

# Dioxin AND Immune system

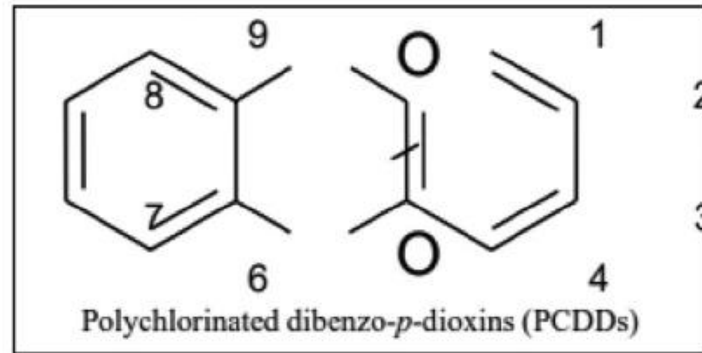
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- *Iran University of Medical Sciences, Tehran, Iran*

# POPs

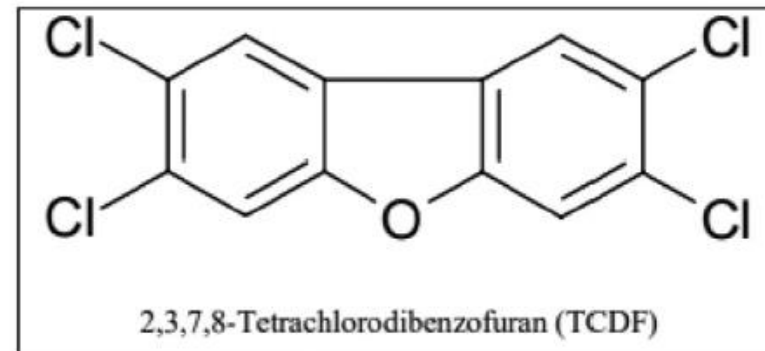
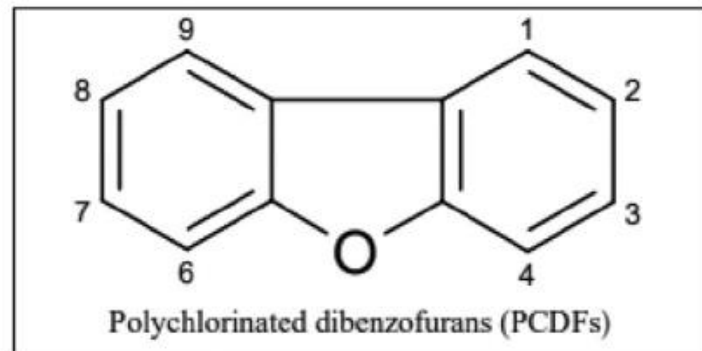
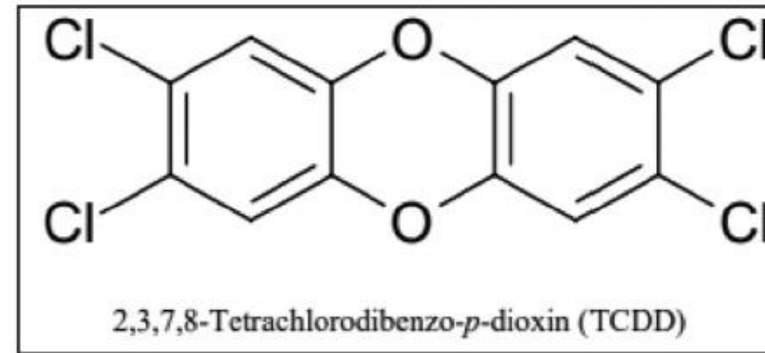
- Persistent Organic Pollutants (POPs) are **toxic substances composed of organic (carbon-based) chemical compounds and mixtures**. They include industrial chemicals like PCBs and pesticides like DDT. They are primarily products and by-products from industrial processes, chemical manufacturing and resulting wastes
- POPs include products of incomplete combustion (PAHs and PCDD/Fs), pesticides (aldrin, chlordanes, chlordecone, DDT, dieldrin, heptachlor, hexachlorobenzene, mirex, toxaphene, and HCHs), and industrial chemicals (PCBs and hexabromobiphenyl).
- Many POPs are currently or were in the past used as **pesticides, solvents, pharmaceuticals, and industrial chemicals**. Although some POPs arise naturally (e.g. from volcanoes), most are man-made.

# Dioxins structure

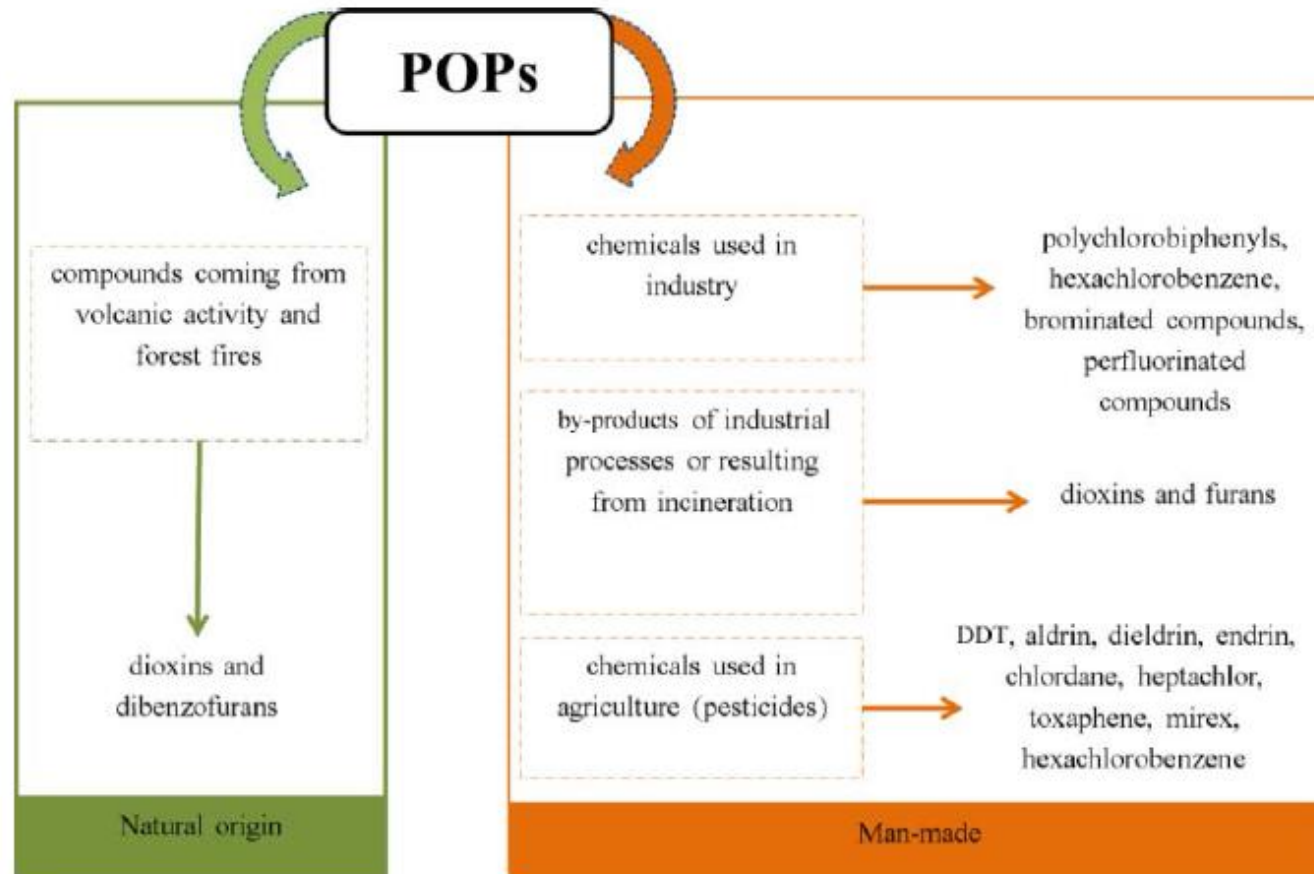
General Structure



Representative Examples



# Classification of persistent organic pollutants according to origin



- Once dioxins enter the body, they last a long time because of their chemical stability and their ability to be absorbed by fat tissue, where they are then stored in the body. Their half-life in the body is estimated to be **7 to 11 years**
- POPs have long been recognized as a serious concern for human health and the environment. As early as the 1960s and 1970s, some POPs such as DDT and PCBs were banned or phased out in many industrialized countries



**Incineration Sources:**

Municipal Waste  
Medical Waste  
Hazardous Waste  
Sewage Sludge



**Industrial Sources:**

Pulp and Paper Mills  
Chemical Manufacturing  
Metal Industry



**Sources of Dioxins  
in the Environment**



**Reservoir Sources:**

Forest Fires  
Biochemical Processes  
Photolytic Processes  
Landfill Burning

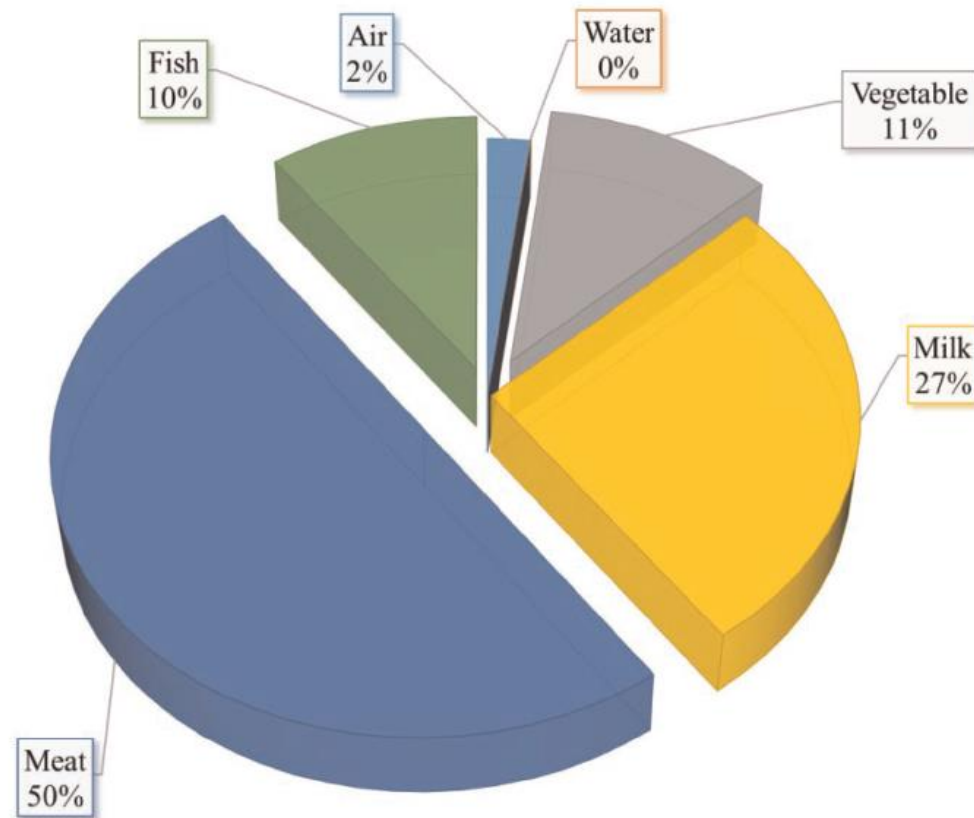


**Combustion Sources:**

Diesel Vehicles  
Coal Fired Utilities  
Wood Burning  
Cement Kilns



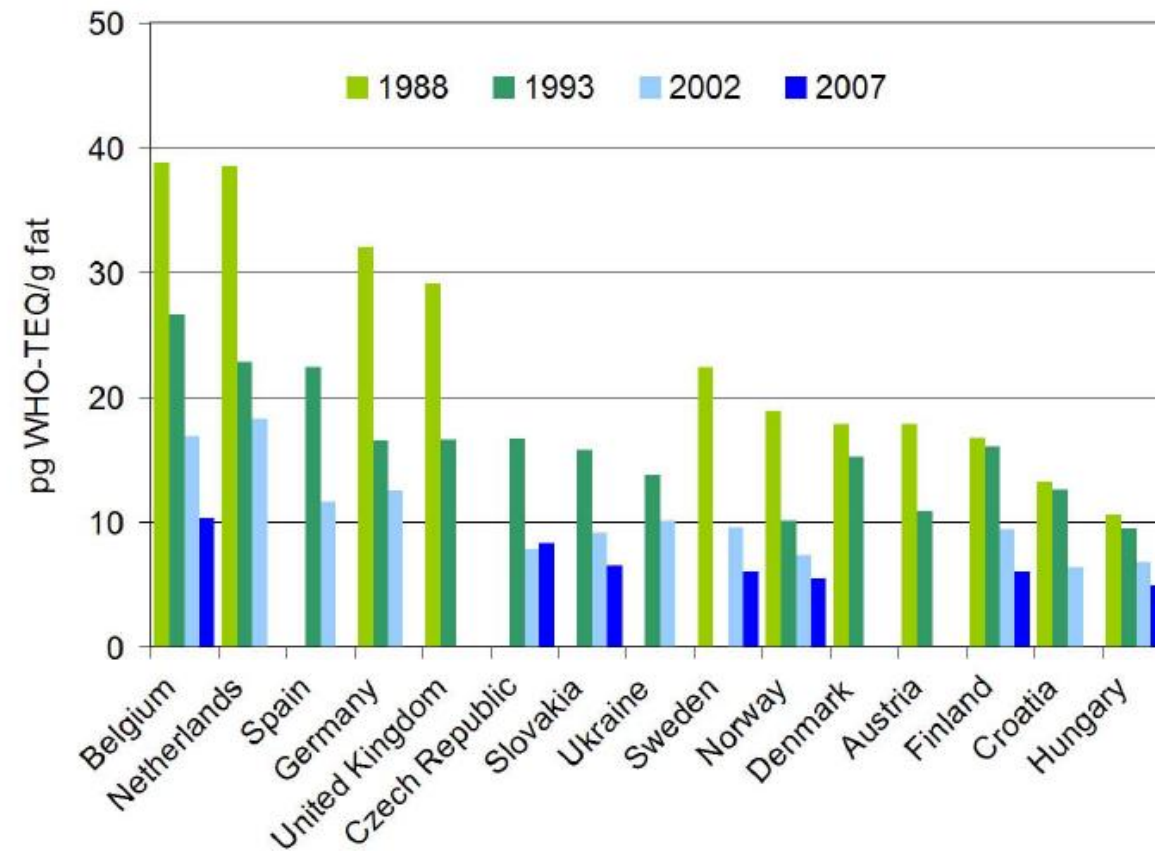
# Exposure of dioxin through various food sources



