TOXICOLOGY

from the Greek words
toxicos "poisonous" and *logos*

A branch of biology, chemistry , and medicine concerned with the study of the adverse effects of chemicals on living organisms.

It is the study of symptoms, mechanisms, treatments and detection of poisonings, especially the poisoning of people.

Aureolus Philippus Theoprastus Bombastus von Hohenheim (*Paracelsus)* 1527

sometimes called the father of toxicology, wrote:

Alle Dinge sind Gift, und nichts ohne Gift; allein die Dosis macht, daß ein Ding kein Gift ist.

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

Or, more commonly

„The dose makes the poison."

"Sola dosis facit venenum."

Substances considered toxic are harmless in small doses, and conversely an ordinarily harmless substance can be deadly if over-consumed.

"Paracelsus", meaning "equal to or greater than Celsus", refers to the Roman encyclopedist Aulus Cornelius Celsus from the 1st century, known for his tract on medicine.

LD Lethal dosis

Kategorie	Přibližná smrtná dávka po požití v mg/kg	celkové množství pro člověka	Příklad
1. prakticky netoxické	> 15 000	víc než litr	$BaSO_4$
2. málo toxické	5 - 10 000	půllitr až litr	Ethanol*
3. mírně toxické	500 - 5 000	půldeci až půllitr	NaCl, $FeSO_4$,
4. silně toxické	50 - 500	lžička až půldeci	Cd^{2+}, Pb^{2+}, methanol
5. extrémně toxické	5 - 50	7 kapek až lžička	$BaCO_3$, $KClO_3$
6. supertoxické	< 5	stopa, méně než 7 kapek	nikotin, As^{3+}, botulotoxin tetrachlordibenzodioxin

* toxicita ethanolu je vyšší u dětí, smrtná dávka je asi 3,5 g/kg

XENOBIOTICS

The term xenobiotic is derived from the Greek words
ξένος (xenos) = foreigner, stranger
and
βίος (bios, vios) = life,

very often used in the context of pollutants
(such as dioxins and PCBs)
and their effect on the biota , because

xenobiotics are understood as substances foreign to an entire biological system, i.e. artificial substances, which did not exist in nature before their synthesis by humans.

APPLIED TOXICOLOGY

1. *Clinical toxicology* is the diagnosis and treatment of human poisoning.
2. *Veterinary toxicology* is the diagnosis and treatment of poisoning in animals other than humans, particularly livestock and companion animals, but not excluding feral species. Other important concerns of veterinary toxicology are the possible transmission of toxins to the human population in meat, fish, milk, and other foodstuffs, and the care and ethical treatment of experimental animals.
3. *Forensic toxicology* concerns the medicolegal aspects, including detection of poisons in clinical and other samples.
4. *Environmental toxicology* is concerned with the movement of toxicants and their metabolites and degradation products in the environment and in food chains, and with the effect of such contaminants on individuals and, especially, populations. Because of the large number of industrial chemicals and possibilities for exposure, as well as the mosaic of overlapping laws that govern such exposure, this area of applied toxicology is well developed.
5. *Industrial toxicology* is a specific area of environmental toxicology that deals with the work environment and constitutes a significant part of *industrial hygiene*.

https://www.youtube.com/watch?v=MYo7puYZwy8

Natural organic substances

Microbial, plant, mushroom, animal toxins

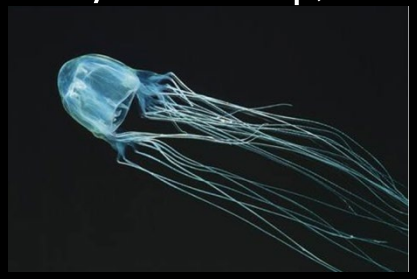
Clostridium botulinum - *botulotoxin (botulinustoxin)* lethal dosis $LD_{50}=3.10^{-11}$ g.kg^{-1}

Castor oil plant (Ricinus communis ,Euphorbiaceae)
lethal dosis LD_{50} for ricin 6.10^{-6} g.kg^{-1}

Mycotoxins : aflatoxin AFB1 acute toxicity dosis 0,4 - 10 mg.kg^{-1}

Mushroom toxins : *alfa-amanitin* (Amanita phalloides)

Animal toxins : *crotalustoxin (rattlesnake)* $LD_{50}=2.10^{-7}$ g.kg^{-1}
tetradotoxin (Fugu species)
(Chironex fleckeri, sea wasp*)*



Major Environmental Contaminants

Asbestos

Lead

Cadmium

Organic mercury

Inorganic Arsenic

Endocrine-Disrupting Chemicals (EDCs)

herbicides: atrazine, phenoxyacetic acids- 2,4-D, 2,4,5-T……
fungicides: benomyl, carbendazim, mancozeb……..
insecticides: aldrin, carbofuran, chlordan, DDT, pyrethrins……
nematocides : aldicarb
industrial chemicals: Al, As, Cd, bisphenol-A, dioxins, epichlorhydrin, furans, PCBs, PCP, phthalates, phenol……

Cadmium or its compounds

Toxic effects

1. Acute effects

'Metal fume fever'
Pseudo-influenza type syndrome usually occurring shortly after acute exposure to cadmium oxide (CdO) fumes and causing irritation and dryness of the nose and throat, coughing, headache, weakness, shivering, fever, etc. Metal fume fever usually resolves spontaneously.

Acute broncho-pneumonia (chemical pneumonitis)

The first stage is very similar to (and often confounded with) the typical "metal fume fever". After some hours, development of symptoms suggesting the onset of an acute upper respiratory tract infection: irritation and dryness of nose and throat, cough, headache, dizziness, weakness, chills, fever, chest pain and breathlessness which may progress to serious consequences such as pulmonary oedema or respiratory failure.
Death occurring several days after acute exposure to cadmium is usually due to pulmonary oedema.

Cadmium or its compounds

Exposure criteria:

It has been estimated that an 8-hour exposure to 5 mg/m³ may be lethal and an 8-hour exposure of 1 mg/m³ is considered as immediately dangerous for life.

Minimum duration of exposure: From a few minutes to a few hours depending on the intensity ofexposure.

Maximum latent period: The first symptoms usually appear within 48 hours following exposure.

Main occupational uses and sources of exposure:

manufacture of Nickel-Cadmium (Ni-Cd) batteries
electroplating other metals, mainly iron and steel
in alloys
as pigments in paints
as stabilizers
in plastics

Cadmium or its compounds

Pulmonary lesions

Long-term inhalation exposure to cadmium can lead to decreased lung function (obstructive syndrome) and emphysema.

Lung cancer

An increased risk of lung cancer has been found among workers in foundries and battery manufacturing plants where exposure to cadmium has been confirmed. However, the causal relationship between lung cancer and prolonged exposure to cadmium or cadmium compounds has not been firmly established.

Bone

Cadmium has been known to cause bone demineralisation with accompanying severe bone pain (well described in 'Itai Itai' disease in Japan). However this resulted from environmental contamination (particularly in elderly women) and not from occupational overexposure.
Individual case reports of bone effects following heavy occupational Cadmium exposure have occurred in specific groups of individuals especially post-menopausal women with vitamin D deficiency.

Cadmium or its compounds

2. Chronic effects

Nephropathy

Nephrotoxicity in occupationally exposed subjects is usually a tubular dysfunction associated with an increased urinary excretion of Low Molecular Weight (LMW) proteins such as ß-2 microglobulins (ß2M) and retinol binding protein (RBP).
An effect on the glomerulus may also be observed in cadmium-exposed workers, as indicated by increased urinary excretion of HMW proteins including albumin, immunoglobulin G (IgG) or transferrin.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure confirmed, if possible assessed, by:

- history and study of working conditions providing evidence of repeated or prolonged exposure to cadmium;
- and, if available:
  biological monitoring (levels below which nephropathy is unlikely to be due to occupational exposure to cadmium)guide values (depending on the duration of exposure): CdU > 5-10 µg/g creatinine

Workplace air monitoring guide values: atmospheric concentration > 2 µg/m^3.

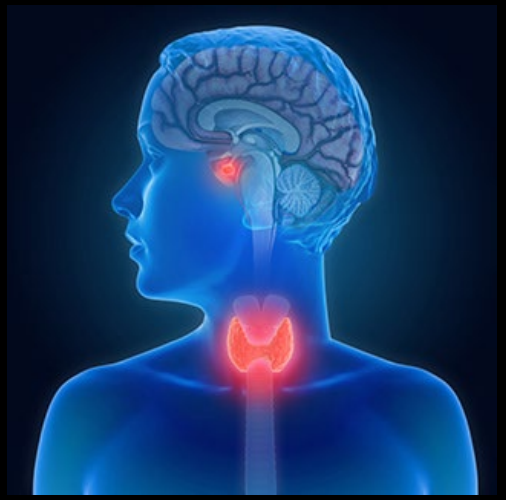
Minimum duration of exposure: Several years depending on the level of exposure

Maximum latent period: Cd is a highly cumulative agent. The first signs of renal damage may develop several years after documented exposure.

Endocrine Disruptors

https://www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm

Introduction



Endocrine-disrupting chemicals (EDCs) are **natural or human-made chemicals** that may **mimic, block, or interfere with the body's hormones**, which are part of the endocrine system. These chemicals are associated with a wide array of health issues.

The Endocrine System

Endocrine glands, distributed throughout the body, produce the hormones that act as signaling molecules after release into the circulatory system. The human body is dependent on hormones for a healthy endocrine system, which controls many biological processes like **normal growth, fertility, and reproduction**. Hormones act in extremely small amounts, and minor disruptions in those levels may cause **significant developmental and biological effects**.

