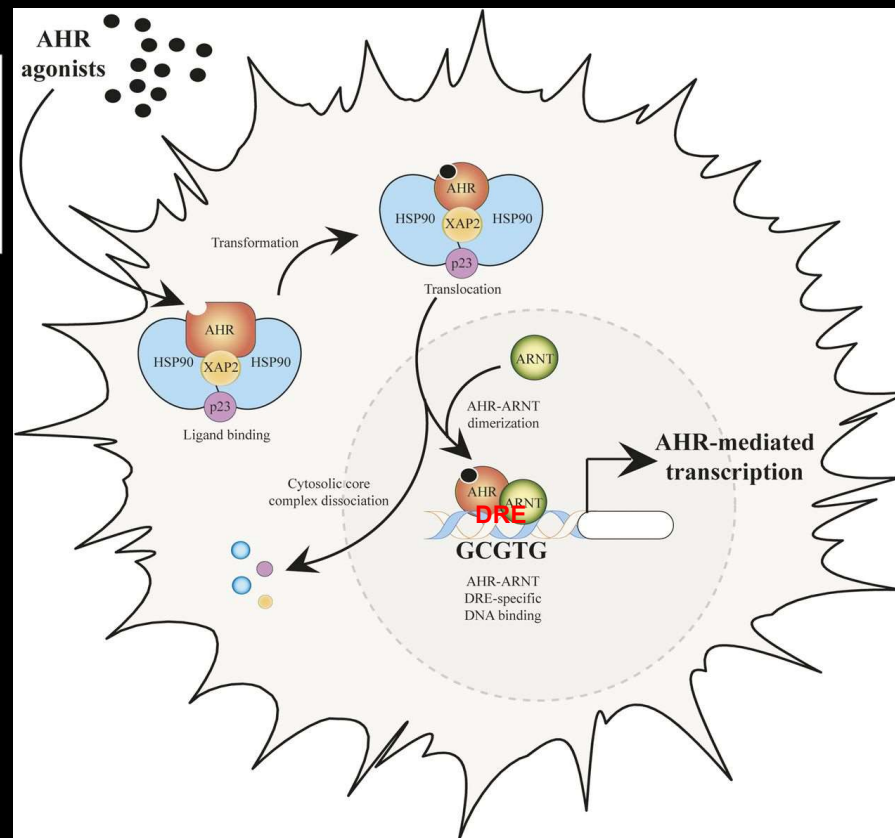
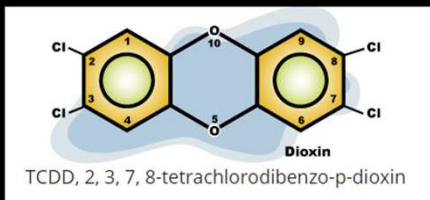
geração e fonte de exposição