- WHO recognizes the concern about the potential risks of POPs in human milk. Nevertheless, the beneficial effect of breastfeeding as the optimal food source for newborn babies should always be emphasized.
- Among the POPs, dioxins (PCDDs) and dioxin-like chemicals (including PCDFs and dioxin-like PCBs) seem to have the lowest safety margin and to be the most likely group to cause adverse effects in humans.
- In Seveso, Italy, after a very high level of accidental exposure, there were reports of developmental effects on teeth, altered sex ratios and a possible increase in some rare types of cancer
- WHO experts to recommending very low tolerable daily intake (TDI) of dioxin, 1-4 pg/kg body weight per day



# Dioxin levels in human milk in selected countries, 1988–2007



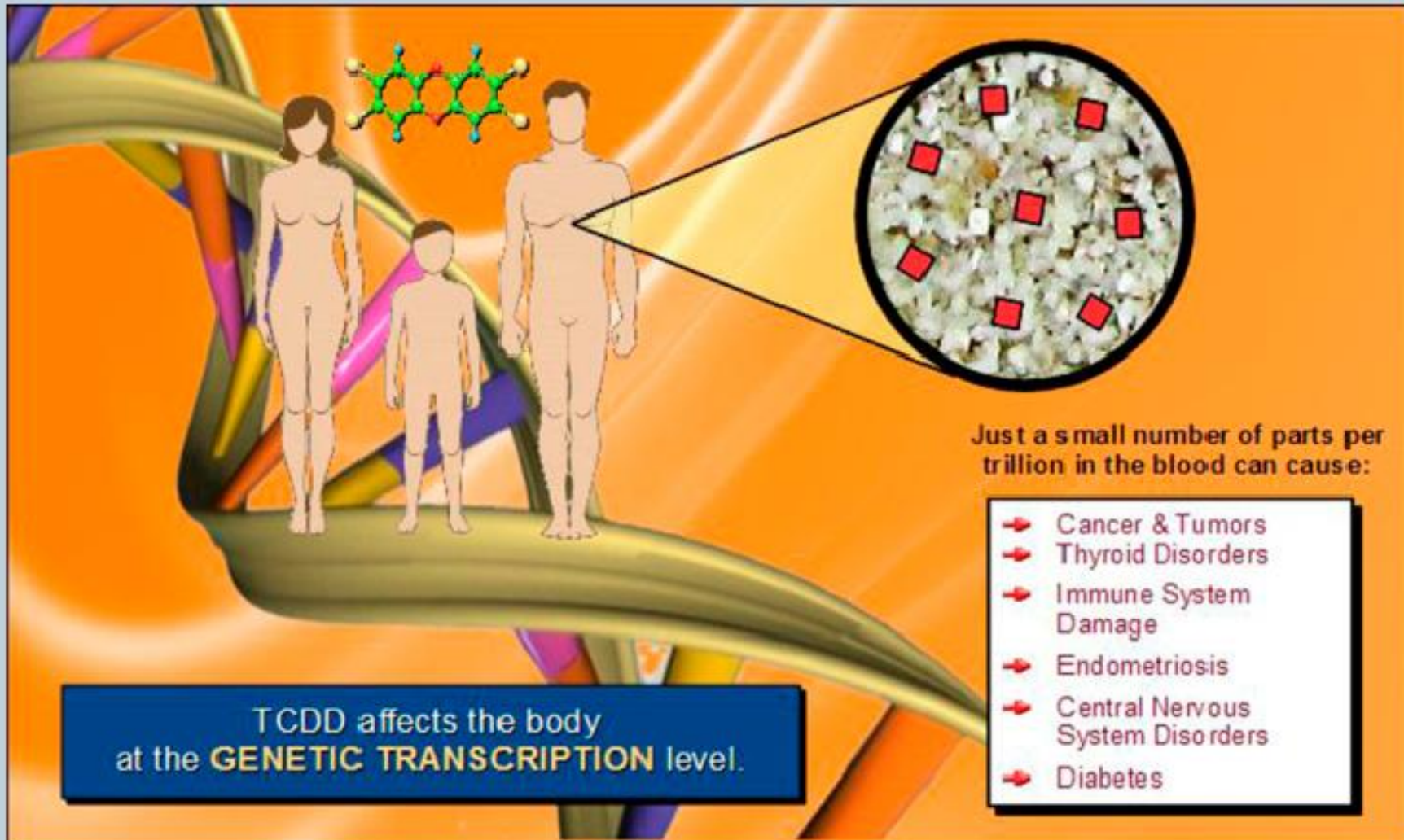
# Important factors for POPs burden

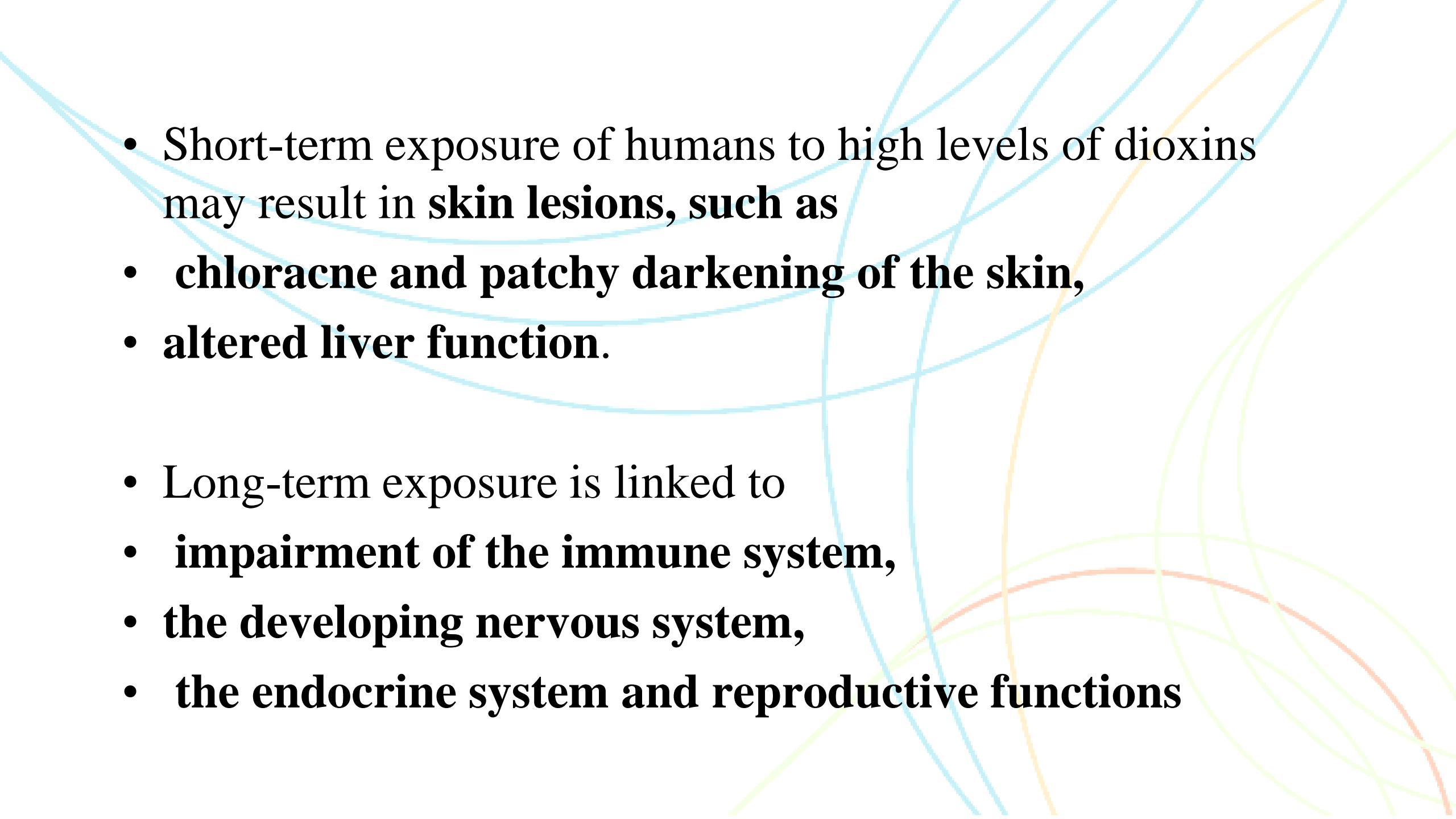
- Age
- Sex
- Dietary habits
- Occupation
- Site of residence
- Local environmental contamination

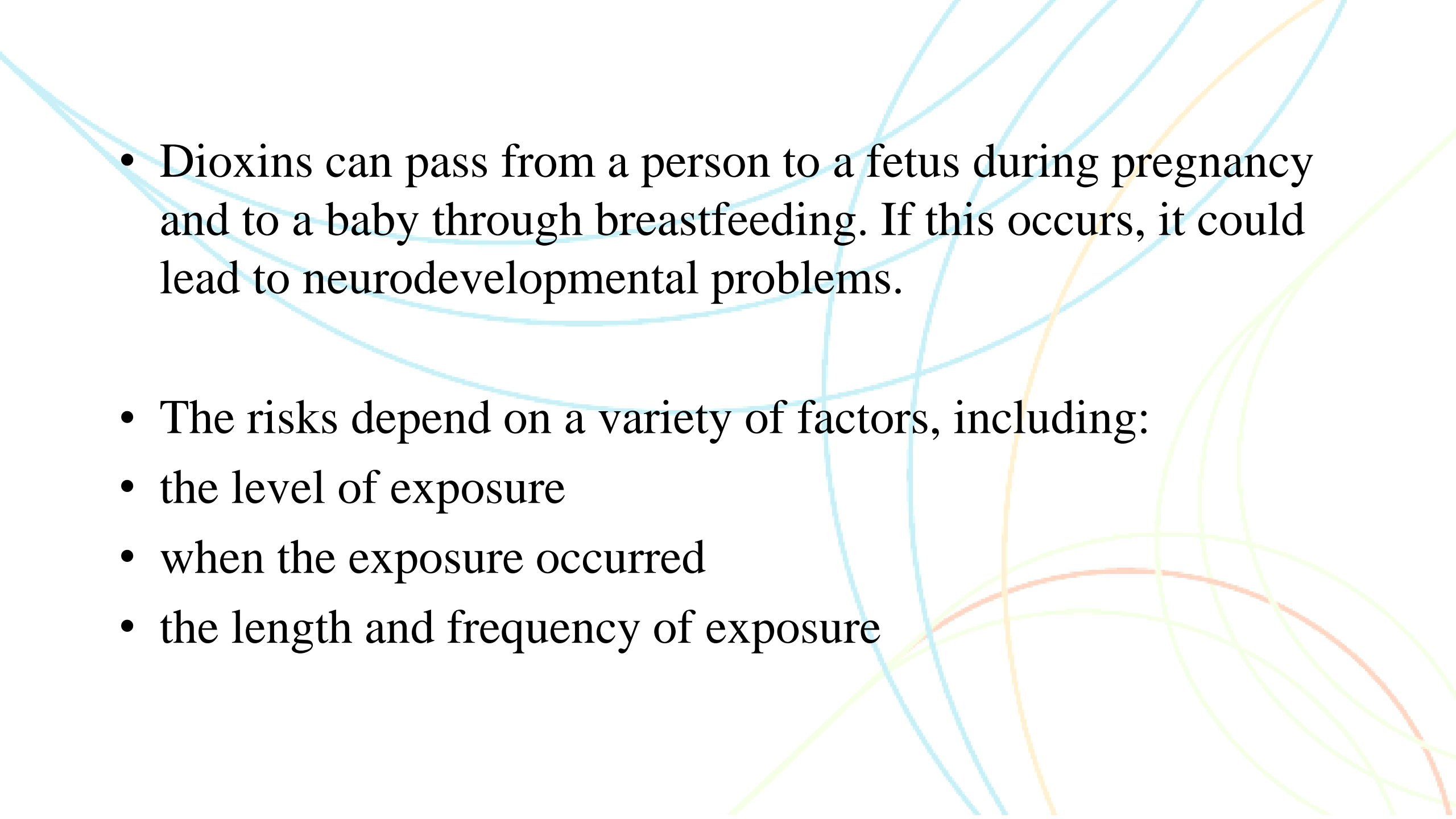
# Health risks

- cancer
- congenital disabilities
- pregnancy loss
- decreased fertility
- reduced sperm counts and low testosterone levels
- endometriosis
- diabetes
- learning disabilities
- immune system suppression
- lung problems
- skin disorders





- 
- Short-term exposure of humans to high levels of dioxins may result in **skin lesions, such as**
    - **chloracne and patchy darkening of the skin,**
    - **altered liver function.**
  - Long-term exposure is linked to
    - **impairment of the immune system,**
    - **the developing nervous system,**
    - **the endocrine system and reproductive functions**

- 
- Dioxins can pass from a person to a fetus during pregnancy and to a baby through breastfeeding. If this occurs, it could lead to neurodevelopmental problems.
  - The risks depend on a variety of factors, including:
    - the level of exposure
    - when the exposure occurred
    - the length and frequency of exposure