Endocrine-Disrupting Chemicals (EDCs) *(WHO 2012)*

Classification	Specific Examples of EDCs[1]
Persistent and bioaccumulative halogenated chemicals	
Persistent Organic Pollutants (POPs) (Stockholm Convention) (section 3.1.1.1)	PCDDs/PCDFs, **PCBs**, HCB, **PFOS**, **PBDEs**, PBBs, Chlordane, Mirex, Toxaphene, **DDT**/DDE, Lindane, Endosulfan
Other Persistent and Bioaccumulative Chemicals (section 3.1.1.2)	**HBCDD,** SCCP, PFCAs (e.g. **PFOA**), Octachlorostyrene, PCB methyl sulfones
Less persistent and less bioaccumulative chemicals	
Plasticizers and Other Additives in Materials and Goods (section 3.1.1.3)	Phthalate esters (**DEHP**, BBP, DBP, DiNP), Triphenyl phosphate, Bis(2-ethylhexyl)adipate, n-Butylbenzene, Triclocarban, Butylated hydroxyanisole
Polycyclic Aromatic Chemicals (PACs) including PAHs (section 3.1.1.4)	**Benzo(a)pyrene**, Benzo(a)anthracene, Pyrene, Anthracene
Halogenated Phenolic Chemicals (HPCs) (section 3.1.1.5)	2,4-Dichlorophenol , Pentachlorophenol, Hydroxy-PCBs, Hydroxy-PBDEs, Tetrabromobisphenol A, 2,4,6-Tribromophenol, **Triclosan**
Non-halogenated Phenolic Chemicals (Non-HPCs) (section 3.1.1.5)	**Bisphenol A**, Bisphenol F, Bisphenol S, Nonylphenol, Octylphenol, Resorcinol
Pesticides, pharmaceuticals and personal care product ingredients	
Current-use Pesticides (section 3.1.1.6)	2,4-D, **Atrazine**, Carbaryl, Malathion, Mancozeb, **Vinclozolin**, Procloraz, Procymidone, Chlorpyrifos, Fenitrothion, Linuron
Pharmaceuticals, Growth Promoters, and Personal Care Product Ingredients (section 3.1.1.7)	Endocrine active (e.g. Diethylstilbestrol, Ethinylestradiol, Tamoxifen, **Levonorgestrel),** Selective serotonin reuptake inhibitors (SSRIs; e.g. **Fluoxetine**), Flutamide, 4-Methylbenzylidene camphor, Octyl-methoxycinnamate, Parabens, **Cyclic methyl siloxanes** (D4, **D5,** D6), Galaxolide, 3-Benzylidene camphor
Other chemicals	
Metals and Organometallic Chemicals (section 3.1.1.8)	Arsenic, Cadmium, Lead, Mercury, **Methylmercury** Tributyltin, Triphenyltin
Natural Hormones (section 3.1.1.9)	17β-Estradiol, Estrone, Testosterone
Phytoestrogens (section 3.1.1.9)	Isoflavones (e.g. Genistein, Daidzein), Coumestans (e.g. Coumestrol), Mycotoxins (e.g. Zearalenone), Prenylflavonoids (e.g. 8-prenylnaringenin)

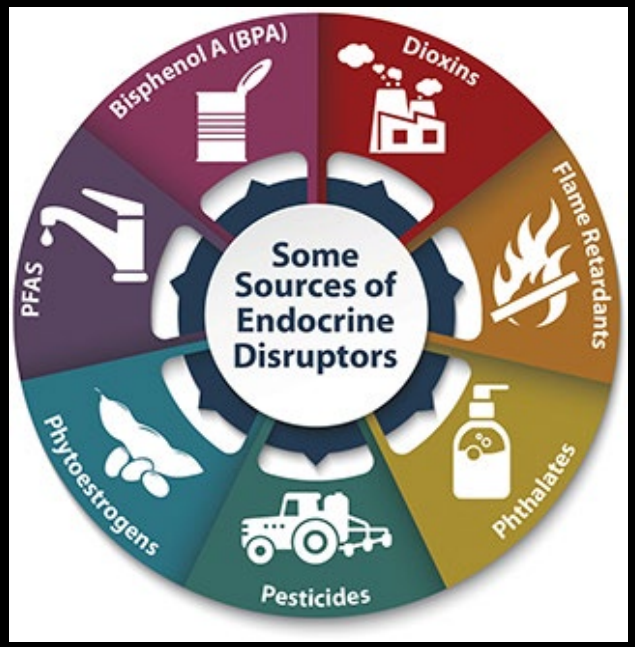
[1]See Appendix II for full names and abbreviations of the chemicals mentioned.

Endocrine Disruptors

https://www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm

How Do We Encounter These Chemicals?

Endocrine disruptors are found **in many everyday products**, including some **cosmetics, food and beverage packaging, toys, carpet, and pesticides**. Some chemicals that act as **flame retardants** may also be endocrine disruptors.
Contact with these chemicals may occur **through air, diet, skin, and water**.
EDCs **cannot be completely avoided or removed**; however, you can make informed choices to reduce exposure and risk of any potential health effects.



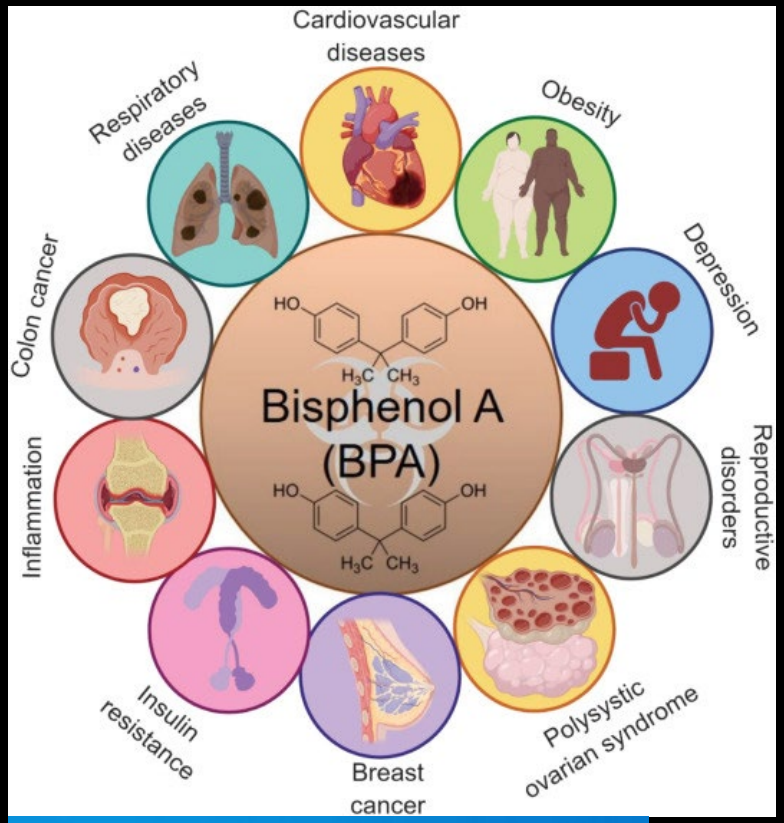
Chemicals That May Disrupt Your Endocrine System
According to the Endocrine Society, there are nearly 85,000 human-made chemicals in the world, and 1,000 or more of those could be endocrine disruptors, based on their unique properties.
The following are among the most common and well-studied.

Endocrine Disruptors

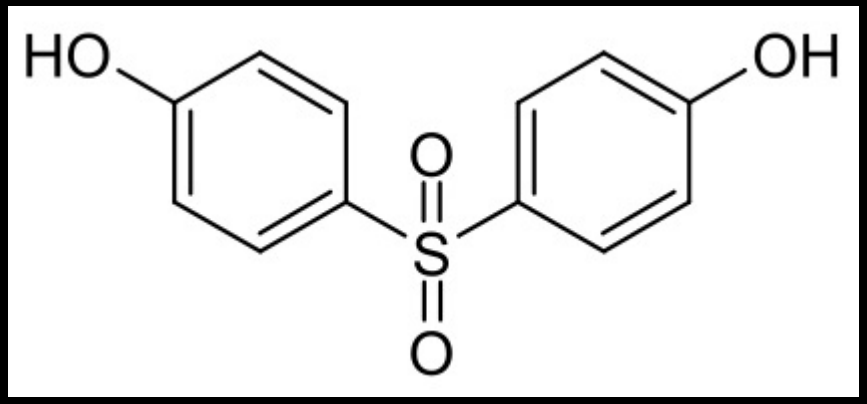
https://www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm

Bisphenol A (BPA)

is used to make
polycarbonate plastics
and
epoxy resins.
It is used in manufacturing, food packaging, toys, and other applications. BPA resins may be found in the lining of some canned foods and beverages.



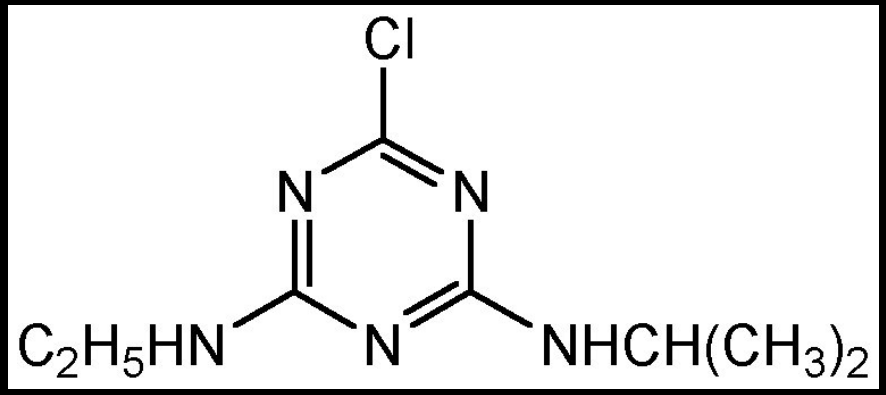
Bisfenol S (BPS)



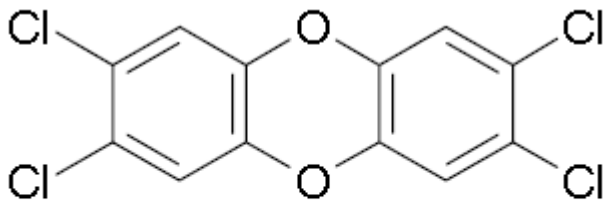
Endocrine Disruptors https://www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm

Atrazine

is one of the most commonly applied **herbicides** in the world, often used to control weeds in corn, sorghum, and sugarcane crops.



Dioxin



2,3,7,8-tetrachlordibenzo-p-dioxin

1. Acute effects:

eye and respiratory tract irritation
skin rush, chloracne
fatigue, nervousness, irritability

2. **Chronic effects:**

chloracne
soft-tissue sarcoma
non –Hodgkin lymphoma
Hodgkin disease

Contaminant of defoliant AGENT ORANGE
Dioxins are a byproduct of certain manufacturing processes, such as **herbicide production** and **paper bleaching**. They can be released into the air from **waste burning and wildfires**.

Vietnam Red Cross List of Diseases Caused by Agent Orange/Dioxin

(combined 1998 and 2000 lists)

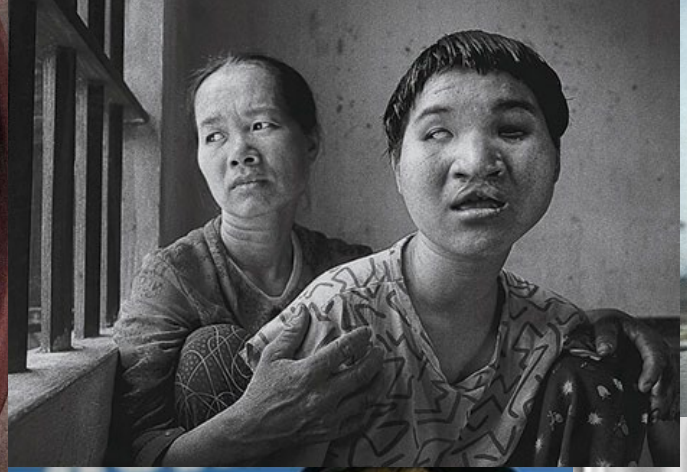
- Acute, chronic and subacute peripheral neuropathy
- Chloracne
- Diabetes (Type 2)
- Hepatoma
- Hodgkin's disease
- Lipid metabolism
- Malignant (non-Hodgkin's) lymphoma
- Multiple myeloma (Kahler's disease)
- Porphyria cutanea tarda
- Prostate cancer
- Reproductive abnormalities
- Respiratory cancers (bronchial, tracheal, and laryngeal)
- Sarcoma
- Spinal bifida