## ***This is where you get your dioxin from:***

Total Exposure = 119 pg/day

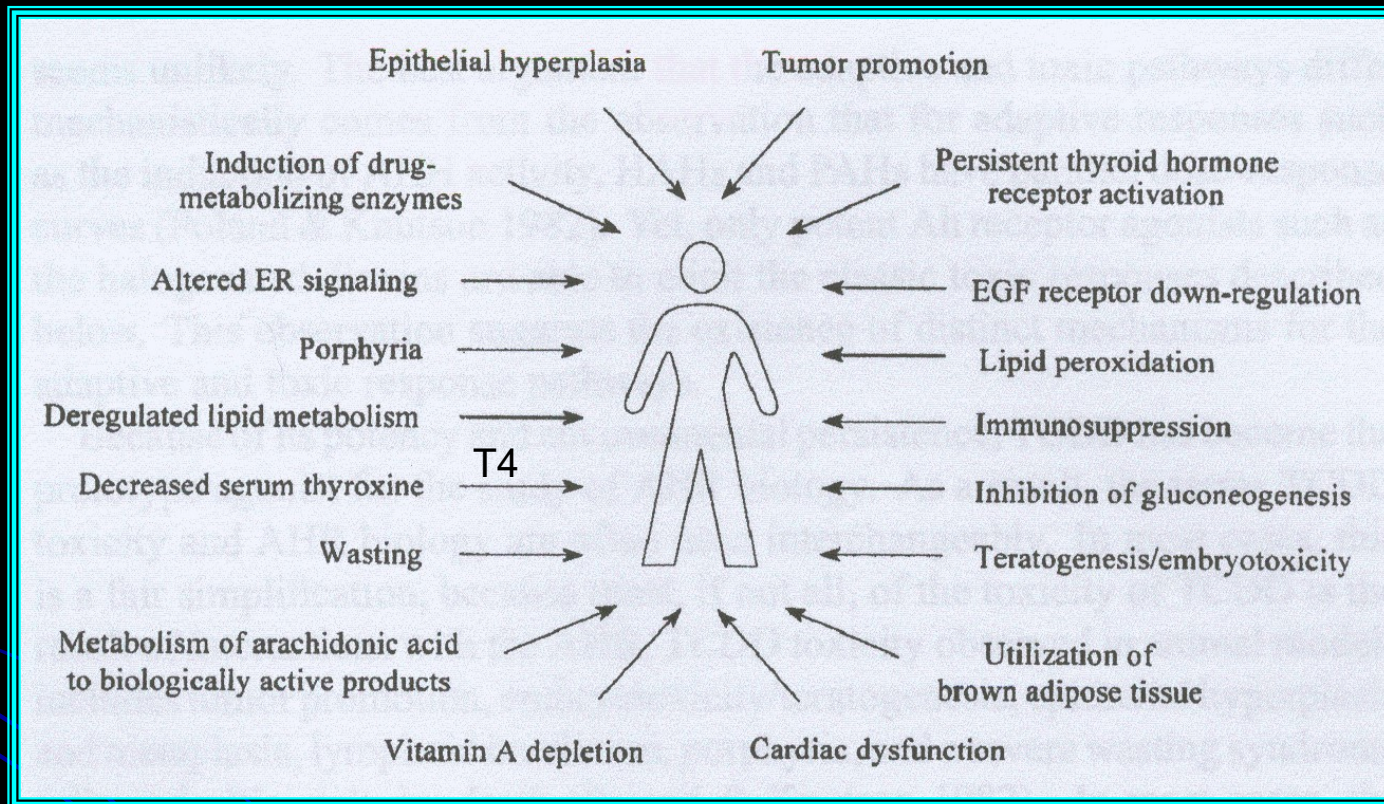


# RECEPTOR ARIL HIDROCARBONETOS (AHR) ou RECEPTOR DA DIOXINA



ARNT= translocador nuclear do receptor AHR

DRE= elemento de resposta à dioxina



**efeitos biológicos da ativação do AHR**

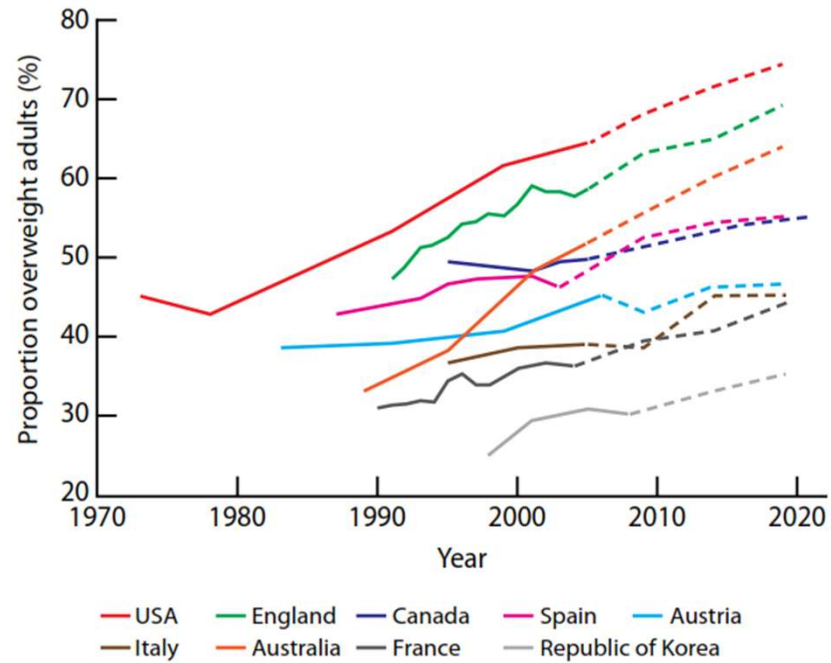
### **Male Reproductive Toxicity**

Reduced sperm count  
Testicular atrophy  
Abnormal testis structure

### **Female Reproductive Toxicity**

Decreases fertility  
Inability to maintain pregnancy  
Ovarian dysfunction  
Endometriosis