## Aryl Hydrocarbon receptor

- Aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor that binds to structurally diverse synthetic and naturally occurring chemicals including dioxins, flavonoids, tryptophan photoproducts
- AhR ligation controls oxidation/anti-oxidation, epidermal barrier function, photo-induced response, melanogenesis, and innate immunity
- AhR and ARNT modulate ER signaling

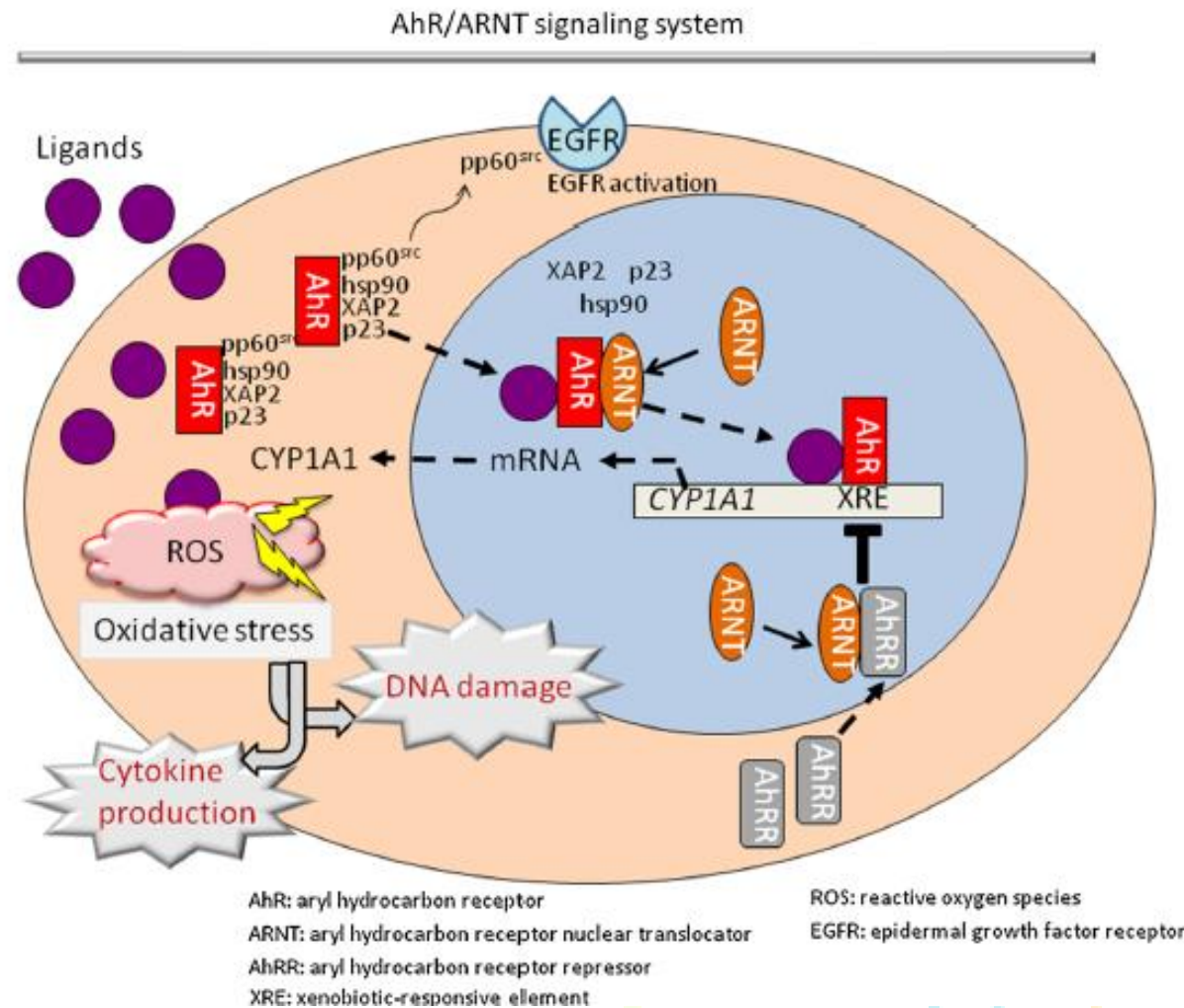


# Aryl Hydrocarbon receptor

The diagram illustrates the AhR/ARNT signaling system. Extracellular ligands (purple dots) bind to the AhR (red rectangle) on the cell membrane. This leads to the recruitment of pp60<sup>src</sup>, hsp90, XAP2, and p23. The complex then translocates into the nucleus. In the nucleus, the AhR (red rectangle) forms a heterodimer with ARNT (orange oval). This complex binds to the XRE (xenobiotic-responsive element) on the CYP1A1 gene, leading to the transcription of CYP1A1 mRNA. The AhR/ARNT complex also interacts with EGFR, leading to EGFR activation and the production of pp60<sup>src</sup>. Additionally, the AhR/ARNT complex can lead to the production of ROS (reactive oxygen species), which causes oxidative stress and DNA damage, ultimately leading to cytokine production. The AhR/ARNT complex also interacts with AhRR (aryl hydrocarbon receptor repressor) and ARNT, leading to the repression of CYP1A1 mRNA.

AhR: aryl hydrocarbon receptor  
ARNT: aryl hydrocarbon receptor nuclear translocator  
AhRR: aryl hydrocarbon receptor repressor  
XRE: xenobiotic-responsive element

ROS: reactive oxygen species  
EGFR: epidermal growth factor receptor





# Protection from immunotoxicity

- Xenobiotic receptors, including the aryl hydrocarbon receptor (AHR), sense and respond to a subset of environmental pollutants by activating the expression of detoxification enzymes to protect the body. However, chronic activation of the AHR leads to immunotoxicity.
- KEAP1–NRF2 is another important system that protects the body against environmental pollutants. KEAP1 is a sensor protein that detects environmental pollutants, leading to activation of the transcription factor NRF2
- . NRF2 protects the body from immunotoxicity by inducing the expression of genes involved in detoxification, antioxidant and anti-inflammatory activities. Intervening in these sensor–response systems could protect the body from the devastating immunotoxicity that can be induced by environmental pollutants.
- Nature Immunology 2020

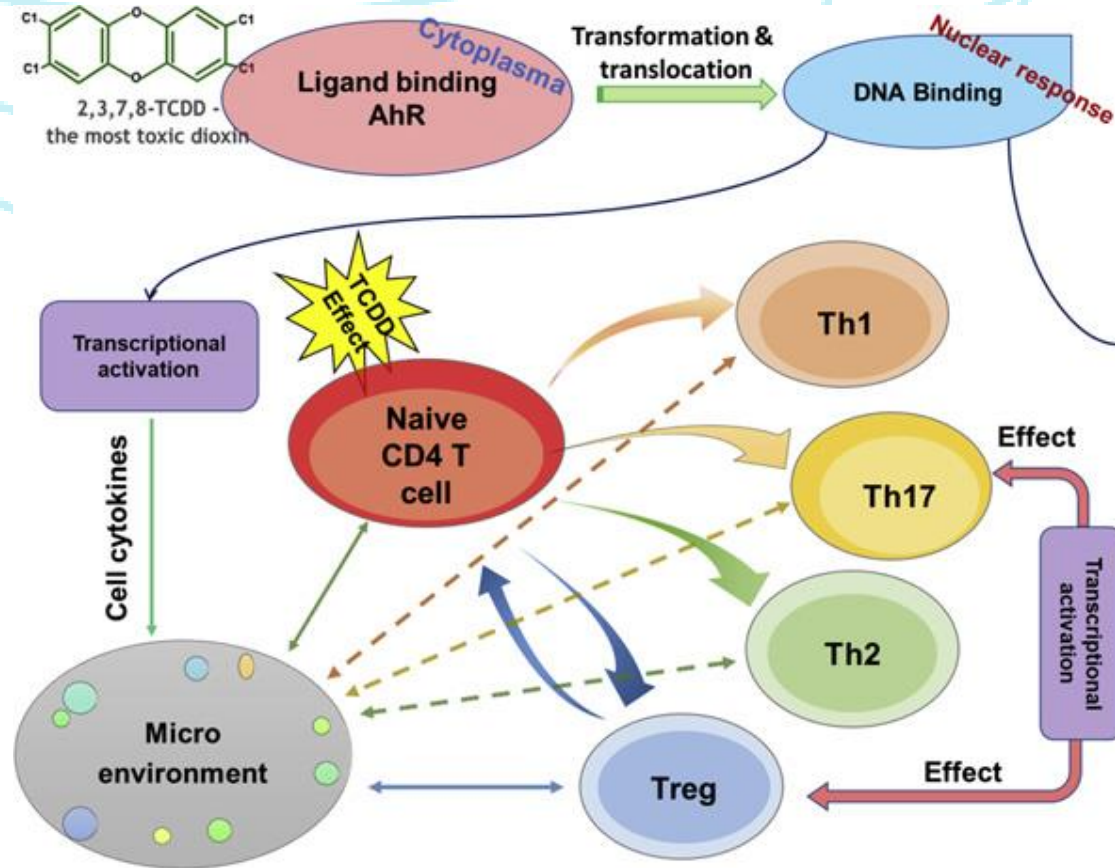
## Low and high dose of TCDD

- The low dose exposure to TCDD triggered regulatory effects in the immune system, while the high dose TCDD exposure resulted in severe immune toxicity
- TCDD can induce a variety of adverse biological and physiological reactions, including immunotoxicity in mammals, e.g., thymus atrophy and suppression of antibody production and cytotoxic T cells activation
- Exposure to TCDD clearly impairs T cell-dependent immune responses, which contribute to promoting inflammatory autoimmune diseases