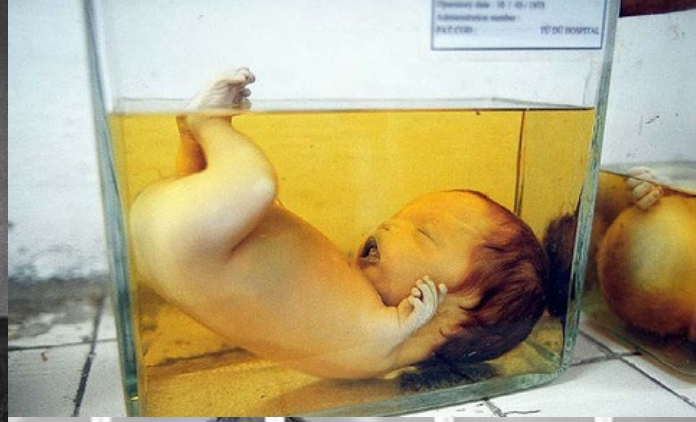
Source: Confidential Vietnamese official

U.S. Department of Veterans Affairs List of Diseases and Conditions Presumed to be Related to Service-Related Exposure to Agent Orange/Dioxin

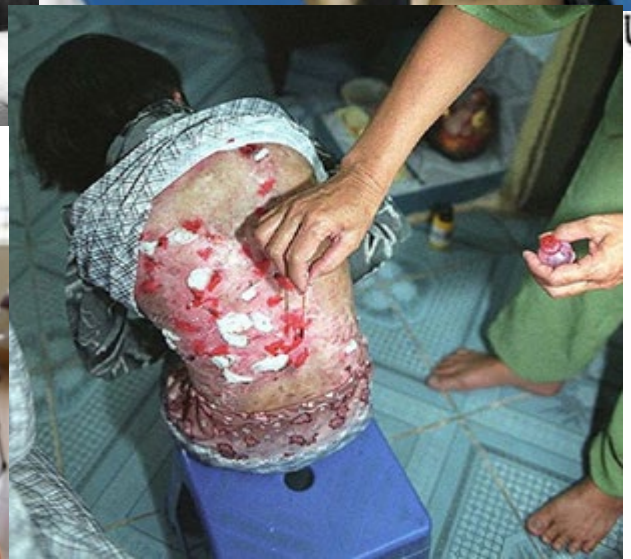
Chloracne
Non-Hodgkin's lymphoma
Soft tissue sarcoma
Hodgkin's disease
Porphyria cutanea tarda
Multiple myeloma
Respiratory cancers (including lung, larynx, trachea, and bronchus
Prostate cancer
Acute and subacute transient peripheral neuropathy
Type 2 diabetes
Chronic lymphocytic leukemia
Primary (AL) amyloidosis
For children of all exposed veterans:
- Spinal bifida (but not spinal bifida occulta)

For children of exposed female veterans:
- Achonodroplasia
- Cleft lip and cleft palate
- Congenital heart disease
- Congenital talipes equinovarus (clubfoot)
- Esophageal and intestinal atresia
- Hallerman-Streiff syndrome
- Hip dysplasia
- Hirschprung's disease (congenital megacolon)
- Hydrocephalus due to aqueductal stenosis
- Hypospadias
- Imperforate anus
- Neural tube defects
- Poland syndrome
- Pyloric stenosis
- Sundactyly (fused digits)
- Tracheoesophageal fistula
- Undescended testicle
- Williams syndrome





US USE OF AGENT ORANGE IS STILL FELT IN VIETNAM



Endocrine Disruptors

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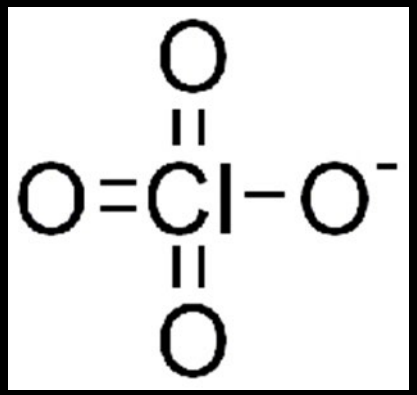
Perchlorate

is a colorless salt manufactured
and used as an industrial chemical
to make **rockets, explosives**,
and **fireworks**,
which can be found in some groundwater.



Endocrine Disruptors

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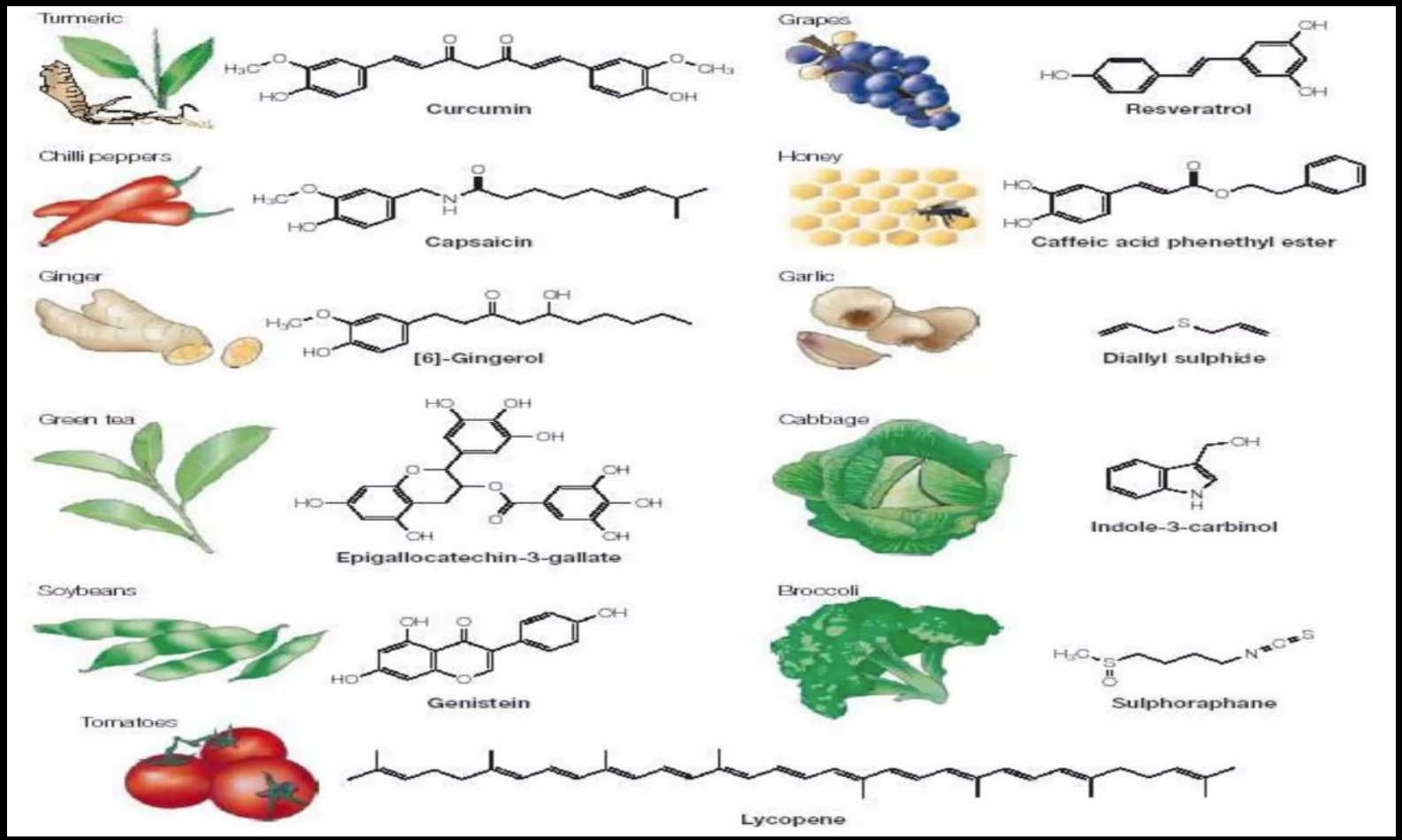
Phytoestrogens

are **naturally occurring** substances with **hormone-like activity found in some plants**; they may have a similar effect to estrogen produced by the body. Soy foods, for example, contain phytoestrogens.



Endocrine Disruptors

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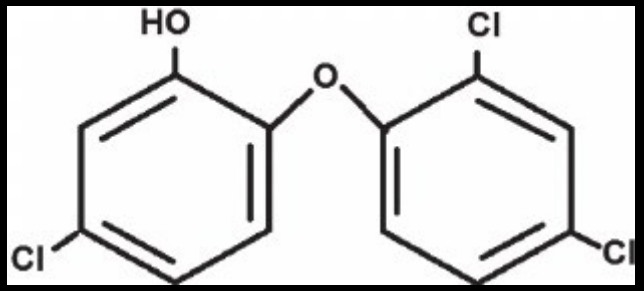
Triclosan

is an ingredient that was previously added to some antimicrobial and personal care products, **like liquid body wash** and **soaps**.



Endocrine Disruptors

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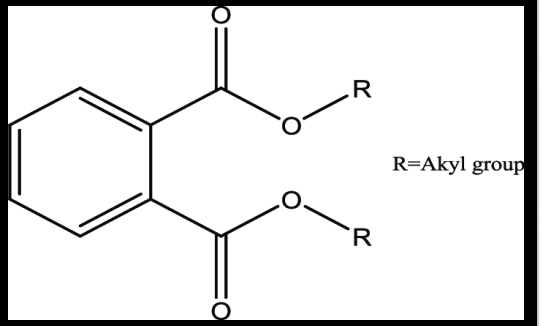
Phthalates

are a large group of compounds used as **liquid plasticizers**.
They are found in hundreds of products including some **food packaging, cosmetics, fragrances, children's toys**, and **medical device tubing**.
Cosmetics that may contain phthalates include **nail polish, hair spray, aftershave lotion, cleanser**, and **shampoo**.