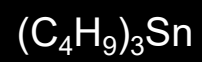
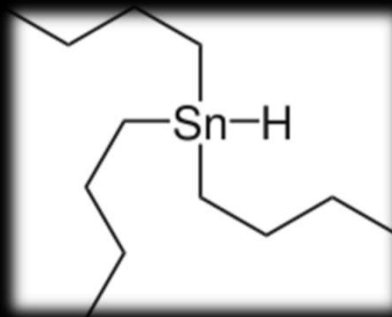
## Toxicantes Induzindo Ganho de Peso



**Figure 2.24.** Past (solid lines) and projected (dashed lines) overweight rates in selected OECD countries (OECD, 2010). Used with publisher's permission.

*The obesity epidemic cannot be explained by diet and exercise alone.*

## TRIBUTIL ESTANHO



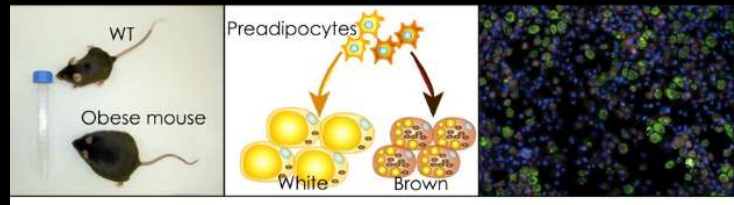
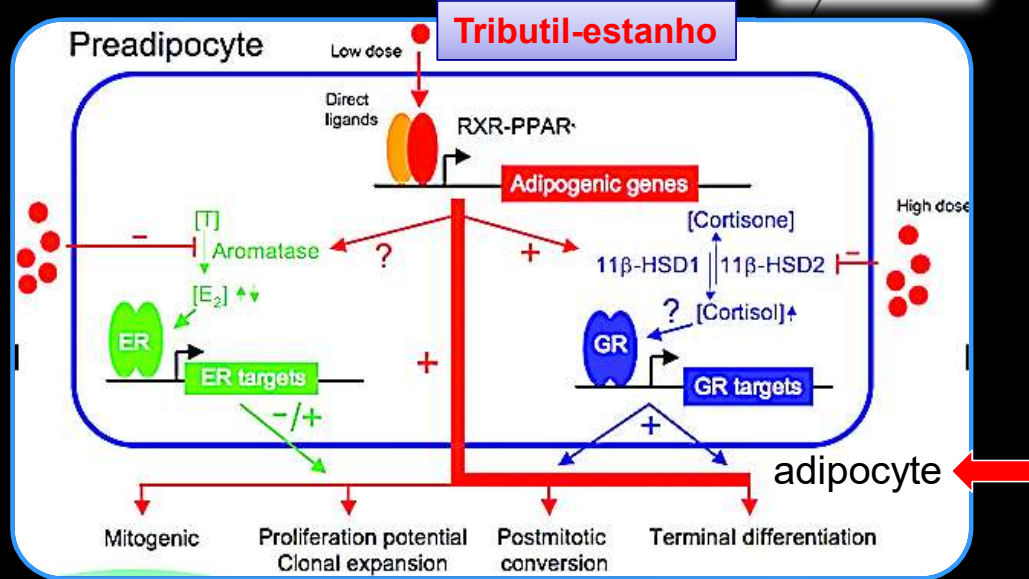
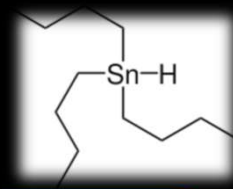
**Table 2.6.** List of known and suspected environmental obesogens (A=Animal study, C=Cell culture study, H=Human study). Janesick & Blumberg (2011) provide more detailed information about obesogens.