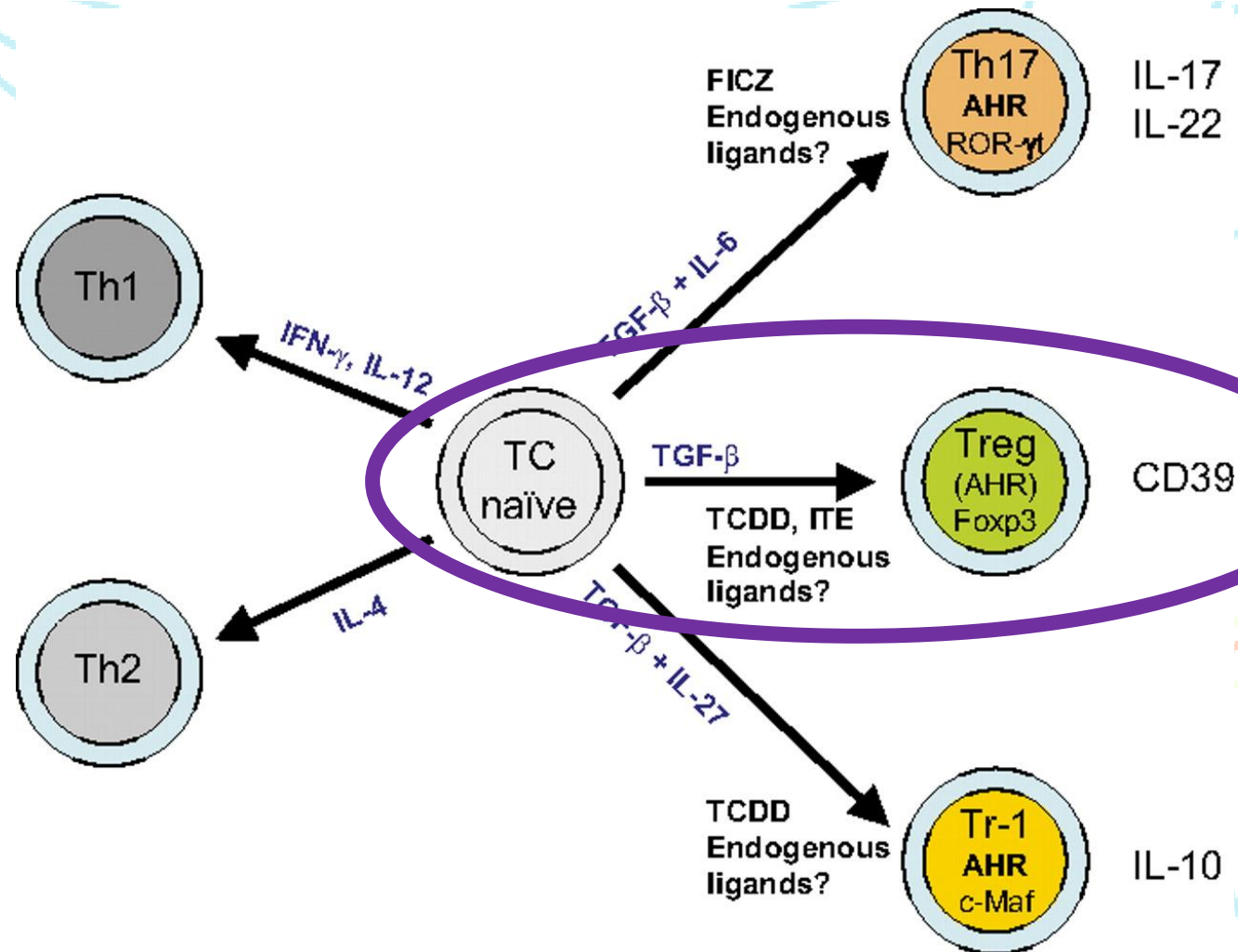
## Immunoregulation of TCDD

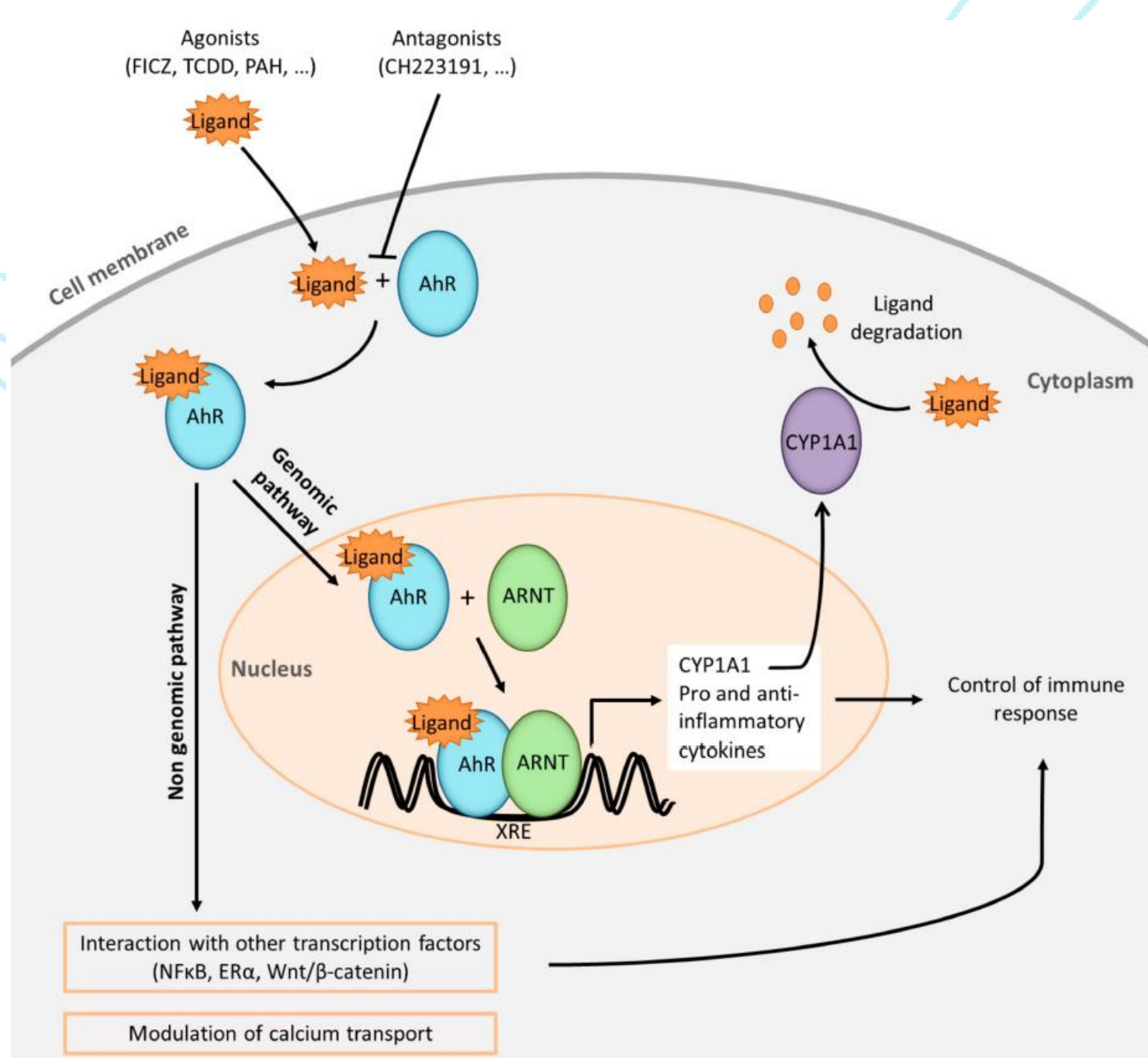
- Previous studies suggested that TCDD had a potential immune suppressive effect, which resulted in decreased inflammatory effector Th cells, and finally alleviated systemic lupus erythematosus (SLE) progression
- TCDD activated-AhR signaling pathways affect the immune response, especially that mediated by the CD4 Th cell subsets, through either inducing differentiation of functional Treg cells, while inhibiting the differentiation of Th17 cell at the same time

# 2,3,7,8-Tetrachlorodibenzo-p-dioxin affects the differentiation of CD4 helper T cell



# Dioxin & T cells differentiation

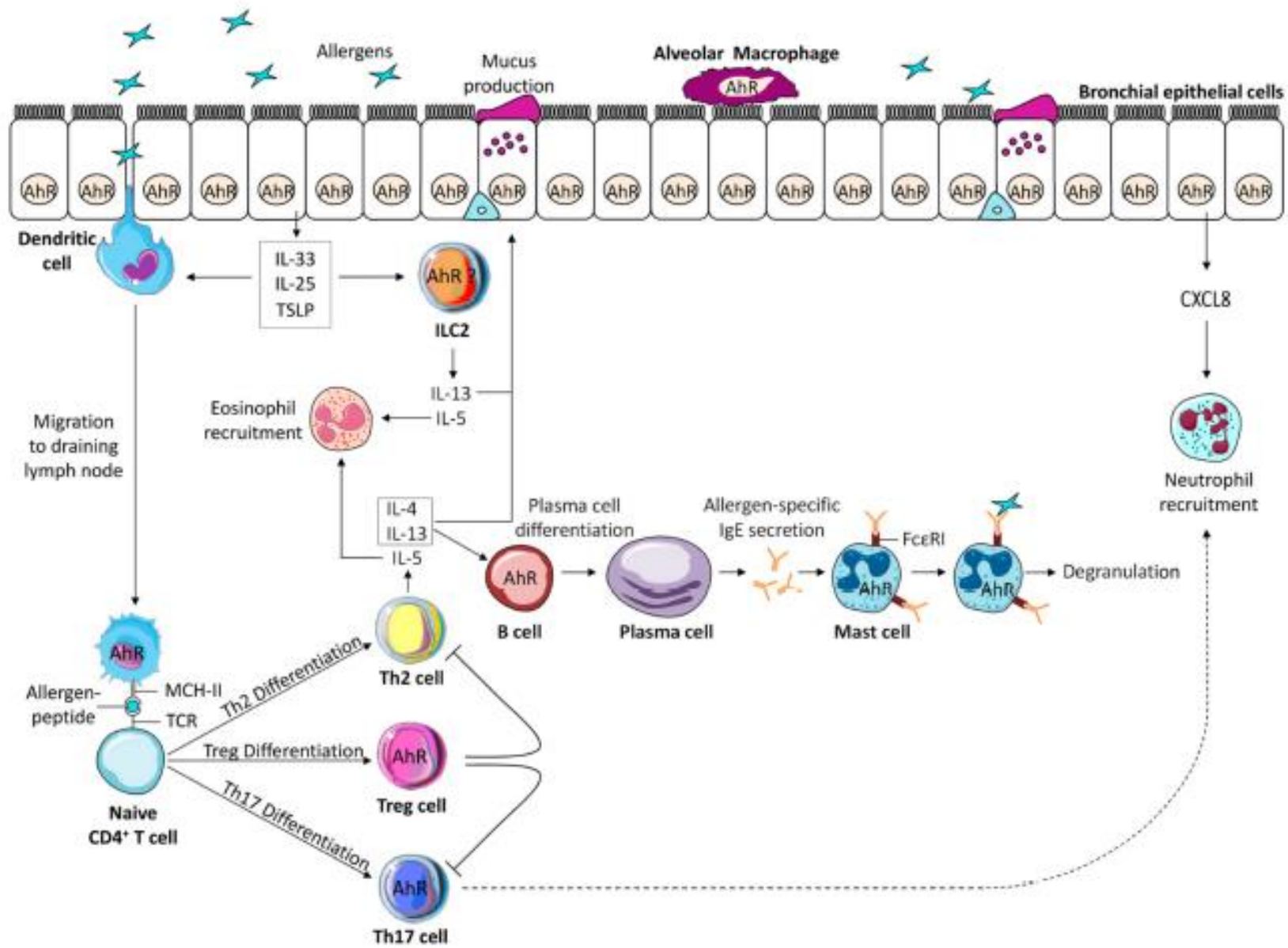




## Ahr activation and Asthma

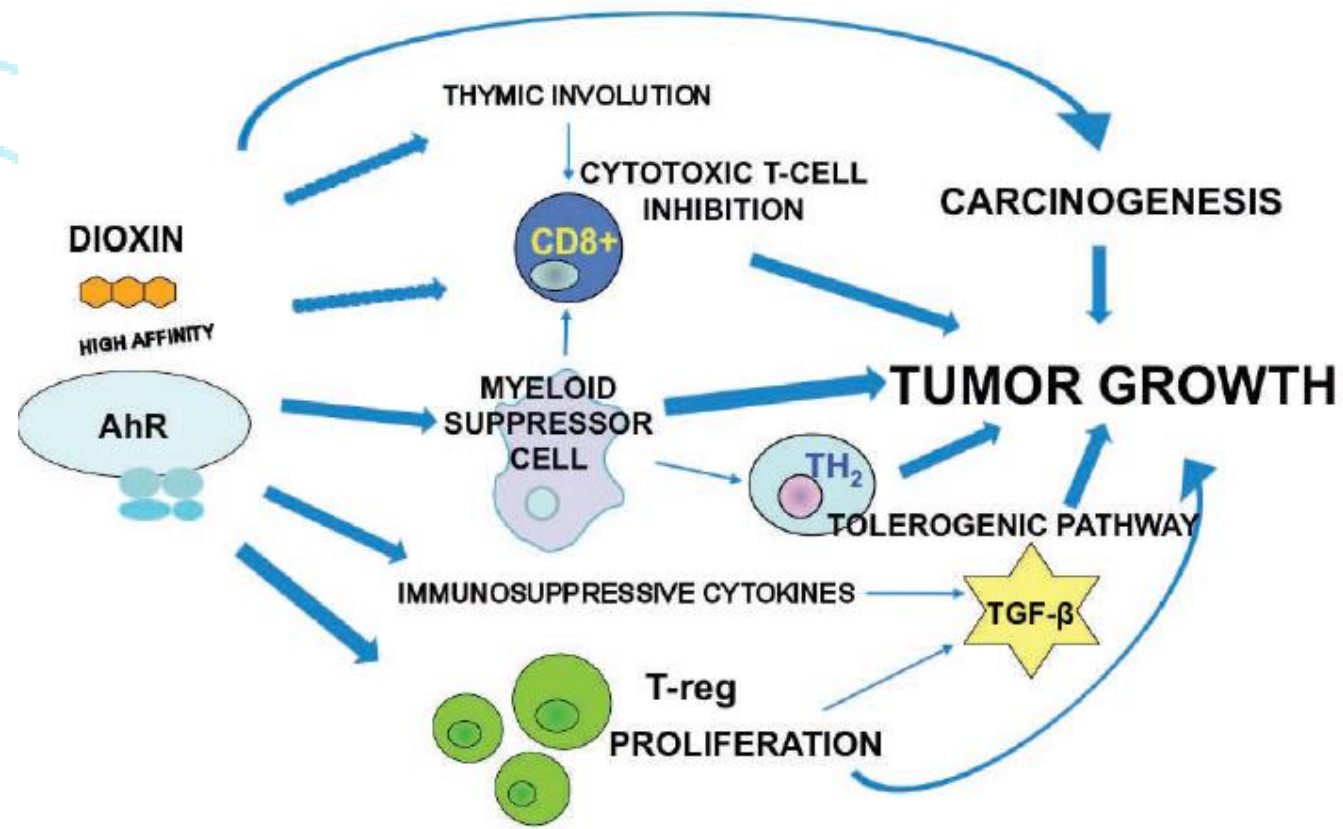
- AhR has an anti-inflammatory role since its activation in dendritic cells blocks the generation of pro-inflammatory T cells or shifts macrophages toward an anti-inflammatory M2 phenotype.
- On the other hand, AhR activation by particle-associated polycyclic aromatic hydrocarbons from the environment is pro-inflammatory, inducing mucus hypersecretion, airway remodelling, dysregulation of antigen presenting cells and exacerbates asthma features