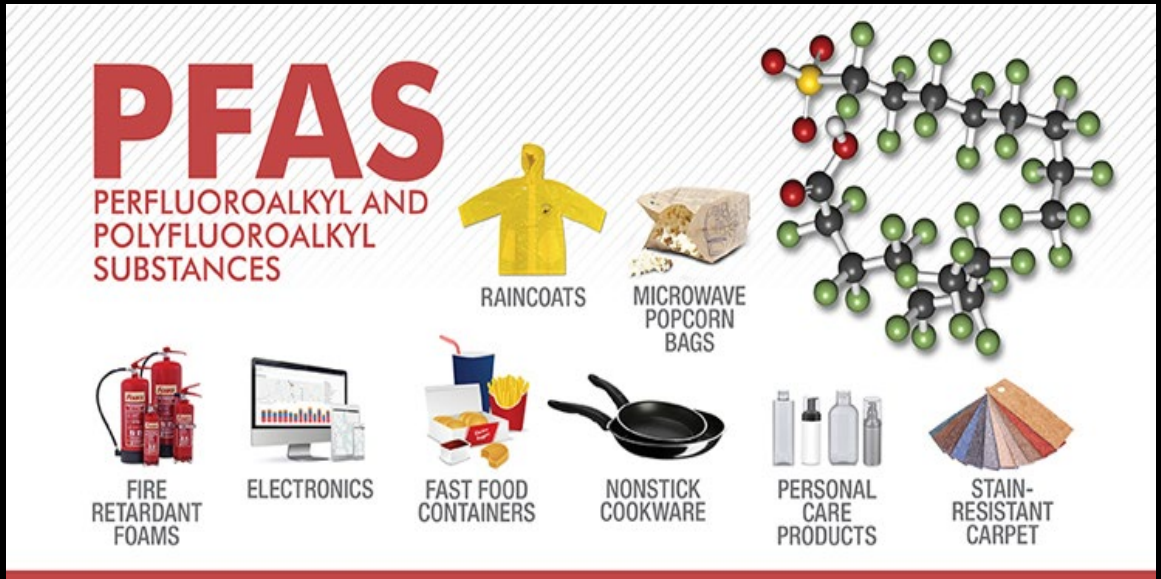


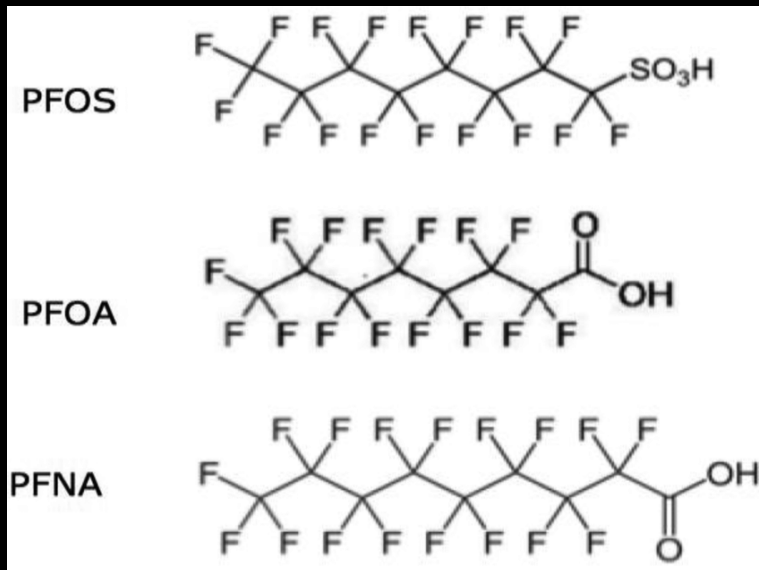
Endocrine Disruptors

https://www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm

Per- and polyfluoroalkyl substances (PFAS)

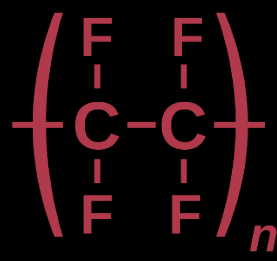
are a large group of chemicals used widely in industrial applications, such as **firefighting foam, nonstick pans, paper**, and **textile coatings.** PFAS are used to **repel water and grease from paper food packaging, outdoor clothing** and even **carpets,** for example. They are mainly known for their use in **Teflon** and **Gore-Tex. Running waxes** also contain them.





perfluorooctanoic acid (PFOA; C8),
perfluorooctane sulfonate (PFOS; C8)
perfluorononanoic acid (PFNA; C9)

Polytetrafluoroethylene



Endocrine Disruptors

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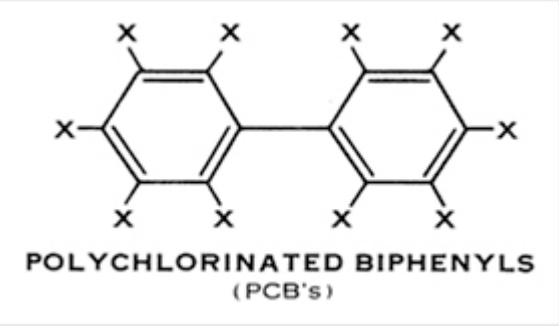
Polychlorinated biphenyls (PCBs)

were used to make **electrical equipment**, such as **transformers**, and are in **hydraulic fluids, heat transfer fluids, lubricants**, and **plasticizers**.
PCBs were mass-produced globally until they were banned in 1979.



Endocrine Disruptors

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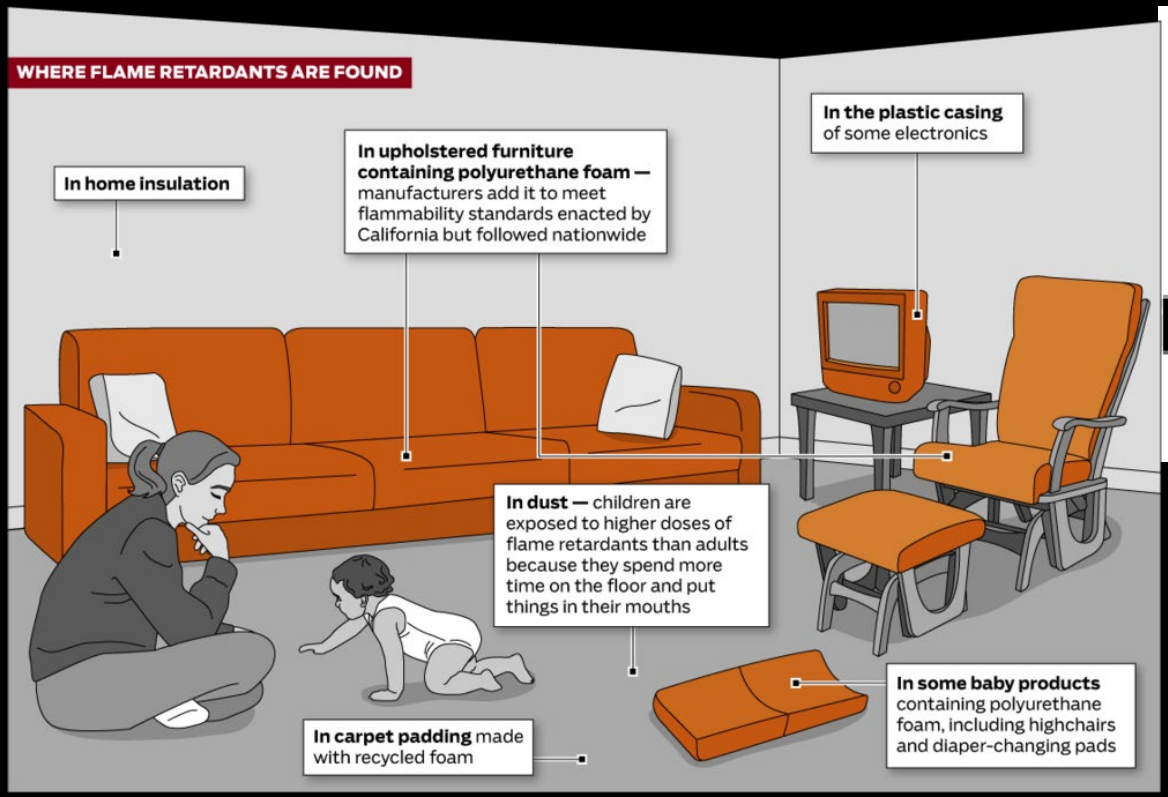
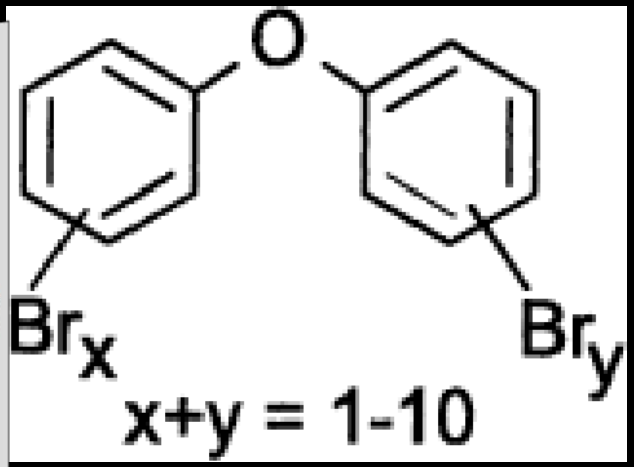
Polybrominated Diphenyl Ethers (PBDEs)

flame-retardants found in consumer goods such as **electrical equipment, construction materials, coatings, textiles** and **polyurethane foam** (furniture padding).





Polychlorinated biphenyls (PCBs)

Characteristics: PCBs are technical mixtures of biphenyls with different numbers of chlorine atoms attached at different positions, making up a theoretical total number of 209 PCB congeners. PCBs exhibit high thermal and chemical stability and are very hydrophobic (log K_{OW} ranges from ~5.0 for Cl_2CBs to ≈ 8.9 for Cl_8CBs).

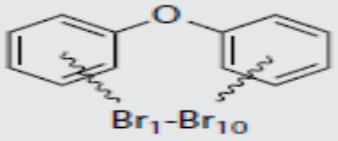
Origin and use: PCBs were produced from 1929 until the mid-1980s for primary use as insulating agents in transformer oils and capacitors, as heat transfer agents, and in sealants for construction (buildings).

Fate: PCBs are highly persistent in the environment, transported over long distances by air and water currents, and are globally distributed. As a result, wildlife and humans worldwide are exposed to PCBs. While some PCB congeners are easily metabolized, others are not. Some PCB congeners, particularly those with substitution at the 2,4 and 2,4,5 positions on the rings, accumulate through food webs to high concentrations in humans and wildlife.

Effects: Extensively studied: Possible endometriosis and fibroids in humans, fibroids, uterine tumours and adrenal problems in seals (Chapter 2.2 & 2.8). Strong experimental and molecular evidence for suppression of thyroid hormone in all vertebrate classes and epidemiological evidence of reduced cognitive function in children (Chapter 2.5 & 2.6). Limited evidence for increased prostate and breast cancer risk in humans and for genital carcinomas in sea lions (Chapter 2.7). Evidence for immune dysfunction in marine mammals and humans (Chapter 2.11). Limited evidence of increased diabetes risk (Chapter 2.10). Probable cause of population declines in fish-eating birds and mammals (Chapter 2.12).

Reviews: Hansen & Robertson, 2001; Ritter, Solomon & Forget, 1995; Waid; 1986; IPCS, 2003; 1992a; 1993

Polybrominated diphenyl ethers (PBDEs)



Characteristics: PBDEs are technical mixtures of diphenyl ethers with different numbers of bromine atoms attached at different positions, making up a theoretical total number of 209 PBDE congeners. PBDEs are brominated aromatic compounds of high chemical stability under natural conditions, but are broken down when heated. The PBDEs are hydrophobic (log K_{OW} of tetraBDEs = 6.77; heptaBDEs = 9.4).

Origin and use: PBDEs have been produced since the early 1970s for applications as flame retardants in textiles, electronics, electric articles, furniture and building materials. PBDEs have been subdivided into PentaBDE, OctaBDE and DecaBDE, representing the types of PBDEs produced commercially. DecaBDE (consisting predominantly of BDE-209) remains the major PBDE mixture in production worldwide with 85% of its global use occurring in North America and East Asia (BSEF, 2003).