Chemical	Commercial use	Relevant EDC action	Obesogenic activity
Tributyltin	Pesticide, wood preservation	Binds PPAR $\gamma$	Changes identity of adipose precursors, increases triglycerides in adipose tissue (A)
Phthalates	Plasticizer	Binds PPAR $\gamma$	Induce adipocyte differentiation (C), men's waist size (H)
PFOA	Non-stick coatings	Weakly activates PPAR $\gamma$	Induce adipocyte differentiation (C)
Flavanone	Natural plant products used as flavourings	Binds PPAR $\gamma$	Induce adipocyte differentiation (C)
PCBs	Electronics	Binds AhR in adipocytes	CB-77 promotes adipocyte differentiation, obesity (C,A)
Bisphenol A	Plastics	Binds ER, ERR $\gamma$	Induces adipogenesis (C), obesity (A)
Hexachlorobenzene	Fungicide	Alters TH signaling	Gestational exposure levels influence BMI (H)
Bisphenol A diglycid ether	Epoxy resins	Unknown	Induces adipogenesis (C)
PBDEs	Fire retardants	Reduces thyroid function	Stimulate fat production (C)
Diethylstilbestrol	Pharmaceutical estrogen	Binds ER	Perinatal exposures cause obesity (A). BMI in young children (H)
Genistein	Natural component in soy	Binds ER	Perinatal exposures cause obesity (A).
Perfluoroalkyl sulfonate	Non-stick coatings	Binds ER	Perinatal exposures cause obesity, alter insulin & leptin levels (A).
Nicotine	Found in tobacco products		Alters development of pancreas & adipose tissue, increases adipose cell size (A)
DDE	DDT metabolite	Binds ER	Concentrations in mothers associated with weight and BMI in female offspring (H)

The mechanisms by which most of these chemicals affect weight gain are largely unclear. Tributyltin, one of the few chemicals studied in detail, activates the combined peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ )/ retinoid-X-receptor (RXR) pathway, the main pathway for fat cell differentiation (Janesick & Blumberg, 2011) and thereby stimulates fat cell differentiation in vitro and increases adipose tissue in vivo in mice. Similarly, chemicals with estrogenic activity like DES, genistein and BPA appear to act via estrogen receptors on fat cells, and cells of the brain and other tissues to regulate adipose tissue and food intake (Janesick & Blumberg, 2011).



# Xenobióticos Obesogênicos



RXR = receptor do ácido retinóico

PPAR = receptor ativador da proliferação de peroxissomos

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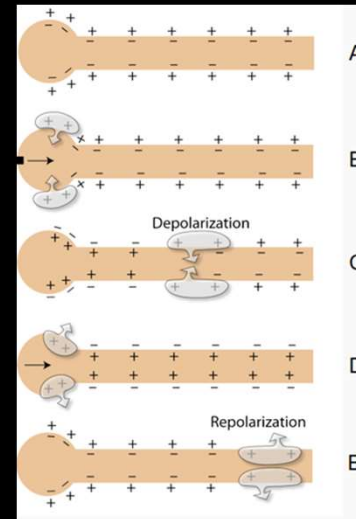
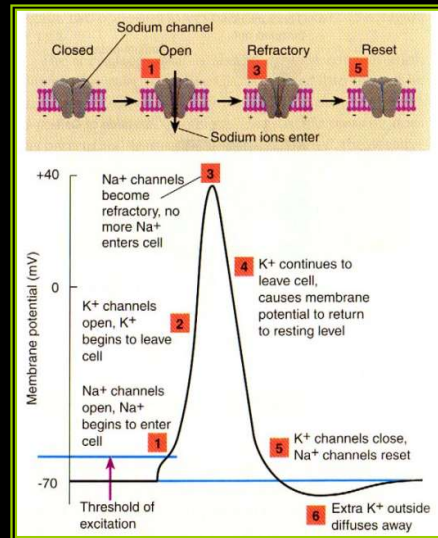
### **I - REGULAÇÃO DA FUNÇÃO CELULAR INDUZIDA PELOS TOXICANTES**

- a – desregulação da expressão gênica
- b – desregulação de células eletricamente excitáveis

### **II – DANOS ESTRUTURAIS INDUZIDOS PELOS TOXICANTES**

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## B - desregulação de células eletricamente excitáveis



Os toxicantes influenciam a atividade celular em células excitáveis por:

- alteração nos níveis de neurotransmissores
- interações do receptor de neurotransmissor com o toxicante