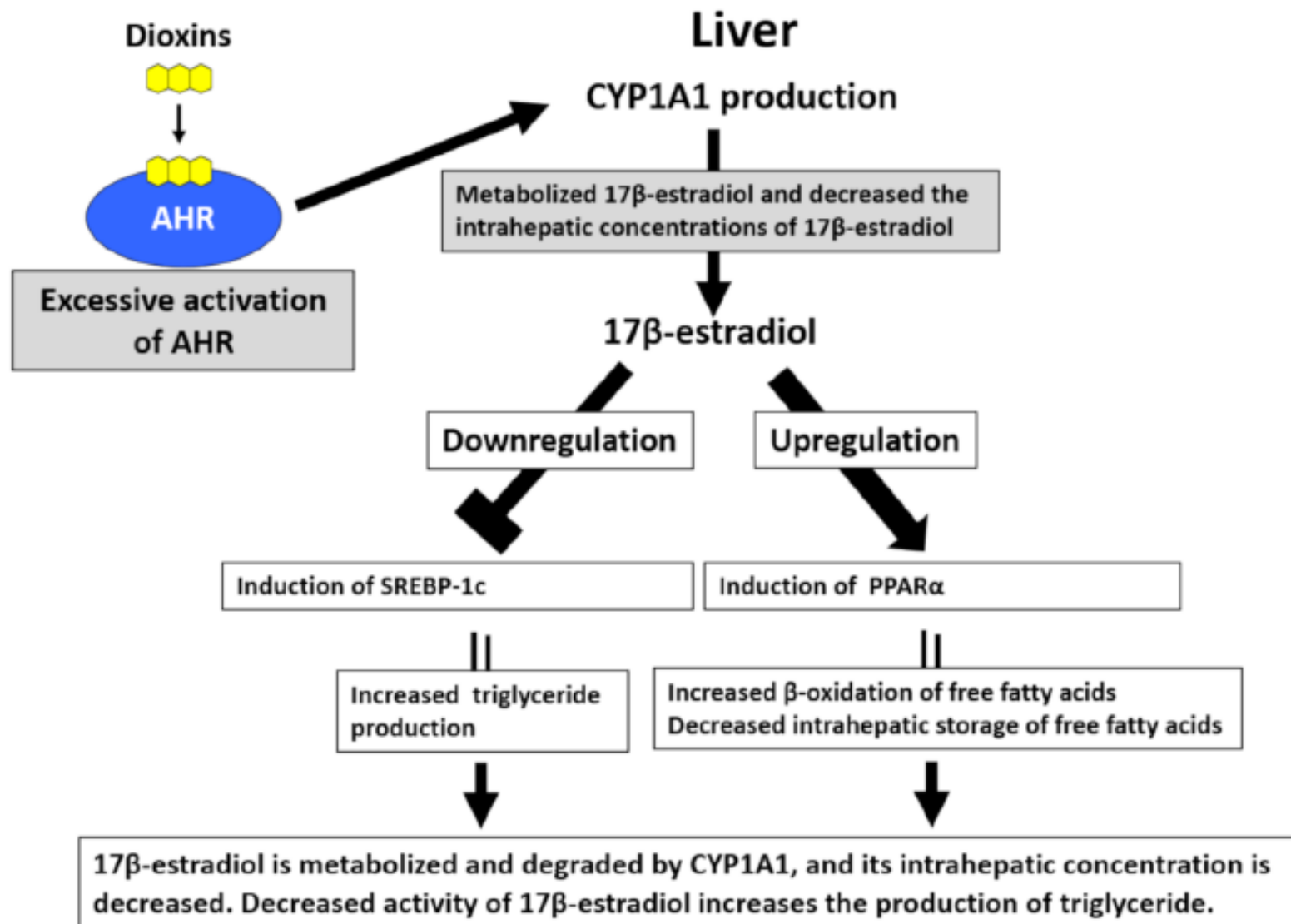




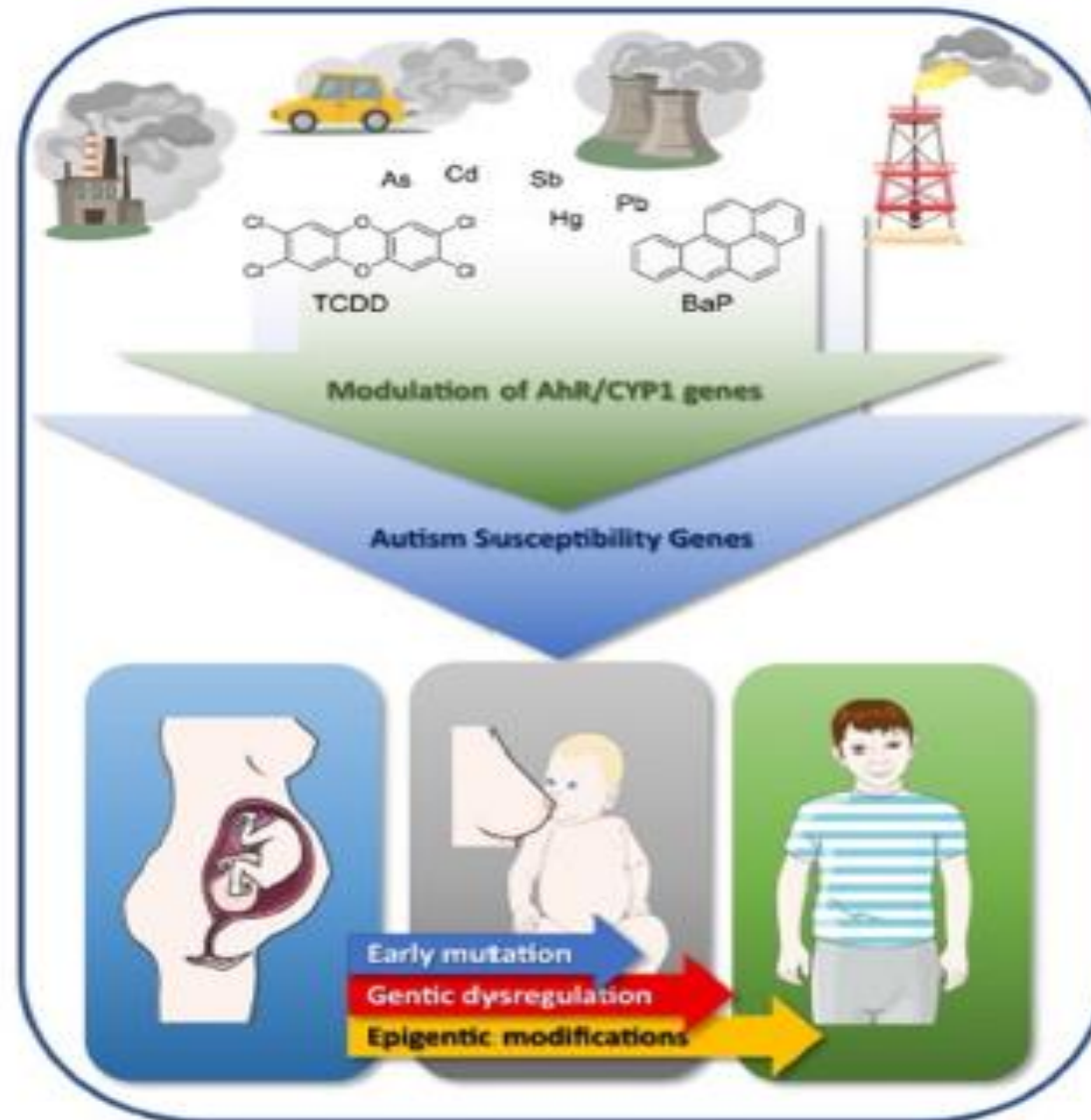


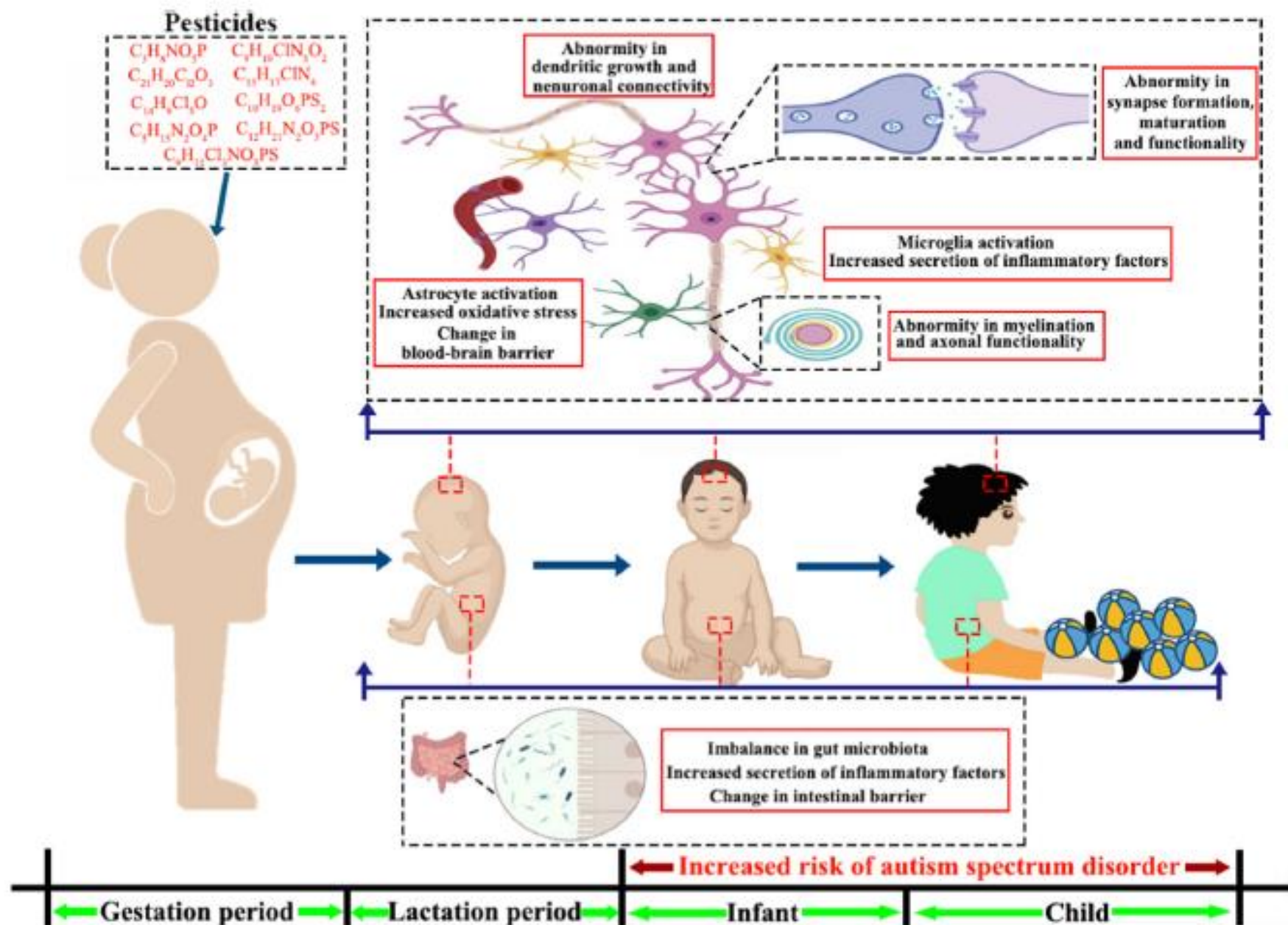
# Immunosuppressive action of dioxin-AhR binding