Fate: PBDEs are very persistent in the environment, transported long distances by wind and air currents, and globally distributed. Debromination of DecaBDE - by sunlight in surface soils and on aerosols, and in the gastrointestinal tract of fish, mammals and birds - is a major transformation process that results in formation of less brominated BDEs (Schenker et al., 2008). Thus while "Penta" and "Octa" BDEs have been phased out, debromination of DecaBDE could be an additional source of emissions of the lower brominated congeners along with the large inventory of in-use PBDE products. While some PBDE congeners are easily metabolized, others are not. Some PBDE congeners bioaccumulate and biomagnify through food webs, and are present in wildlife and humans at high concentrations. Wildlife and humans worldwide are exposed to PBDEs.

Effects: Limited evidence for earlier age at menarche and cryptorchidism in humans (Chapter 2.2 and 2.3), eggshell thinning, delayed hatching and reduced weight of hatchlings in birds (Chapter 2.2). Strong experimental evidence for suppression of thyroid hormone in humans and Arctic wildlife (Chapter 2.5 & 2.6). Limited evidence for cognitive disorders. Probable contributing cause of population declines in marine mammals (Chapter 2.12).

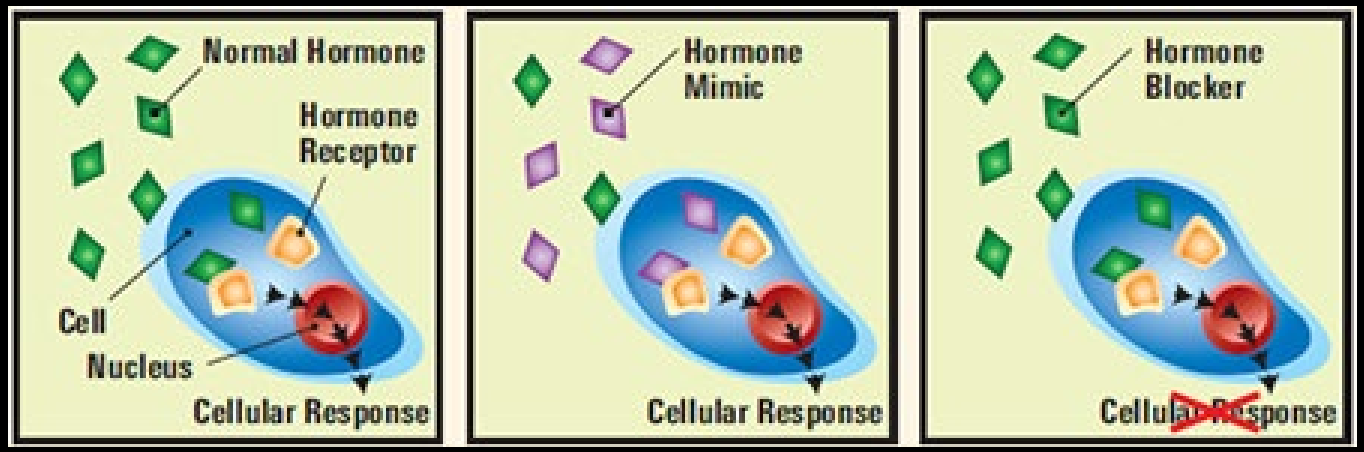
Reviews: Alcock, Mac Gillivray & Busby, 2011; Daso et al.,

Endocrine Disruptors

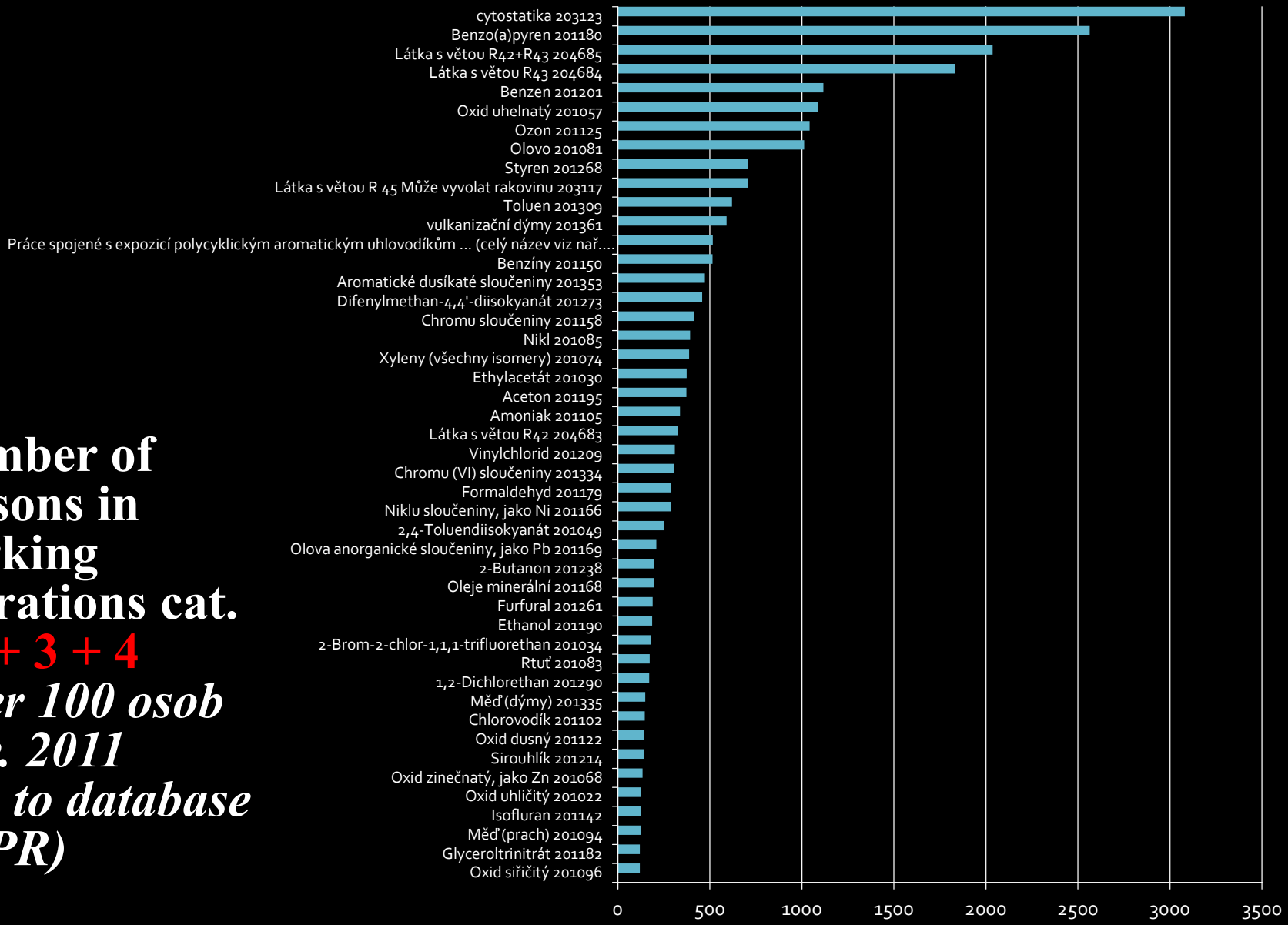
https://www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm

How do people encounter endocrine-disrupting chemicals?
People may be **exposed** to endocrine disruptors **through food and beverages consumed, pesticides applied, and cosmetics used**.
In essence, your contact with these chemicals may occur through **diet, air, skin, and water**.

Even low doses of endocrine-disrupting chemicals may be unsafe.
The body's normal endocrine functioning involves very small changes in hormone levels, yet we know even these small changes can cause **significant developmental and biological effects**.
This observation leads scientists to think that endocrine-disrupting chemical exposures, even at low amounts, **can alter the body's sensitive systems and lead to health problems.**



Major Industrial Contaminants (CZ)



Number of persons in working operations cat. 2R + 3 + 4

(over 100 osob Nov. 2011 acc. to database KAPR)

Some occupational hazards and associated cancers

Agent	Tumor Sites	Occupation
Asbestos	Lung, pleura, peritoneum	Miners, manufacturers, users
Arsenic	Skin, lung, liver	Miners and smelters, oil refinery, pesticide workers
Benzene	Hemopoietic tissue	Process workers, textile workers
Cadmium	Lung, kidney, prostate	Battery workers, smelters
Chloroethers	Lung	Chemical plant workers, process workers
Chromium	Lung, nasal cavity, sinuses	Process and production workers, pigment workers
Mustard gas	Bronchi, lung, larynx	Production workers
Naphthylamines	Bladder	Dyestuff makers and workers, chemical workers, printers
Nickel	Lung, nasal sinuses	Smelters and process workers
Polycyclic aromatic hydrocarbons	Respiratory system, bladder	Furnace, foundry, shale, and gas workers; chimney sweeps
Radon, radium, uranium	Skin, lung, bone tissue, bone marrow	Medical and industrial chemists, miners
UV radiation	Skin	Outdoor exposure
X-rays	Bone marrow, skin	Medical and industrial workers

Carcinogenic substances

Under the EU system, substances and preparations can be classified for carcinogenic effects as follows:

Category 1: Substances known to be carcinogenic to man.
There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

Category 2: Substances which should be regarded as if they are carcinogenic to man.
There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of :
- appropriate long term animal studies,
- other relevant information.

Category 3: Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in category 2.

Carcinogenic substances

The International Agency for Research on Cancer (IARC) evaluates and lists substances, mixtures,and processes, grouping them into:

Group 1 agents: Carcinogenic to humans
Group 2A agents: Probably carcinogenic to humans
Group 2B agents: Possibly carcinogenic to humans
Group 3 agents: Not classifiable as to carcinogenicity to humans
Group 4 agents: Probably not carcinogenic to humans

The American Conference of Governmental Industrial Hygienists, Inc. (ACGIH) has a similar allocation of five categories for carcinogenicity:

Category A1: Confirmed human carcinogen
Category A2: Suspected human carcinogen
Category A3: Confirmed animal carcinogen with unknown relevance to humans
Category A4: Not classifiable as a human carcinogen
Category A5: Not suspected a s a human carcinogen

Occupational allergies

The target organs most commonly affected by occupational allergens are the skin and the respiratory tract.

Individual susceptibility is especially relevant, as atopic individuals (those with a personal or family history of eczema, asthma, hay fever, or allergic rhinitis)
are more likely to develop allergies to some agents compared to non-atopics.

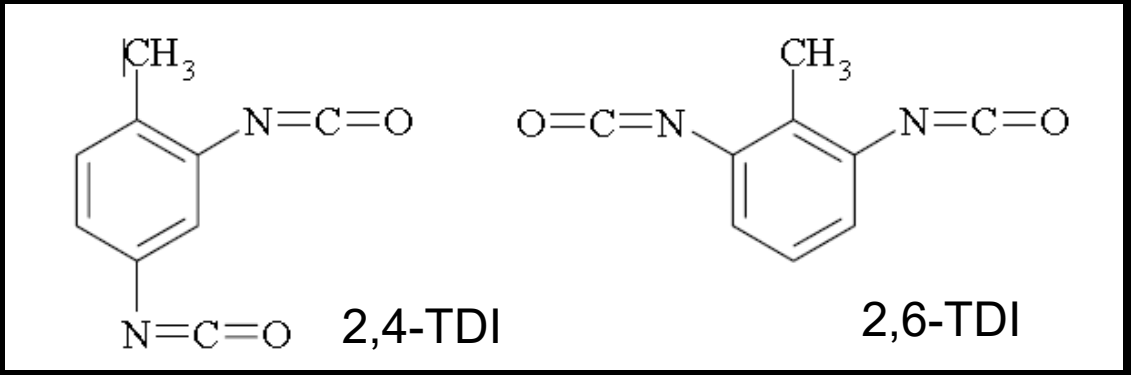
Skin patch tests can be used in confirming a diagnosis of occupational skin allergy.

