



Combined exposures of radiation and other stressors

DNA damage induced by chemical mutagens

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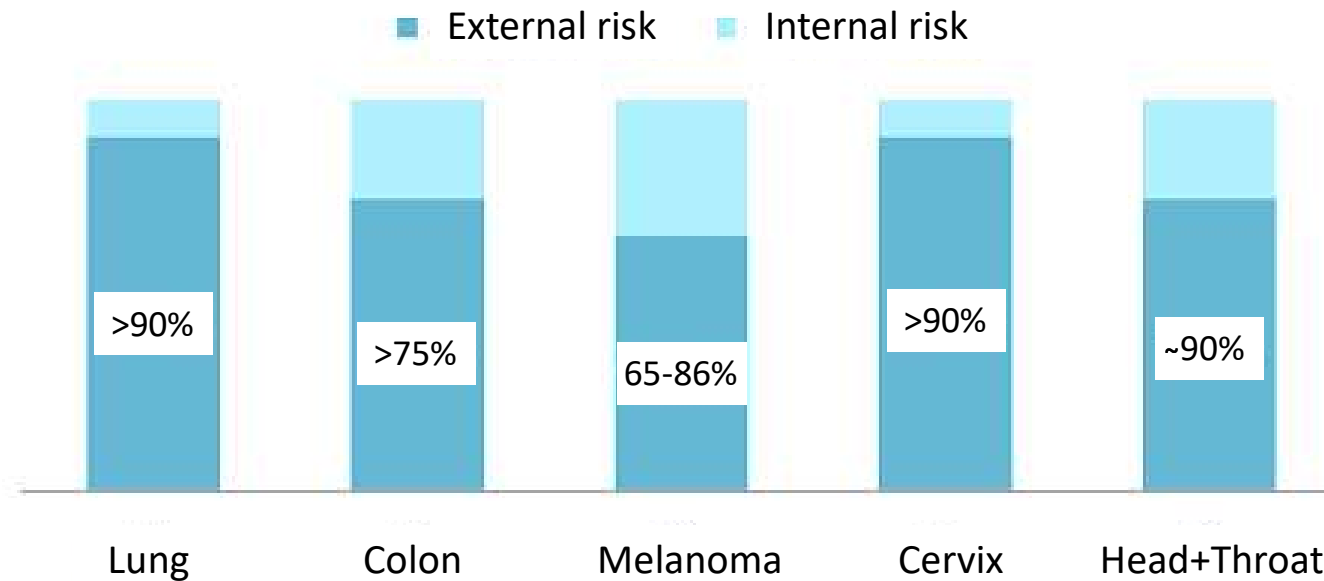


How many people get cancer ?

Europe

- Lifetime risk: about half of all people will be diagnosed with some form of cancer during their lifetime
- >40% of cancer cases are thought to be preventable

Substantial contribution of extrinsic risk factors to cancer development



Source: Wu S., Powers S., Zhu W. & Hannun YA.. *Nature* (2016)

http://www.krebsdaten.de/Krebs/DE/Content/ZfKD/Archiv/weltkrebstag_2016.html

Can chemicals really cause cancer?

Induction of cancer by substances: historical examples



<https://intriguing-history.com/chimney-sweeps-act-1834/> (18.10.21)

1775
Chimney sweeps
Scrotum skin tumors



<https://www.med.unc.edu/urology/patientcare/cancer/bladder-cancer/> (18.10.21)