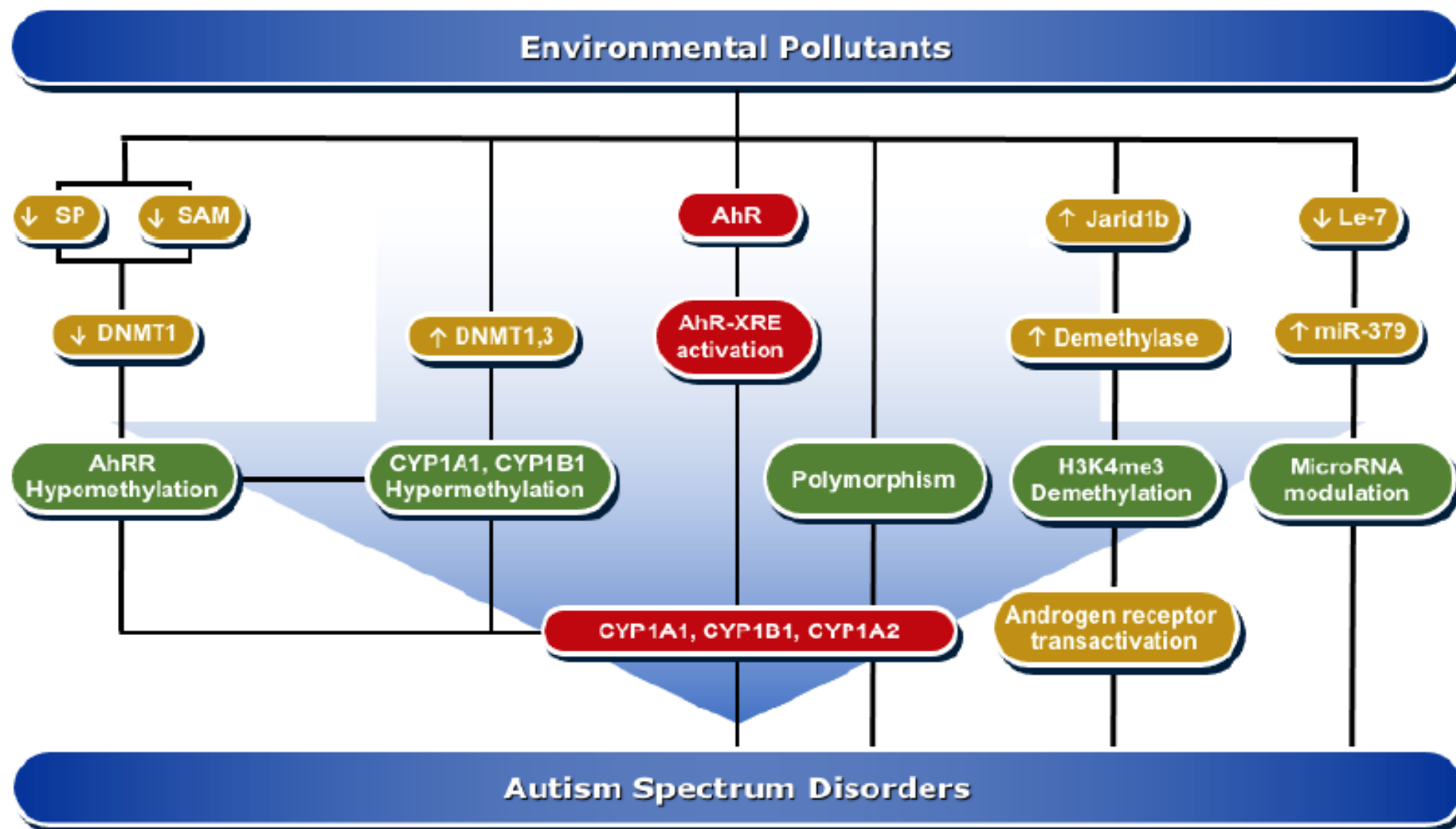




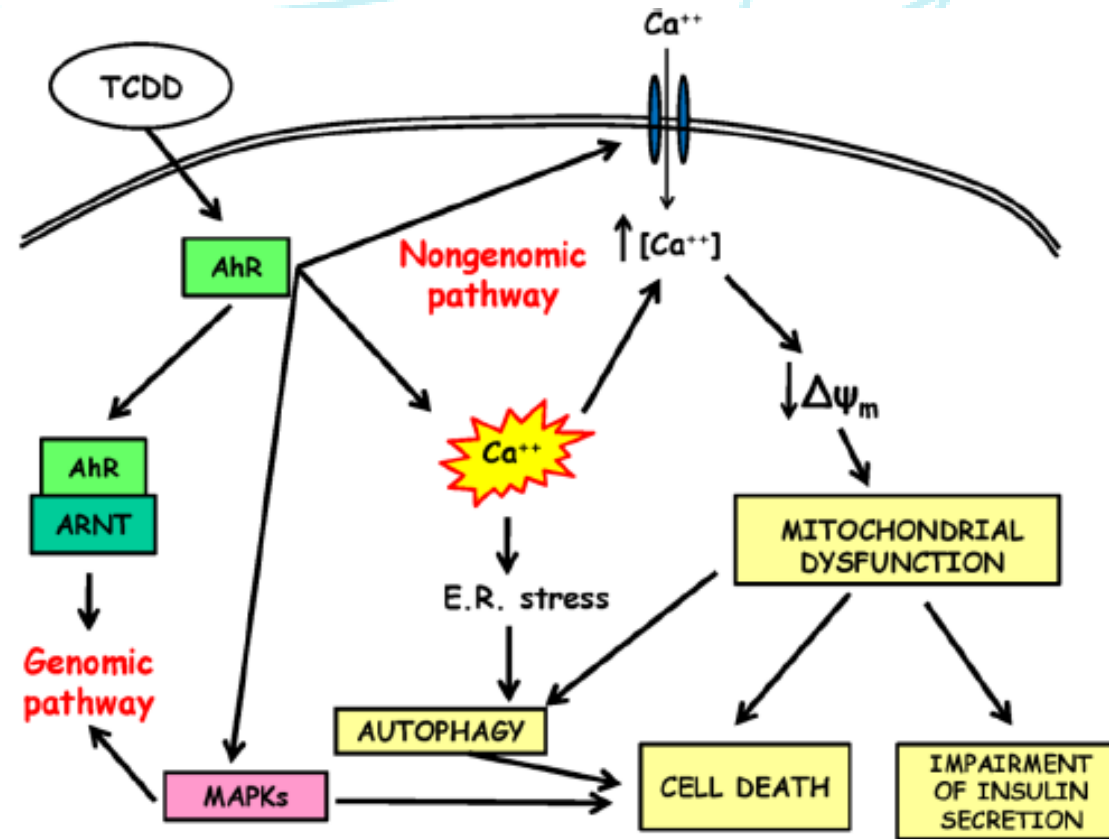
# Dioxin and Autism





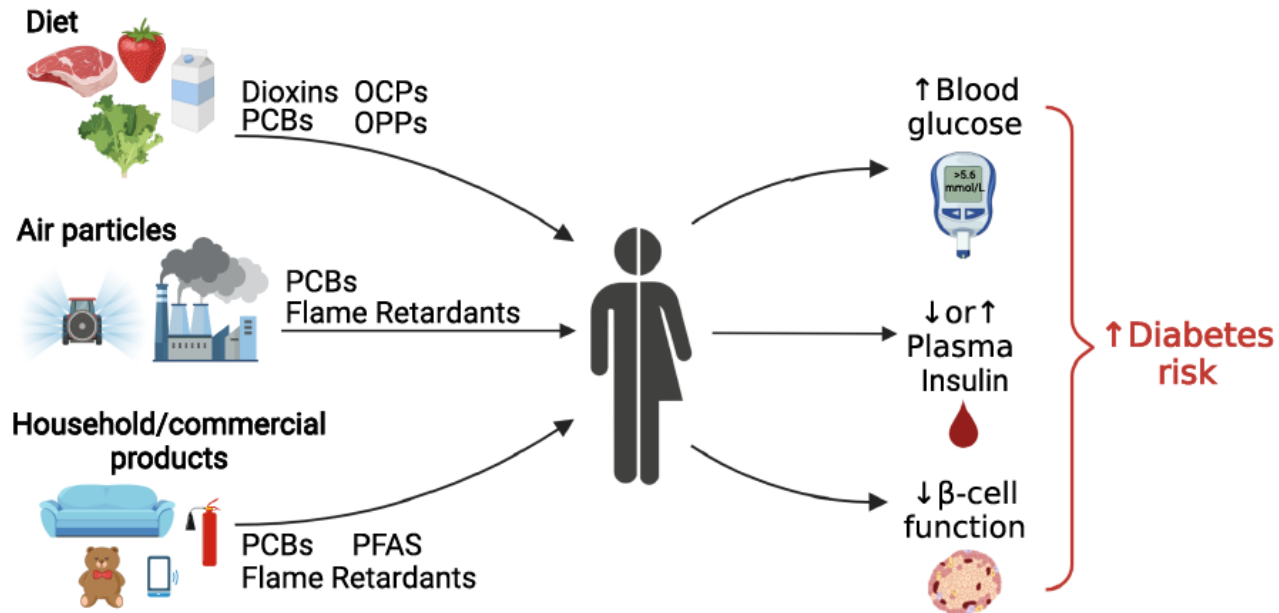


# Schematic representation of the proposed pathways involved in the acute dioxin toxicity in pancreatic beta cells



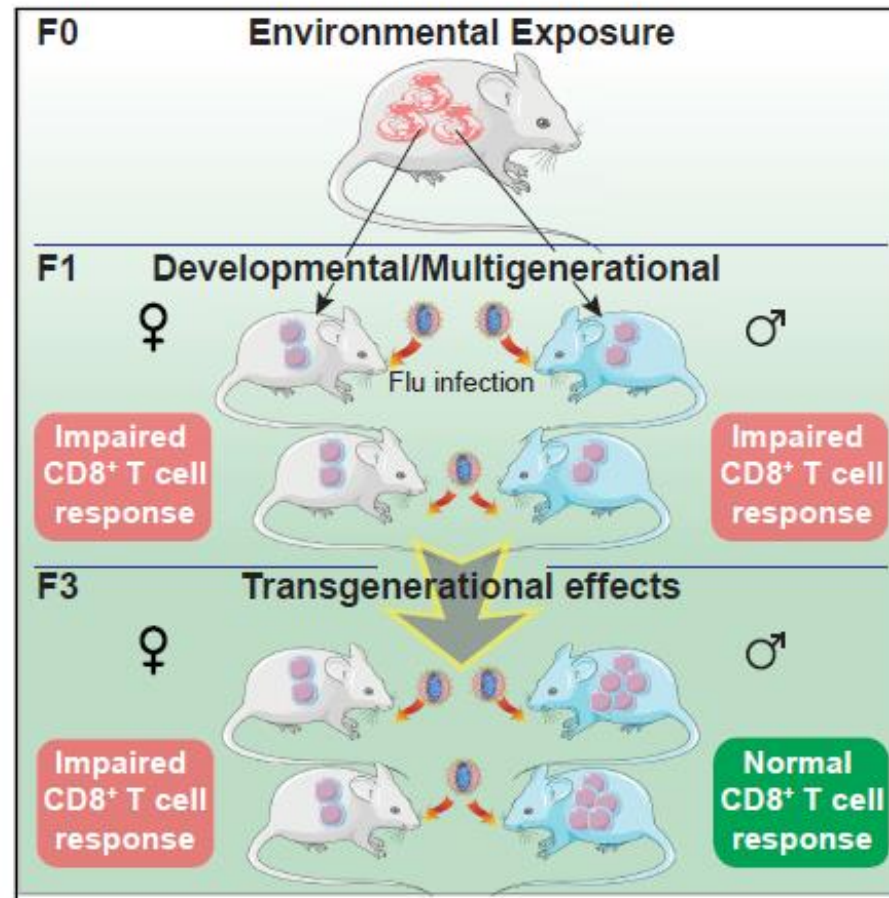


## Persistent organic pollutants as $\beta$ -cell toxins



**Conclusion:** there is strong epidemiological, *in vivo*, and *in vitro* evidence implicating persistent organic pollutants as contributing factors driving impaired glucose homeostasis and  $\beta$ -cell dysfunction.

# The Ancestral Environment Shapes Antiviral CD8<sup>+</sup> T cell Responses across Generations

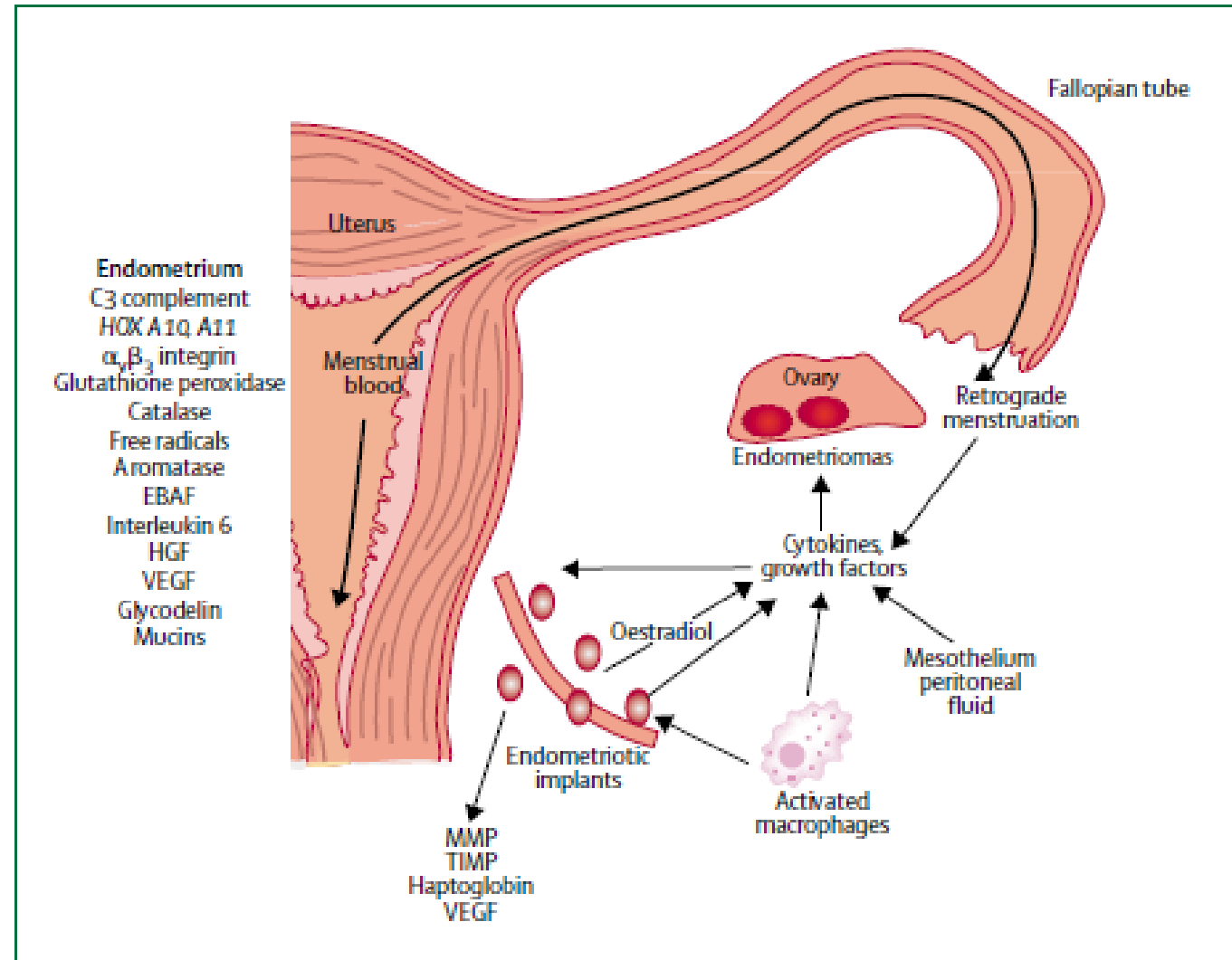




# Endometriosis

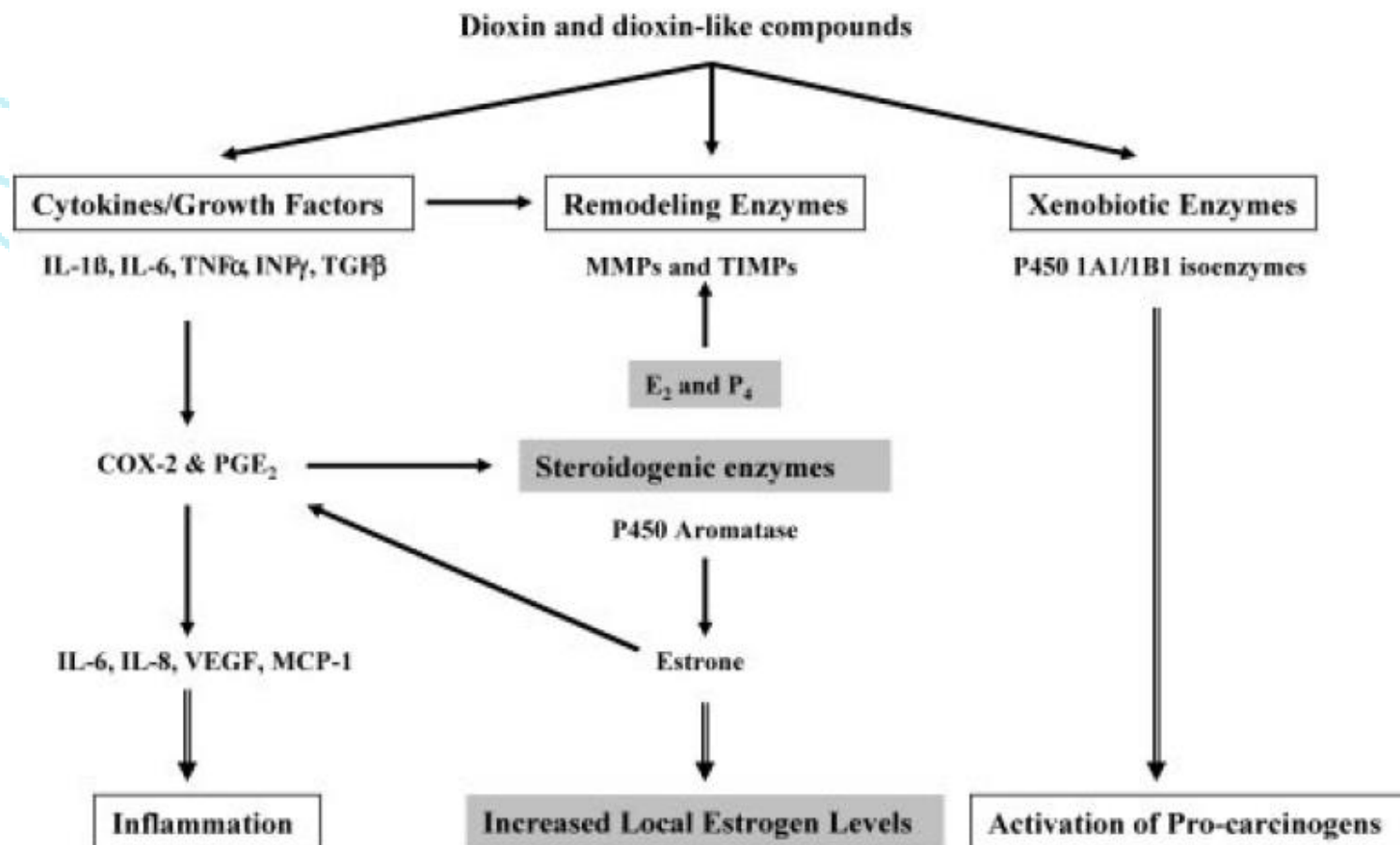
- Endometriosis is an estrogen-dependent disorder with features of chronic inflammation defined by the presence of tissue implants resembling endometrial glands and stroma outside of the uterus.
- Common symptoms of endometriosis include chronic pelvic pain, dyspareunia, dysmenorrhea and infertility
- is associated with disturbed local and systemic immune responses