Clinical investigations for respiratory allergy include skin prick tests, measurement of immunoglobulins, and bronchial provocation test.

Isocyanates

Toxic effects

1. Irritant and corrosive effects



Crucial mechanism of toxicity : direct influence of isocyanates on oxidative stress in cells. These chemicals can create quite persistent connections with gluthatione and they are the cause of increased production of reactive free radicals.
Isocyanates irritate the skin and the ocular and respiratory mucous membranes.
Direct contact (or exposure to high concentrations) can lead to palpebral and corneal disorders with eye burns, photophobia, blepharospasm, conjunctival hyperhaemia and superficial corneal ulcerations.
Irritation of the airways may lead to an acute pulmonary oedema with bronchoconstriction and possible development of severe bronchiolitis, death from acute respiratory distress syndrome or fibrosis-type sequelae.

Guide values: (methyl isocyanate)

irritation of ocular mucous membrane: exposure > (470µg/m^3); 0.2 ppm
palpebral and corneal disorders: exposure > (117.5 mg/m^3); 50 ppm
acute pulmonary oedema: exposure > (117.5 mg/m^3); 50 ppm

Isocyanates

3. Chronic obstructive bronchopathy

Expert evaluation is necessary to determine to causal link between exposure to isocyanates and the onset of chronic obstructive bronchopathy.

Exposure criteria:

Minimum intensity of exposure: Occupational exposure to isocyanates confirmed, if possibleassessed, by:

- History and study of exposure conditions providing evidence of prolonged or repeated exposure to isocyanates;
- and, if available:
- biological monitoring;
- workplace air monitoring;

Guide value: atmospheric concentration
TDI > 0.036 mg/m^3 (0.005 ppm)
MDI > 0.047 mg/m^3 (0.02 ppm)
Minimum duration of exposure: 10 years
Maximum latent period: Five years

Isocyanates

2. Immuno-allergic effects (diisocyanates)

ironing fabric with heat-activated adhesive

Allergic contact dermatitis

Allergic contact dermatitis due to isocyanates is observed very rarely.

Allergic rhinitis and conjunctivitis

Asthma

It is well documented that isocyanates are a cause of occupational asthma. Humoral as well as cellular mechanisms are involved in the pathogenesis. Immediate or late allergic reactions or both can occur. The specific humoral immune response can be IgE as well as IgG mediated, but many patients with sensitisation to isocyanates have no demonstrative serum antibodies against isocyanates.

Allergic alveolitis

COMMISSION REGULATION (EU) 2020/1149

of 3 August 2020

amending Annex XVII to Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards diisocyanates

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC [1], and in particular Article 68(1) thereof,

Whereas:

(1) Diisocyanates have a harmonised classification as a respiratory sensitiser category 1 and as a skin sensitiser category 1 according to Regulation (EC) No 1272/2008 of the European Parliament and of the Council [2]. Diisocyanates are used as chemical building blocks in a wide range of sectors and applications, in particular in foams, sealants and coatings, inter alia, throughout the Union.

(2) On 6 October 2016, Germany submitted to the European Chemicals Agency ('the Agency') a dossier [3] pursuant to Article 69(4) of Regulation (EC) No 1907/2006 ('the Annex XV dossier'), in order to initiate the restriction procedure set out in Articles 69 to 73 of that Regulation. The Annex XV dossier indicated that respiratory sensitisation, due to both dermal and inhalation exposure to diisocyanates, leads to occupational asthma in workers, which has been identified as a significant occupational health problem in the Union. The annual number of new occupational diseases caused by diisocyanates (estimated to be more than 5 000 cases) is considered unacceptably high. The Annex XV dossier demonstrated that action on a Union-wide basis is necessary and proposed to restrict the industrial and professional use, as well as the placing on the market, of diisocyanates on their own, and as constituent of other substances and in mixtures.

(3) The restriction proposed in the Annex XV dossier aims to limit the use of diisocyanates in industrial and professional applications to those cases where a combination of technical and organisational measures are implemented, and a minimum standardised training course has been followed. Information on how to get access to the course should be communicated throughout the supply chain and it should be the responsibility of the operators placing these substances and mixtures on the market to ensure that training courses are available to the recipients of such substances or mixtures.

pressing the fabric using adhesive

'74. Diisocyanates, O = C=N-R-N = C=O, with R an aliphatic or aromatic hydrocarbon unit of unspecified length	1. Shall not be used as substances on their own, as a constituent in other substances or in mixtures for industrial and professional use(s) after 24 August 2023, unless: (a) the concentration of diisocyanates individually and in combination is less than 0,1 % by weight, or (b) the employer or self-employed ensures that industrial or professional user(s) have successfully completed training on the safe use of diisocyanates prior to the use of the substance(s) or mixture(s). 2. Shall not be placed on the market as substances on their own, as a constituent in other substances or in mixtures for industrial and professional use(s) after 24 February 2022, unless: (a) the concentration of diisocyanates individually and in combination is less than 0,1 % by weight, or (b) the supplier ensures that the recipient of the substance(s) or mixture(s) is provided with information on the requirements referred to in point (b) of paragraph 1 and the following statement is placed on the packaging, in a manner that is visibly distinct from the rest of the label information: "As from 24 August 2023 adequate training is required before industrial or professional use". 3. For the purpose of this entry "industrial and professional user(s)" means any worker or self-employed worker handling diisocyanates on their own, as a constituent in other substances or in mixtures for industrial and professional use(s) or supervising these tasks. 4. The training referred to in point (b) of paragraph 1 shall include the instructions for the control of dermal and inhalation exposure to diisocyanates at the workplace without prejudice to any national occupational exposure limit value or other appropriate risk management measures at national level. Such training shall be conducted by an expert on occupational safety and health with competence acquired by relevant vocational training. That training shall cover as a minimum: (a) the training elements in point (a) of paragraph 5 for all industrial and professional use(s). (b) the training elements in points (a) and (b) of paragraph 5 for the following uses: — handling open mixtures at ambient temperature (including foam tunnels); — spraying in a ventilated booth; — application by roller; — application by brush; — application by dipping and pouring; — mechanical post treatment (e.g. cutting) of not fully cured articles which are not warm anymore; — cleaning and waste; — any other uses with similar exposure through the dermal and/or inhalation route; (c) the training elements in points (a), (b) and (c) of paragraph 5 for the following uses: — handling incompletely cured articles (e.g. freshly cured, still warm); — foundry applications; — maintenance and repair that needs access to equipment; — open handling of warm or hot formulations (> 45 °C); — spraying in open air, with limited or only natural ventilation (includes large industry working halls) and spraying with high energy (e.g. foams, elastomers); — and any other uses with similar exposure through the dermal and/or inhalation route.

REGULATORY TOXICOLOGY

Regulatory Toxicology. These aspects, concerned with the formulation of laws, and regulations authorized by laws, are intended to minimize the effect of toxic chemicals on human health and the environment.

1. *Legal aspects* are the formulation of laws and regulations and their enforcement. In the United States, enforcement falls under such government agencies as the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA) and the Occupational Safety and Health Administration (OSHA). Similar government agencies exist in many other countries.
2. *Risk assessment* is the definition of risks, potential risks, and the risk–benefit equations necessary for the regulation of toxic substances. Risk assessment is logically followed by *risk communication* and *risk management*. Risk assessment, risk communication, and risk management are frequently referred to as *risk analysis*.

A typical dose–response curve is shown in Figure 1.2, in which the percentage of organisms or systems responding to a chemical is plotted against the dose. For many chemicals and effects, there will be a dose below where no effect or response is observed. This is known as the *threshold dose*. This concept is of significance because it implies that a *no observed effect level* (NOEL) can be determined and that this value can be used to determine the safe intake for food additives and contaminants such as pesticides. Although this is generally accepted for most types of chemicals and toxic effects, for chemical carcinogens acting by a genotoxic mechanism, the shape of the curve is controversial, and for regulatory purposes, their effect is assumed to be a no-threshold phenomenon.

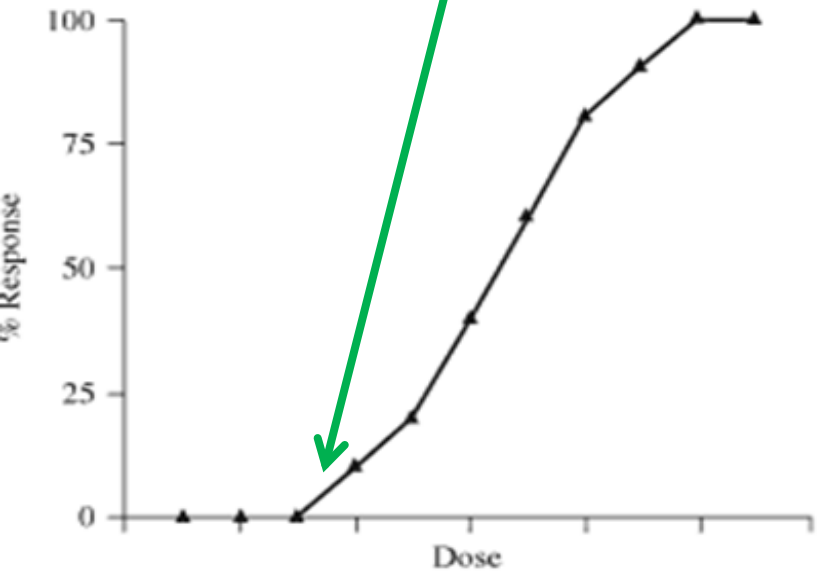
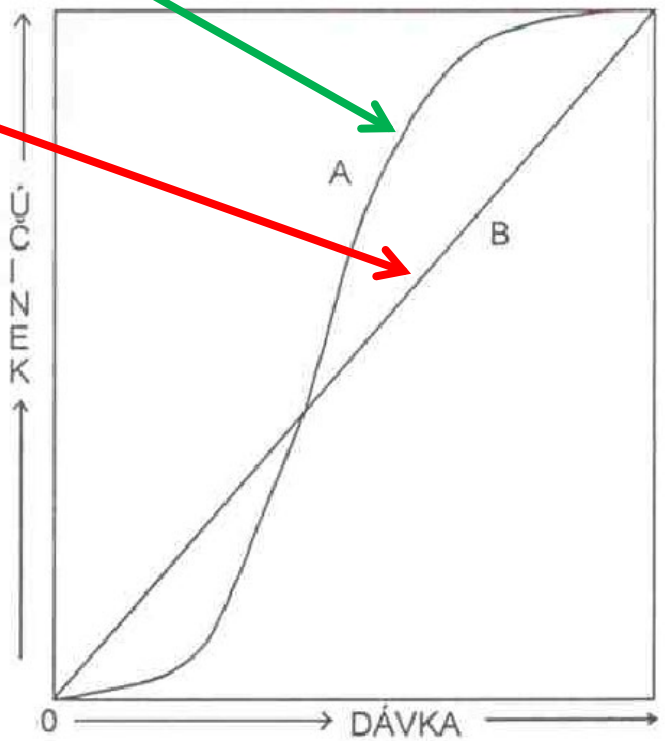


Figure 1.2 A typical dose–response curve.