1895
Workers exposed to anilin
Bladder tumors

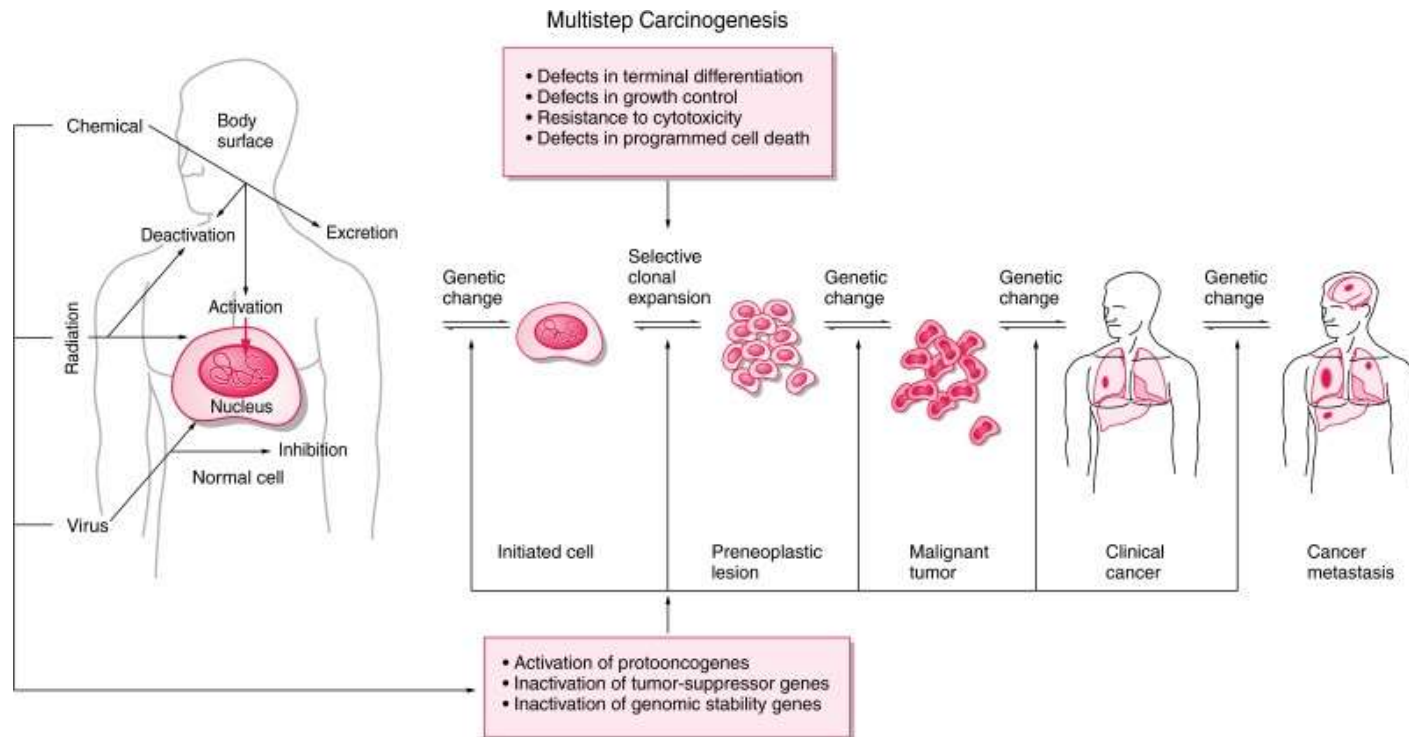


<http://www.hormonesmatter.com/des-drug-to-prevent-miscarriage-ruins-lives-of-millions/> (18.10.21)

1971
Unborn children
Vaginal tumors

How do chemicals cause cancer?