# Pathogenesis of endometriosis



## Increased levels of dioxin-like substances in adipose tissue in patients with deep infiltrating endometriosis

- This study shows, for the first time, that the total concentration of dioxins and PCBs in adipose tissue is higher in patients with DIE compared with controls without endometriosis.
- Furthermore, dioxins and PCBs accumulate in tissues with a high fat content and, therefore, adipose tissue seems to be more representative of the body burden of dioxin and dioxin-like substances, and is considered to be the preferred indicator of biological human exposure



# Toxic Chemicals in Pads & Tampons

## Undisclosed fragrance chemicals

linked to skin irritation & other long-term health problems



## Pesticide residues

linked to cancer

## Dioxins & furans

linked to cancer, hormone disruption and reproductive toxicity

## *Are your tampons toxic?*

**Non organic cotton tampons contain:**

- Glyphosate (a known cancer causing agent)
- Dioxins (from bleaching)
- Odor neutralizers
- Pesticides
- Fragrances
- Dyes
- Undisclosed chemicals.

Anything we put in our bodies is absorbed into the blood stream. Exposure increases risks to cancer, metabolic changes and disruptions to the endocrine system.

## The results?

Conditions such as infertility, endometriosis, thyroid disorders, and exposure to known carcinogens.

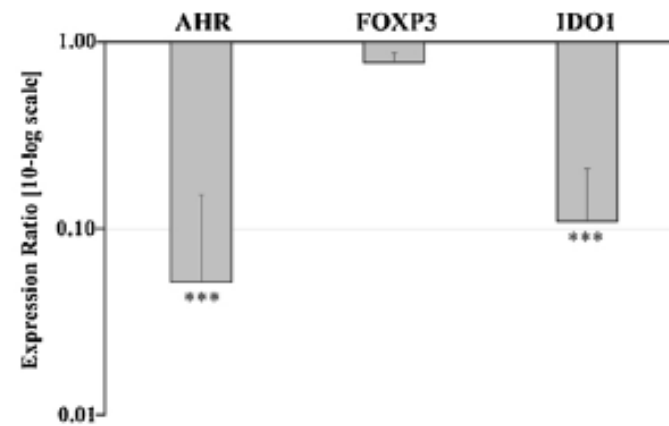


*Make life easier. Know what's in your products!*

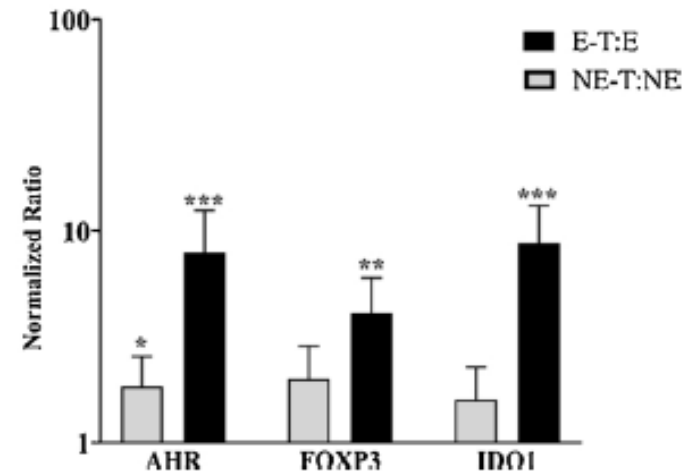
## 2, 3, 7, 8-Tetrachlorodibenzo-p-dioxin potential impacts on peripheral blood mononuclear cells of endometriosis women

*M. Tanha et al.*

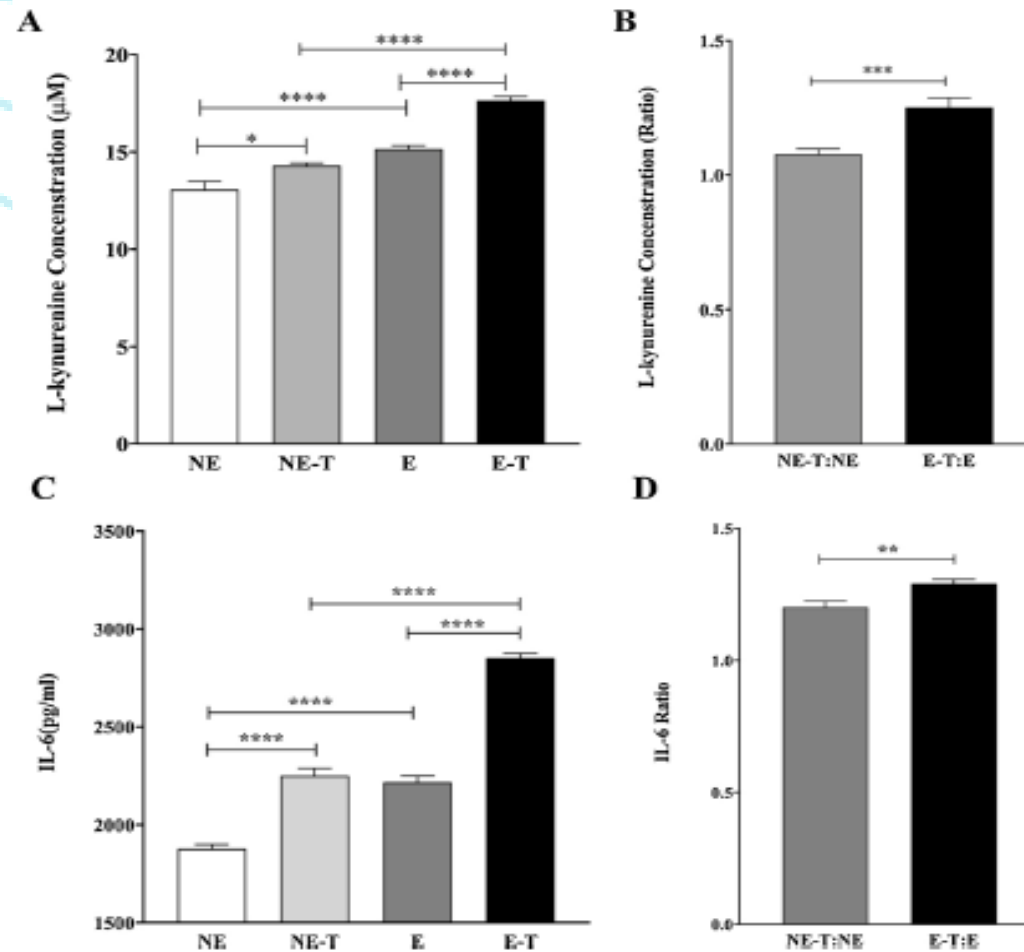
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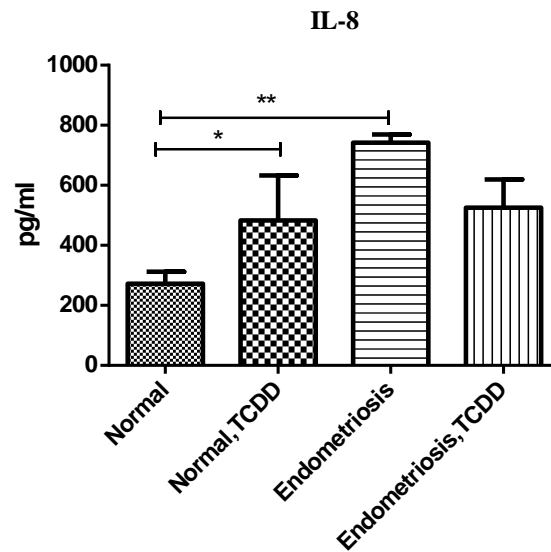
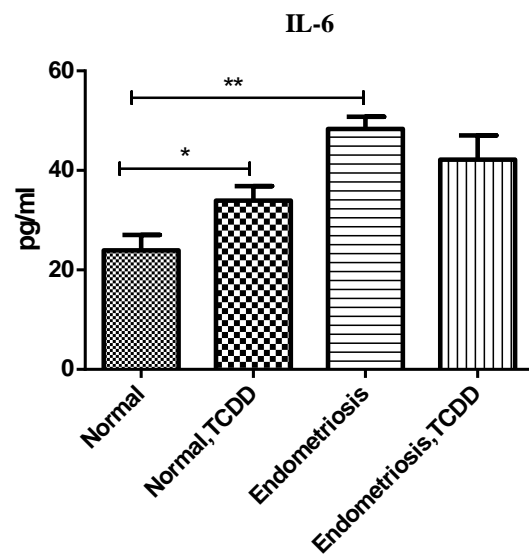
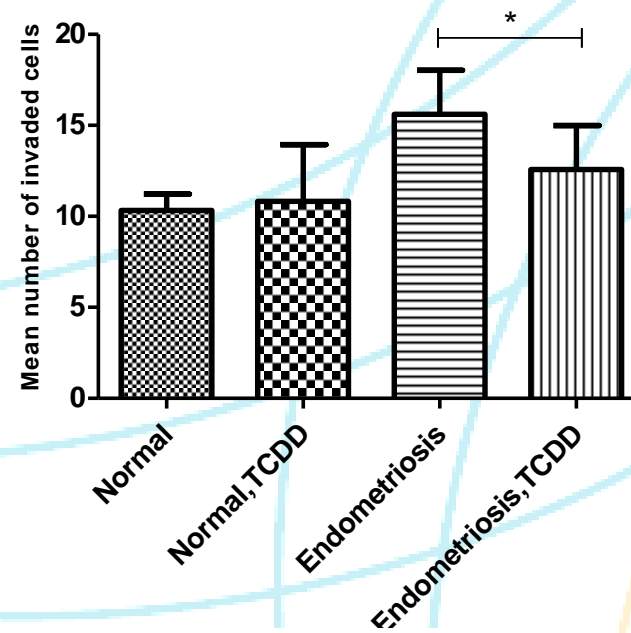
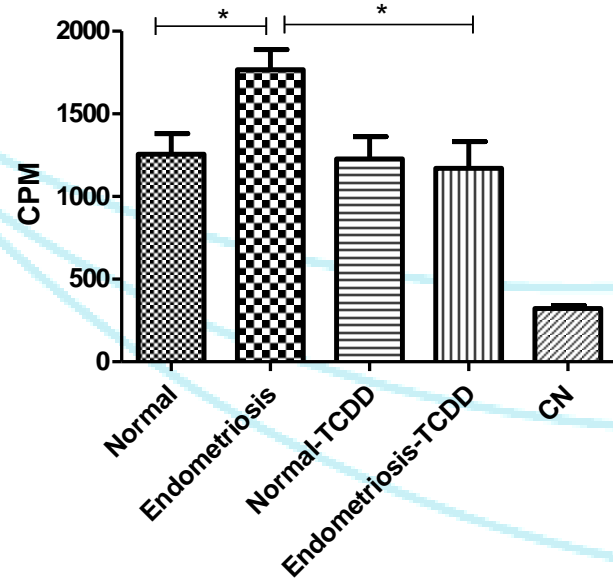