NOAEL LOAEL

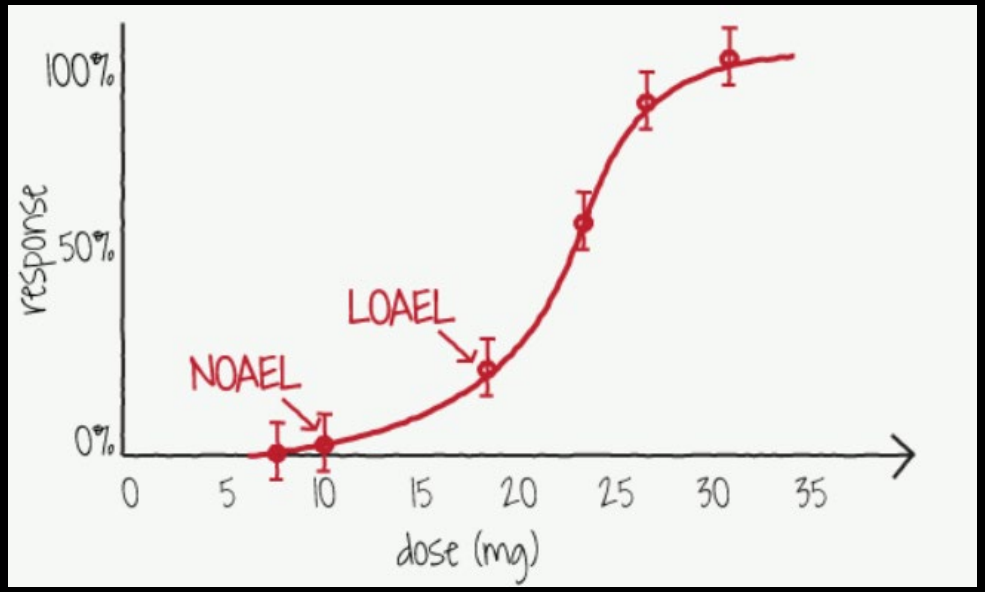
Results from research studies establish the highest doses at which no toxic effects were identified and the lowest doses at which toxic or adverse effects were observed. The terms often used to describe these outcomes are:

No Observed Adverse Effect Level (NOAEL)
Lowest Observed Adverse Effect Level (LOAEL)

These terms refer to the actual doses used in human clinical or experimental animal studies. They are defined as follows:

NOAEL — Highest dose at which there was not an observed toxic or adverse effect.
LOAEL — Lowest dose at which there was an observed toxic or adverse effect.

NOAEL LOAEL



A dose-response curve showing doses where the NOAEL and LOAEL occur for a substance
(Image Source: NLM)

Figure shows a dose-response curve where the NOAEL occurs at 10 mg and the LOAEL occurs at 18 mg.
A dose response curve of a hypothetical example where NOAEL occurs at 10 mg and LOAEL is at about 18 mg.

Sometimes the terms No Observed Effect Level (NOEL) and Lowest Observed Effect Level (LOEL) are also used. NOELs and LOELs do not necessarily imply toxic or harmful effects and can be used to describe beneficial effects of substances.

The NOAEL, LOAEL, NOEL, and LOEL are commonly used in risk assessments and research.
For example the U.S. Food and Drug Administration (FDA) publication for industry describes a process for estimating the maximum safe starting dose of drugs tested in clinical trials. It provides extensive information about these concepts and their utility when developing new drugs.

NOEALs and LOAELs are also included in the Noncarcinogenic Risk Assessment section where they are applied using the benchmark dose (BMD) method.

In vitro testing

simple organisms - protozoa, flagellata, bacteria, algae, cyanobacteria, worms, plant seed

cells – white blood cells, hepatocytes, tumor cells

mutagenicity testing on bacteria
Salmonella typhimurium (Ames test)

acute toxicity testing on tubifex worms
(Tubifex tubifex)

Animal testing principles (*in vivo testing*)

Acute 4 different doses or concentrations till 2 weeks

- oral exposure (per os)
- dermal exposure
- inhalation
- intraperitoneal exposure (injection)

Subacute 28 - 90 days

10% of lifetime, 2 species: rodent+other animal

Chronic

Long time, usually the whole lifetime (rat cca 2 years)

Testing of chemical substances on human population Epidemiological studies

1. Drug testing only after succesful animal testing
2. Study of metabolism and excretion of drugs and industrial chemicals , but used doses must be safely nontoxic

Regulations of exposure levels I

The **threshold limit value TLV** of a chemical substance is a level to which it is believed a worker can be exposed
day after day for a working lifetime without adverse health effects.

Strictly speaking, TLV is a reserved term of the American Conference of Governmental Industrial Hygienists (ACGIH). However, it is sometimes loosely used to refer to other similar concepts used in occupational health and toxicology.

The TLV for chemical substances is defined as a concentration in air, typically for inhalation or skin exposure.

Its units are in ppm for gases and in milligrams per cubic meter (mg/m^3) for particulates such as dust, smoke and mist.

Regulations of exposure levels II

Three types of TLVs for chemical substances are defined:

Threshold limit value – Time-weighted average TLV-TWA:
average exposure on the basis of a 8h/day, 40h/week work schedule PEL

Threshold limit value - Short-term exposure limit TLV-STEL:
spot exposure for a duration of 15 minutes, that cannot be repeated more than 4 times per day

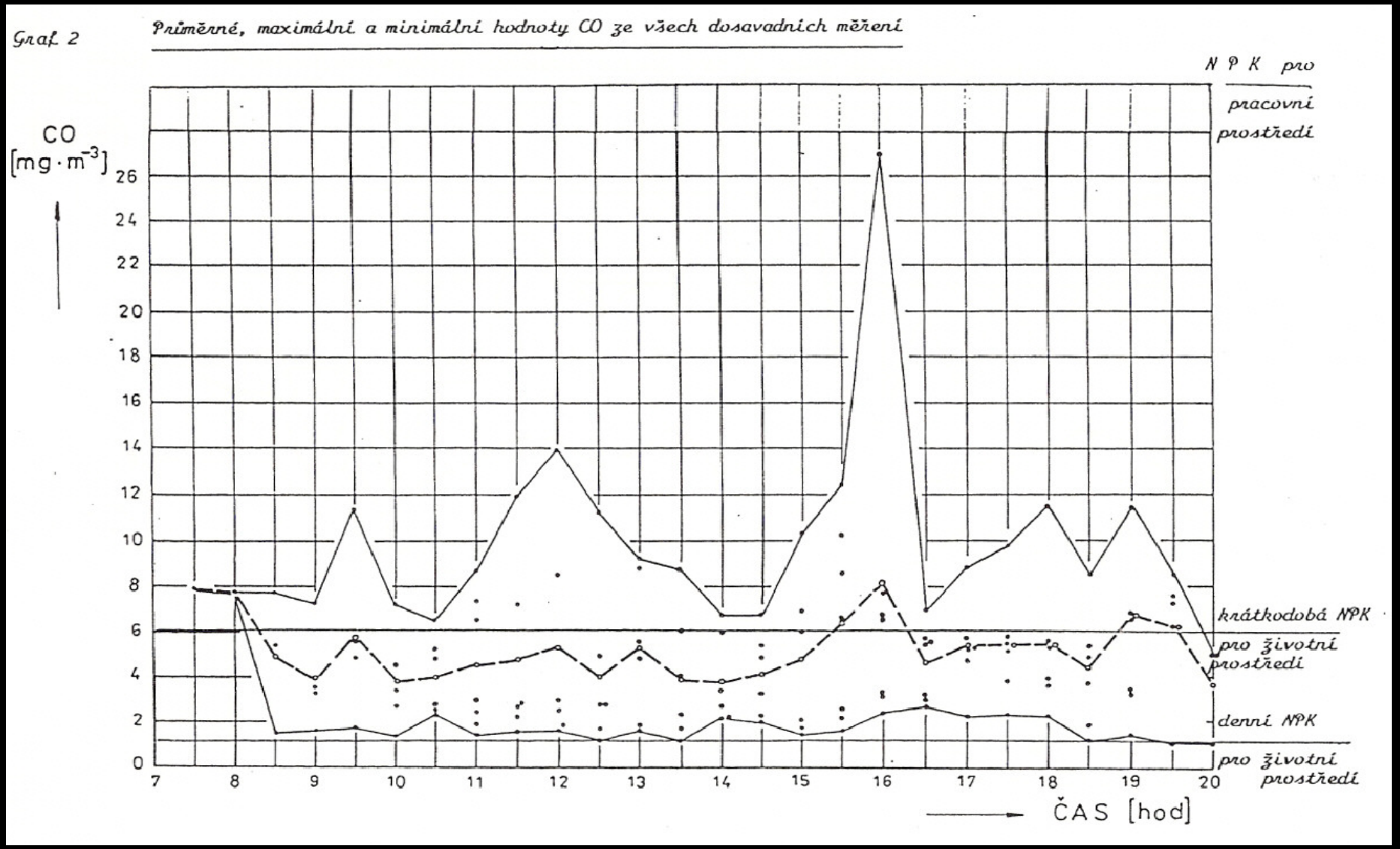
Threshold limit value - Ceiling limit TLV-C:
absolute exposure limit that should not be exceeded at any time NPK-P (MAC)

Exposure limits
TWA (PEL) and TLV-C (NPK-P)

Škodlivina	PEL	NPK-P	[mg/m^3]
Amoniak	14	36	
Akrylonitril	2	6	
Benzen	3	10	
Formaldehyd	0,5	1	
Oxid siřičitý	5	10	
Oxid uhelnatý	30	150	
Nitrosní plyny (NO_x)	10	20	

Exposure assessment

Air monitoring



Regulations of exposure levels III

Biologic limit values BLVs represent limits of amounts of substances to which the worker may be exposed without hazard to health or well-being as determined by measuring the worker´s tissues, fluids, or exhaled breath.