## desregulação da função celular em adamento

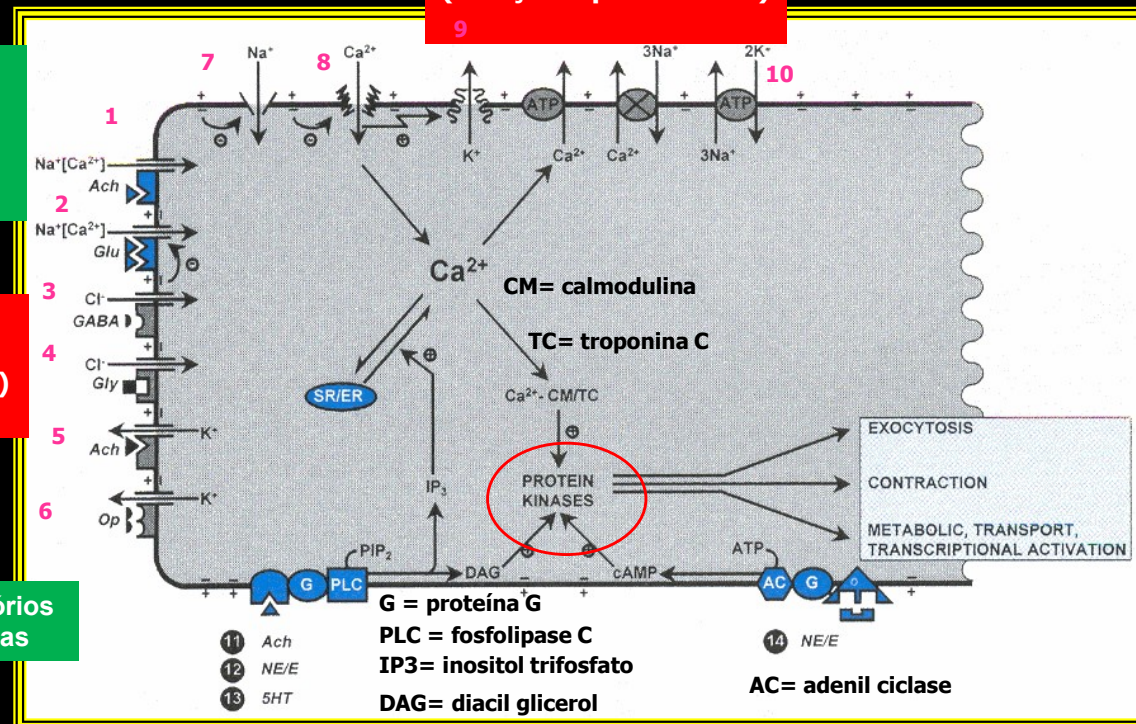
canais iônicos voltagem-dependentes (transdução rápida do sinal)

exportadores de cátions (inibição rápida do sinal)

receptores excitatórios ligados a canais iônicos (sinalização rápida)

receptores inibitórios ligados a canais iônicos (supressão rápida de sinais)

receptores excitatórios ligados a enzimas



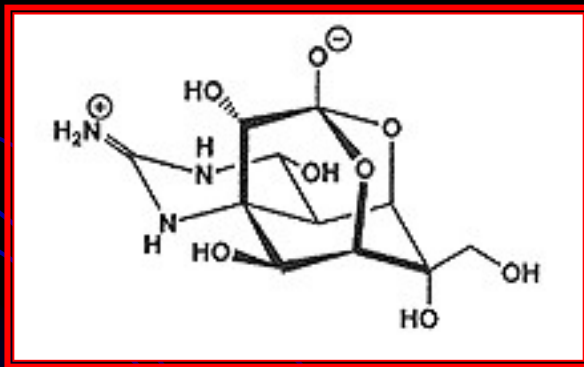
Tocicantes atuando com ativadores ou inibidores dos mecanismos celulares de sinalização em neurônios e músculo esquelético

**Agents Acting on Signaling Systems for Neurotransmitters and Causing Dysregulation of the Momentary Activity of Electrically Excitable Cells such as Neurons and Muscle Cells\***