**B**



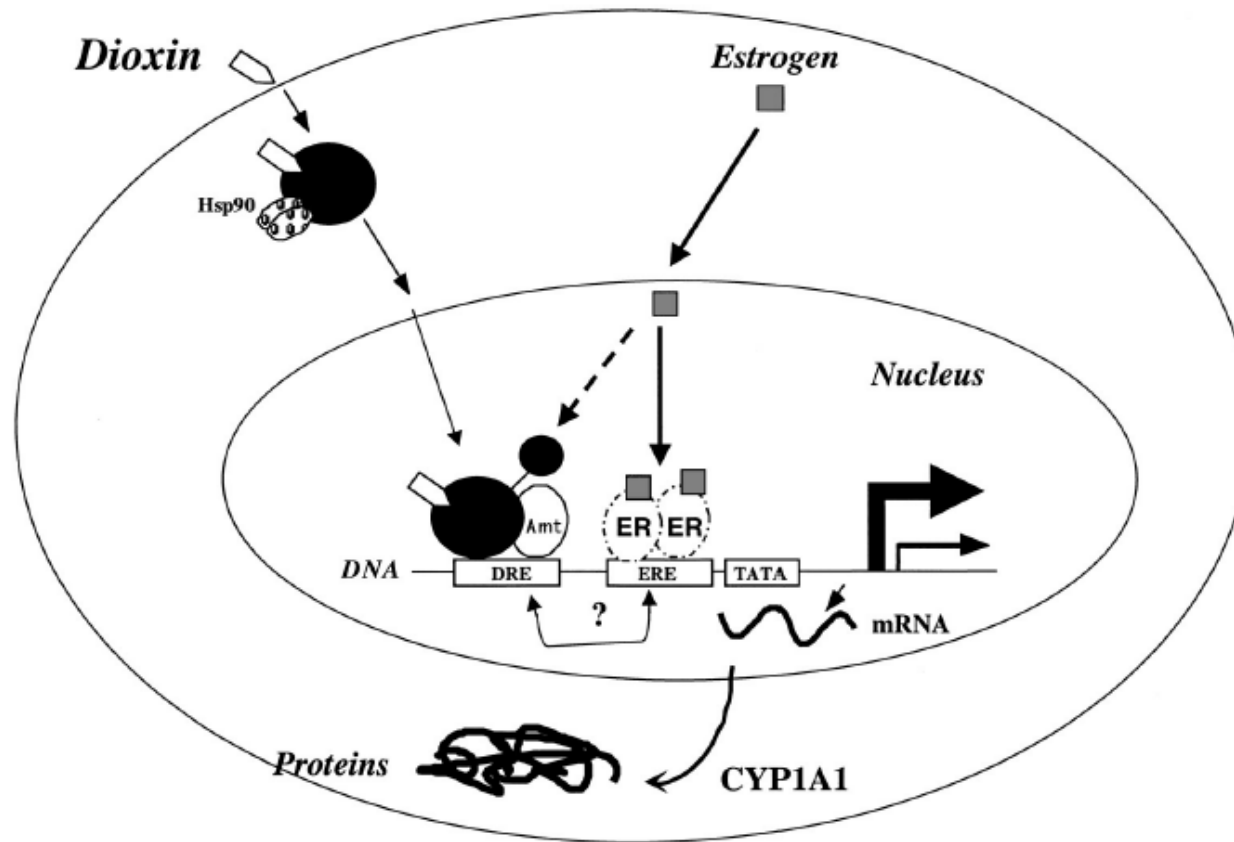
## Assessment of IDO1 activity and IL-6 in the PBMCs supernatants of endometriosis and non-endometriosis groups after stimulation with TCDD.







## Ahr/ER cross-talk pathway



# مطالعات انجام گرفته در ایران

- سنجش میزان آلودگی های دیوکسین در نمونه آب ایران با استفاده از روش بیولومینسانس
- اندازه گیری میزان غلظت PCBs در برندهای مختلف تخم مرغ عرضه شده در سطح شهر تهران
- نتایج این مطالعه نشان می دهد بیشترین میزان PCBs موجود در تخم مرغ مربوط به PCB 28 بوده است و فصل زمستان دارای بیشترین میزان غلظت PCB ها بوده است و در مناطق مختلف تهران میزان غلظت این آلاینده ها اختلاف معنی داری با هم نداشتند، ولی در مجموع می توان اظهار نمود که میزان میانگین کل آن از استاندارد های موجود بین المللی پایین تر است.
- اندازه گیری دیوکسین در کره های مناطق مختلف ایران

# Endocrine disrupting chemicals (EDCs)

- Endocrine disrupting chemicals (EDCs) are a group of exogenous agents that interfere with the synthesis, secretion, transport, binding, or elimination of natural hormones in the body
- It is estimated that there are thousands of chemicals that could exhibit endocrine-disrupting properties including bisphenol A(BPA), phthalates (PAEs), organochlorine pesticides (OCPs), and poly-chlorinated biphenyls (PCBs).
- Human beings are ubiquitously exposed to EDCs through food, drink, and skin contact

# Endocrine disrupting chemicals (EDCs)

- The positive associations between PAEs and **CRP, IL-6 and IL-10** were significant in the high-molecular-weight phthalate (HMWP) exposure group ,not the low-molecular-weight phthalate (LMWP) exposure group.
- Exposure to OCPs was positively associated with **CRP, IL-1 $\beta$ , IL-2, and IL-10**. No significant association was found between PCBs and inflammatory markers .These findings demonstrate that exposure to EDCs is closely linked to **dysregulated inflammatory responses** .
- [Ecotoxicology and Environmental Safety 234 \(2022\) 113382](#)

# Organochlorine Pesticides

- The most widely known organochlorine pesticide is dichlorodiphenyltrichloroethane, i.e., the insecticide **DDT**, the uncontrolled use of which raised many environmental and human health issues . Dieldrin, endosulfan, heptachlor, dicofol, and methoxychlor are some other organochlorines used as pesticides.
- There are a few countries that still use DDT or plan to reintroduce it for public health purposes . Furthermore, DDT is also used as a solution in certain solvents . It is a ubiquitous chemical substance, and **it is believed that every living organism on Earth has a DDT body burden, mainly stored in the fat .**
- There is also evidence that DDT and its metabolite p,p-dichlorodiphenyldichloroethylene (DDE) may **have endocrine-disrupting potential** and carcinogenic action . *In utero* exposure to both DDT and DDE has been associated with neurodevelopmental effects in children .
- **The general class of organochlorine pesticides has been associated with health effects, such as endocrine disorders , effects on embryonic development , lipid metabolism , and hematological and hepatic alterations**

# Organophosphorus Pesticides

- Organophosphates, which were promoted as a more ecological alternative to organochlorines include a great variety of pesticides, **the most common of which is glyphosate**. This class also includes other known pesticides, such as malathion, parathion, and dimethoate; some are known for their endocrine-disrupting potential
- This class of pesticides has been associated with effects on the function of cholinesterase enzymes **decrease in insulin secretion, disruption of normal cellular metabolism of proteins, carbohydrates and fats , and also with genotoxic effects and effects on mitochondrial function, causing cellular oxidative stress and problems to the nervous and endocrine systems.**
- Population-based studies have revealed possible relations between the exposure to organophosphorus pesticides and **serious health effects including cardiovascular diseases , negative effects on the male reproductive system ) and on the nervous system dementia , and also a possible increased risk for non-Hodgkin's lymphoma**

# Glyphosate (Gly)

- Glyphosate (Gly) is the most utilised herbicide in agriculture, although its widespread use is generating controversy in the scientific world because of its probable carcinogenic effect on human cells.
- Gly performs as an inhibitor of 5-enolpyruvylshikimate-3-phosphate synthase (EPSP synthase), not only in plants, but also in bacteria. An inhibiting effect on EPSP synthase from intestinal microbiota has been reported, affecting mainly beneficial bacteria.
- Consequently, **researchers have suggested that Gly can cause dysbiosis**, a phenomenon which is characterized by an imbalance between beneficial and pathogenic microorganisms. **The overgrowth of bacteria such as clostridia generates high levels of noxious metabolites in the brain, which can contribute to the development of neurological deviations.**
- Neuro Toxicology 2019



## Glyphosate and MS

- Glyphosate, an analogue of glycine, can be expected to be found in all tissues, including the milk of all mammals consuming glyphosate residues in the diet.
- Most disturbing is the presence of glyphosate in many popular vaccines including the measles, mumps and rubella (MMR) vaccine, which we have verified here for the first time.
- Contamination may come through bovine protein, bovine calf serum, bovine casein, egg protein and/or gelatin

# Pesticide residues from human/ cow milk samples Tehran, Iran

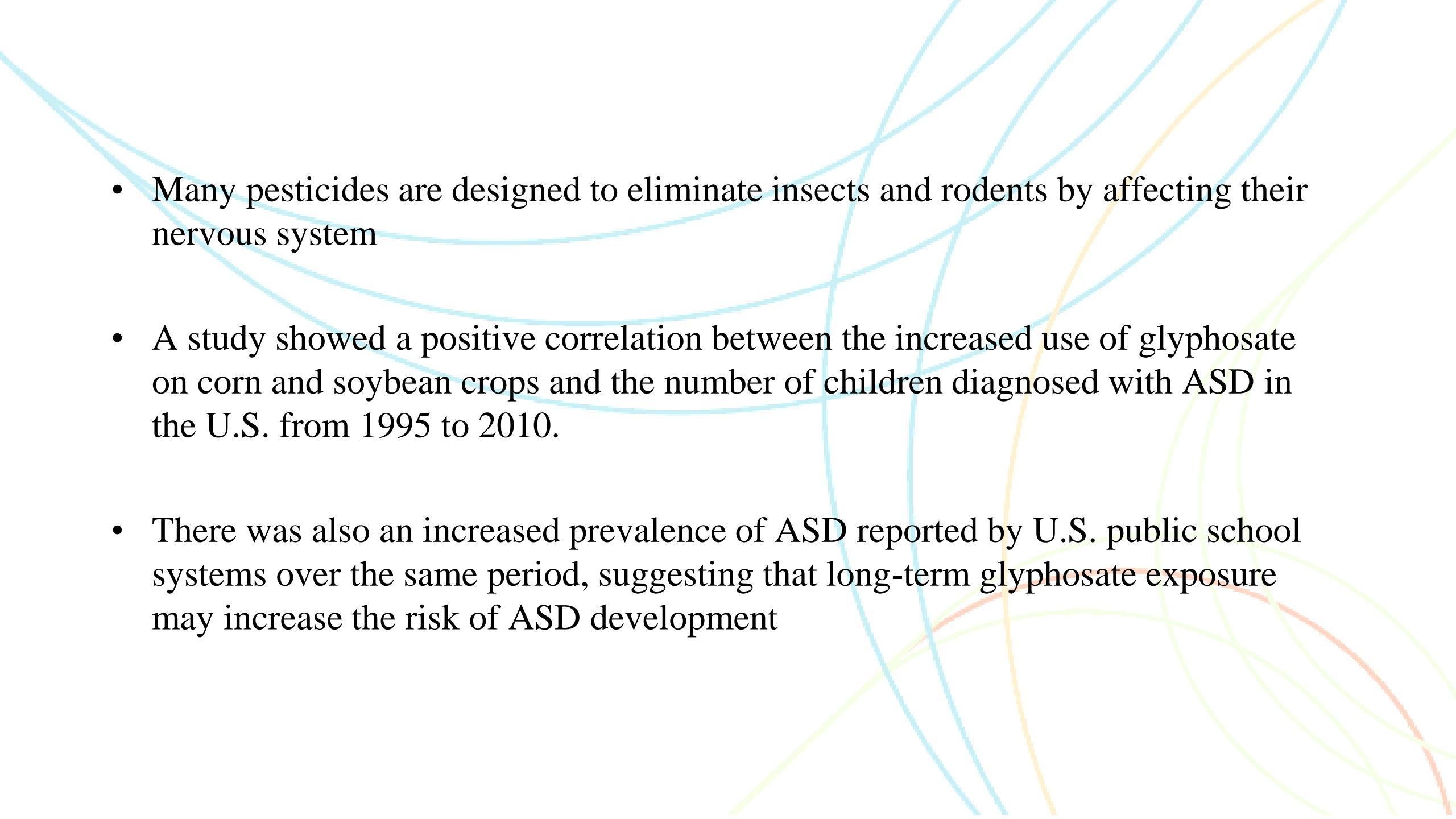
## Environmental Research 2022

### Sara Ramezani et al

- Raw, pasteurized, powdered cow milk and human milk samples from Tehran were investigated for residual of fifty pesticides with aid of gas chromatography coupled with electron capture detector (GC-ECD) and mass detector for confirmation; and ultra-high performance liquid chromatography-tandem mass spectroscopy
- **No pesticide residue was determined in more than 91% of examined samples.** However, dimethoate residue was detected in 3 raw milk samples in levels higher than EU recommended MRL.
- While in 3 human milk samples, organochlorine pesticides residue, p,p'-DDT, and p,p'-DDD was recognized below MRLs, only in 1 human sample residue of p,p'-DDE was more than CODEX recommended MRL. HI in adults and children were 0.72 and 3.55, respectively.
- However, the health risk assessment based on HI demonstrated that adult consumers are not at considerable risk.
- **The HI, higher than 1 in children, confirms the risks raised due to ingestion of organochlorine (OCP) and organophosphorus (OPP) pesticides via milk consumption.**
- In addition, no carcinogenic risk to milk consumers was calculated. Therefore, implementation of good farming practices, improving knowledge and consciousness of pesticide users, use safe methods for pest control such as biotechnology-based, and use a rational program for application of pesticides, continuous monitoring of pesticides in crops, and strict government regulations on pesticide residues in food are recommended.

## The relationship between pesticide exposure during critical neurodevelopment and autism spectrum disorder

- Recent studies have shown that low-level agricultural pesticide exposure during the critical period of neurodevelopment (pregnancy and lactation) is closely related to autism spectrum disorder (ASD).
- Inhibition of acetylcholine esterase, gut microbiota, neural dendrite morphology, synaptic function, and glial cells are targets for the effects of pesticides during nervous system development.

- 
- Many pesticides are designed to eliminate insects and rodents by affecting their nervous system
  - A study showed a positive correlation between the increased use of glyphosate on corn and soybean crops and the number of children diagnosed with ASD in the U.S. from 1995 to 2010.
  - There was also an increased prevalence of ASD reported by U.S. public school systems over the same period, suggesting that long-term glyphosate exposure may increase the risk of ASD development

# Reduce the risk of Dioxin exposure

- Trimming fat from meat and consuming low fat dairy products may decrease the exposure to dioxin compounds.
- Also, a balanced diet (including adequate amounts of fruits, vegetables and cereals) will help to avoid excessive exposure from a single source
- Eating snacks containing a fat substitute called Olestra can speed up the removal of dioxins and polychlorinated biphenyls ( pcbs ) from the body.
- Microbial degradation of chlorinated dioxins
- Incineration at temperatures above 1200°C is considered the most effective way of destroying dioxins

## composting of diapers



چشم‌ها را باید شست،  
جوهر دیگر باید دید