The biologic measurements on which the BLVs are based can furnish two kinds of information useful in the control of worker exposure:

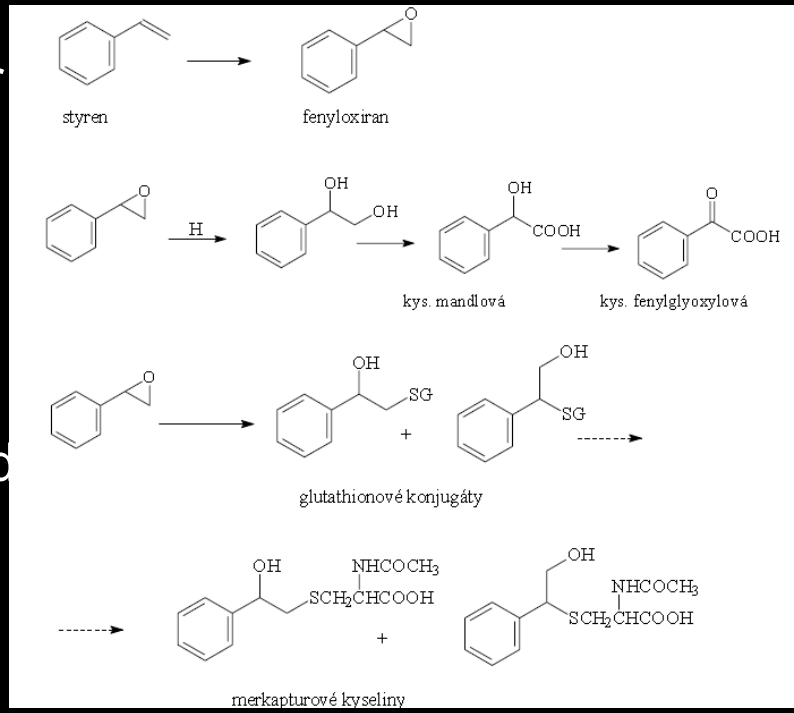
(1) Measure of worker´s overall exposure, and

(2) Measure of the worker´s individual and characteristic response

Regulations of exposure levels IV

Measurements of response furnish a superior estimate of the physiological status of the worker, and may consist of

(1) changes in amount of some critical biochemical constituent
(1) changes in activity or a critical enzyme,and
(2) changes in some physiological function



Measurement of exposure may be made by

(1) determining in blood, urine, hair, nails, or body tissues and fluids the amount of substance to which the worker was exposed
(2) determining the amount of the metabolite(s) of the substance in tissues and fluids, and
(3) determining the amount of the substance in the exhaled breath

The biological limits may be used as an adjunct to the TLVs for air, or in place of them.

Biological monitoring

Limitní hodnoty ukazatelů biologických expozičních testů v moči

Pro hodnocení je vhodná pouze moč s koncentrací kreatininu v rozmezí od 0,3 g/l do 3 g/l (t.j. od 2,65 mmol/l do 26,5 mmol/l).

Látka	Ukazatel	Limitní hodnoty		Doba odběru
Anilin	p-Aminofenol	50 mg/g kreatininu	52 µmol/mmol kreatininu	Konec směny
Arsen a arsenovodík	Arsen	0,05 mg/g kreatininu	0,075 µmol/mmol kreatininu	Konec pracovního týdne
Benzen	S-Fenylmerkapturová kyselina	0,05 mg/g kreatininu	0,024 µmol/mmol kreatininu	Konec směny
Dimethylformamid	N-Methylformamid	15 mg/l	0,25 mmol/l	Konec směny
Ethylbenzen	Mandlová kyselina	1500 mg/g kreatininu	1100 µmol/mmol kreatininu	Konec směny
Ethylenglykolmono butylether	Butoxyoctová kyselina	100 mg/l	0,76 mmol/l	Konec směny
Ethylenglykolmono butyletheracetát	Butoxyoctová kyselina	100 mg/l	0,76 mmol/l	Konec směny
Ethylenglykolmono ethylether	Ethoxyoctová kyselina	50 mg/l	0,48 mmol/l	Konec směny
Ethylenglykolmono ethyletheracetát	Ethoxyoctová kyselina	50 mg/l	0,48 mmol/l	Konec směny
Fenol	Fenol	300 mg/g kreatininu	360 µmol/mmol kreatininu	Konec směny
Fluoridy	Fluorid	10 mg/g kreatininu	60 µmol/mmol kreatininu	Konec směny
Fural	Pyroslizová kyselina	200 mg/g kreatininu	200 µmol/mmol kreatininu	Konec směny
Chrom (VI) sloučeniny	Celkový chrom	0,030 mg/g kreatininu	0,065 µmol/mmol kreatininu	Konec směny na konci pracovního týdne
Kadmium	Kadmium	0,005 mg/g kreatininu	0,005 µmol/mmol kreatininu	Nerozhoduje
Methanol	Methanol	15 mg/l	0,47 mmol/l	Konec směny
Nikl	Nikl	0,04 mg/g kreatininu	0,077 µmol/mmol kreatininu	Nerozhoduje
Nitrobenzen	p-Nitrofenol	5 mg/g kreatininu	4 µmol/mmol kreatininu	Konec směny

Látka	Ukazatel	Limitní hodnoty		Doba odběru
Olovo*	5-Aminolevulová kyselina	15 mg/g kreatininu	13 µmol/mmol kreatininu	Nerozhoduje
	Koproporfyrin	0,2 mg/g kreatininu	0,035 µmol/mmol kreatininu	
Pentachlorfenol	Pentachlorfenol	2 mg/g kreatininu	0,85 µmol/mmol kreatininu	Před poslední směnou pracovního týdne
Rtuť a její sloučeniny anorganické a fenylrtuťnaté	Rtuť	0,1 mg/g kreatininu	0,056 µmol/mmol kreatininu	Nerozhoduje
Styren	Mandlová kyselina	400 mg/g kreatininu	300 µmol/mmol kreatininu	Konec směny
	Mandlová+ Fenylglyoxylová kyselina	600 mg/g kreatininu		Konec směny
Toluen	Hippurová kyselina	1600 mg/g kreatininu	1000 µmol/mmol kreatininu	Konec směny
	o- Kresol	0,5 mg/l	4,6 µmol/l	Konec směny
Trichloethylen	Trichloroctová kyselina	100 mg/g kreatininu	70 µmol/mmol kreatininu	Konec pracovního týdne
	Trichlorethanol	200 mg/g kreatininu	150 µmol/mmol kreatininu	Konec směny
Xyleny	Methylhippurové kyseliny	1400 mg/g kreatininu	820 µmol/mmol kreatininu	Konec směny

* Vhodné pro krátkodobé kontinuální expozice zaměstnanců nepřekračující jeden měsíc.

Limitní hodnoty ukazatelů biologických expozičních testů v krvi

Látka v krvi	Ukazatel	Limity	Doba odběru
Anilin	Methemoglobin	1,5 % hemoglobinu	Konec směny
Kadmium	Kadmium	0,005 mg/l 0,045 µmol/l	Nerozhoduje
Inhibitory cholinesterazy a acetylcholinesterazy	Aktivita cholinesterazy a acetylcholinesterazy	pokles o 20% z hodnoty před započetím prací	Konec směny
Nitrobenzen	Methemoglobin	1,5% hemoglobinu	Konec směny
Oxid uhelnatý	Karbonylhemoglobin	5 % hemoglobinu	Konec směny
Olovo	Plumbaemie	0,4 mg/l	Nerozhoduje
Polychlorované bifenyly	Polychlorované bifenyly	0,05 mg/l	Nerozhoduje

SAFETY DATA SHEETS (SDS)

Safety data sheets provide information on chemical products that help users of those chemicals to make a risk assessment.
They describe the hazards the chemical presents, and give information on handling, storage and emergency measures in case of accident.
Safety data sheet information may lead to guidance appropriate for your task.

CAUTION
A safety data sheet is not a risk assessment. You should use the information it contains to help make your own assessment.
As well as receiving chemicals you may supply them to others.
If you do, you must pass on information (as safety data sheets)
to those whom you supply.

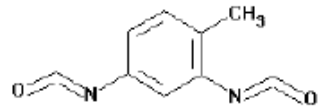
REACH (Registration, Evaluation, Authorisation and restriction of Chemicals) is the system for controlling chemicals in Europe.
REACH adopted some of the older aspects of the chemicals system in Europe, including Safety Data Sheets (SDS).

SAFETY DATA SHEETS

Písmenný symbol	Slovní vyjádření	Anglické označení
E	výbušný	explosive
O	oxidující	oxidising
F^+	extrémně hořlavý	extremely flammable
F	vysoce hořlavý	highly flammable
T^+	vysoce toxický	highly toxic
T	toxický	toxic
Xn	zdraví škodlivý	hazardous to health
C	žíravý	corrosive
Xi	dráždivý	irritating
N	nebezpečný pro životní prostředí	hazardous for environment

H Hazard Statement(s)

P Precautionary Statement(s)



MERCK

808264 Toluylene diisocyanate

(mixture of isomeres) for synthesis

For general questions please contact our Customer Service:

Merck KGaA
Frankfurter Str. 250
64293 Darmstadt
Germany
Phone: +49 6151 72-0
Fax: +49 6151 72 2000

03 January 2012

Product number	Packaging	Size	Price
8082640100	Glass bottle	100 ml	price on request
8082640500	Glass bottle	500 ml	price on request

Prices are subject to change without notice.

Product information

Synonyms	4-Methyl-m-phenylene diisocyanate, TDI
Hill Formula	$C_9H_6N_2O_2$
Chemical formula	$(NCO)_2C_6H_3CH_3$
HS Code	2929 10 00
EC number	247-722-4
Molar mass	174.16 g/mol
EC index number	615-006-00-4
CAS number	26471-62-5

Chemical and physical data

Ignition temperature	620 °C
Solubility	(20 °C) insoluble,(decomposition)
Melting point	12 - 14 °C
Molar mass	174.16 g/mol
Density	1.22 g/cm^3 (20 °C)
pH value	(H_2O) not applicable
Boiling point	247 °C (1013 hPa)
Vapor pressure	0.03 hPa (20 °C)
Explosion limit	0.9 - 9.5 %(V)
Flash point	132 °C
Refractive index	1.5689 (20 °C, 589 nm)

Safety information according to GHS

Hazard Statement(s)	H315: Causes skin irritation. H317: May cause an allergic skin reaction. H319: Causes serious eye irritation. H330: Fatal if inhaled. H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled. H335: May cause respiratory irritation. H351: Suspected of causing cancer. H412: Harmful to aquatic life with long lasting effects.
Precautionary Statement(s)	P260: Do not breathe vapour. P273: Avoid release to the environment. P280: Wear protective gloves/ protective clothing/ eye protection/ face protection. P281: Use personal protective equipment as required. P302 + P352: IF ON SKIN: Wash with plenty of soap and water. P304 + P340: IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing. P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
Signal Word	Danger
Hazard Pictogram(s)	
RTECS	NQ9490000
Storage class	6.1A Combustible, acute toxic Cat. 1 and 2 / very toxic hazardous materials
WGK	WGK 2 water endangering
Disposal	11 Organic acid halides, anhydrides and isocyanates can be added dropwise to an excess of methanol (Cat. No. 822283) to convert them into the corresponding methyl esters or methyl carbamates. If necessary, neutralize with sodium hydroxide solution (Cat. No. 105587). Fill into container A.

Safety information

R Phrase	R 26-36/37/38-40-42/43-52/53 Very toxic by inhalation.Irritating to eyes, respiratory system and skin.Limited evidence of a carcinogenic effect.May cause sensitization by inhalation and skin contact.Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
S Phrase	S 23-36/37-45-61 Do not breathe vapour.Wear suitable protective clothing and gloves.In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).Avoid release to the environment. Refer to special instructions/ Safety data sheets.
Categories of danger	very toxic, irritant, carcinogenic, sensitizing, dangerous for the environment
Hazard Symbol	 Very toxic

Transport information

Declaration (railroad and road) ADR, RID	UN 2078 Toluendiisocyanat, 6.1, II
Declaration (transport by sea) IMDG-Code	UN 2078 TOLUENE DIISOCYANATE, 6.1, II
Declaration (transport by air) IATA-DGR	UN 2078 TOLUENE DIISOCYANATE, 6.1, II