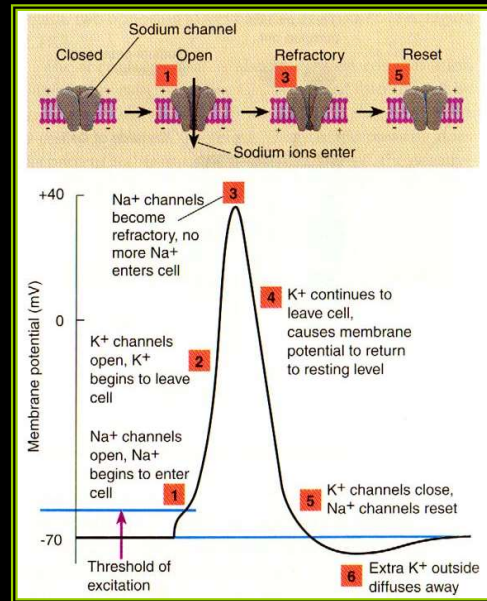
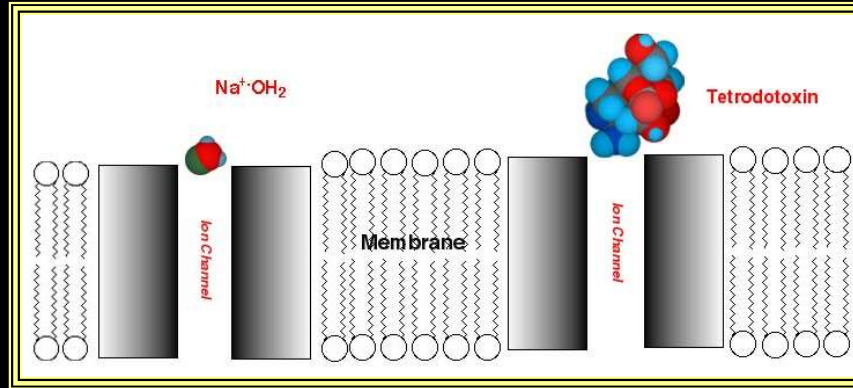
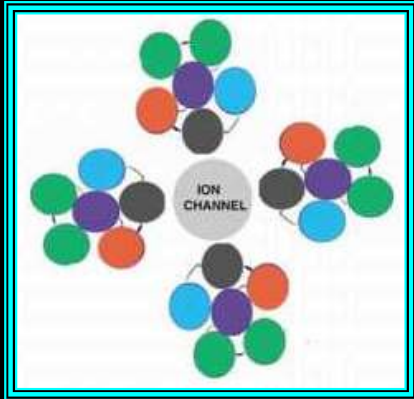
RECEPTOR/CHANNEL/PUMP		AGONIST/ACTIVATOR		ANTAGONIST/INHIBITOR	
NAME	LOCATION	AGENT	EFFECT	AGENT	EFFECT
1. Acetyl-choline nicotinic receptor	Skeletal muscle	Nicotine Anatoxin-a Cytisine <i>Ind:</i> ChE inhibitors	Muscle fibrillation, and then paralysis	Tubocurarine, lophotoxin $\alpha$ -Bungarotoxin $\alpha$ -Cobrotoxin $\alpha$ -Conotoxin Erabutoxin b <i>Ind:</i> botulinum toxin	Muscle paralysis
	Neurons	See above	Neuronal activation	Pb <sup>2+</sup> , general anesthetics	Neuronal inhibition
2. Glutamate receptor	CNS neurons	<i>N</i> -Methyl-D-aspartate Kainate, domoate Quinolate Quisqualate <i>Ind:</i> hypoxia, HCN → glutamate release	Neuronal activation → convulsion, neuronal injury (“excitotoxicity”)	Phencyclidine Ketamine General anesthetics	Neuronal inhibition → anesthesia Protection against “excitotoxicity”
3. GABA <sub>A</sub> receptor	CNS neurons	Muscimol, Avermectins, Sedatives (barbiturates, benzodiazepines), General anesthetics (halothane), Alcohols (ethanol)	Neuronal inhibition → sedation, general anesthesia, coma, depression of vital centers	Bicuculline Picrotoxin Pentylentetrazole Cyclodiene insecticides Lindane, TCAD <i>Ind:</i> isoniazid	Neuronal activation → tremor, convulsion
4. Glycine receptor	CNS neurons, motor neurons	Avermectins (?), General anesthetics	Inhibition of motor neurons → paralysis	Strychnine <i>Ind:</i> tetanus toxin	Disinhibition of motor neurons → tetanic convulsion

**Toxina**, num contexto científico, é uma substância de origem biológica que provoca danos à saúde de um ser vivo ao entrar em contacto ou através de absorção, tipicamente por interação com macromoléculas biológicas, tais como enzimas e receptor. As toxinas animais que são aplicadas subcutaneamente ou intramuscular (por exemplo, através de picadas ou mordidas) são chamadas de veneno. (<https://pt.wikipedia.org/wiki/Toxina>)

## TETRODOTOXINA



Dose mortal = 1mg



mecanismo de ação da tetrodotoxina

# anatoxina-a