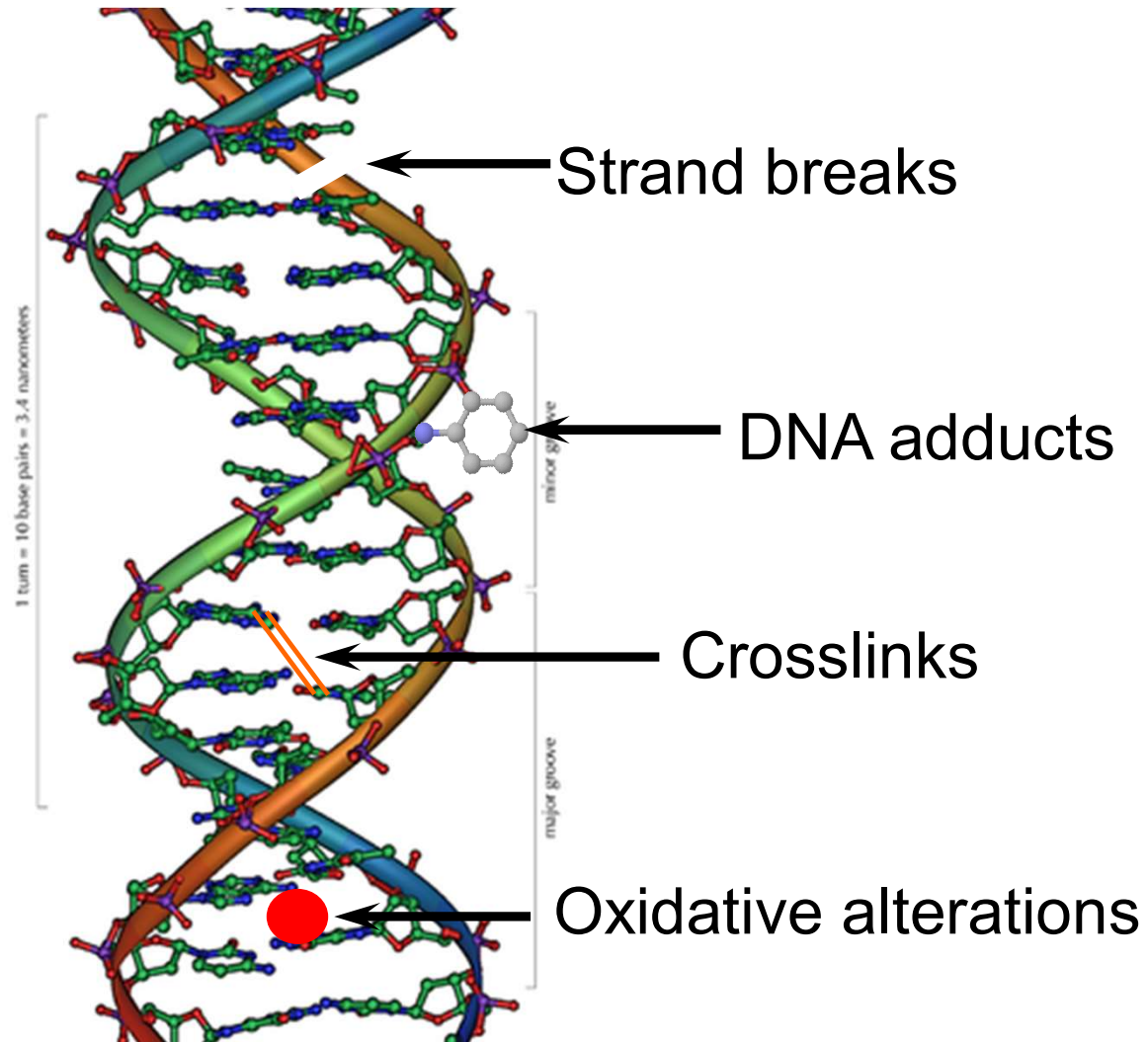
Multistage model of chemical carcinogenesis



From: Multistage Carcinogenesis; Holland-Frei Cancer Medicine. 6th edition. Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Hamilton (ON): BC Decker; 2003.

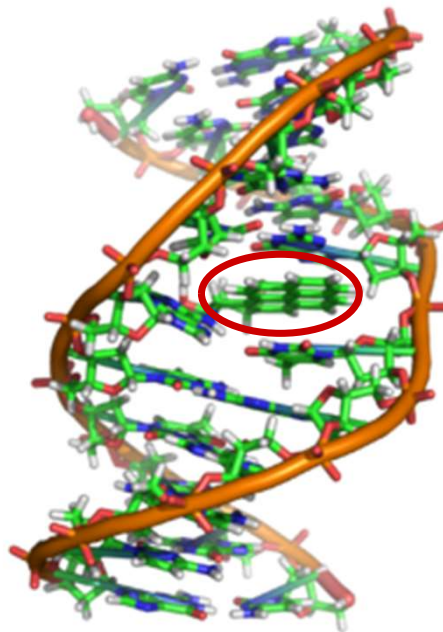
Which DNA alterations can chemicals cause?

Various types of DNA damage



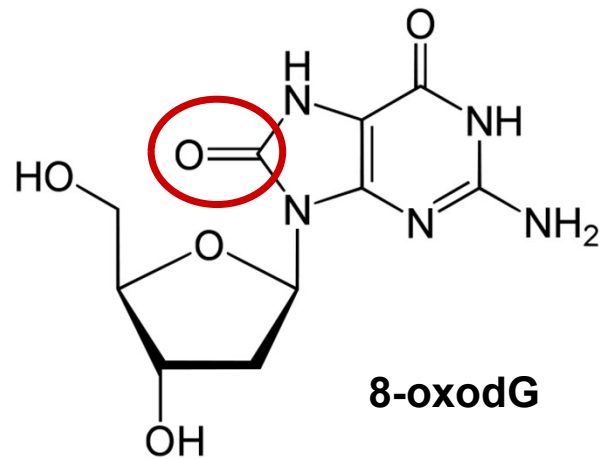
Modified after: <http://genwiki.genealogy.net/DNA-Genealogie> (10.11.20)

DNA-Damage	Mechanism	Example
DNA-Adducts	Binding of a substance to DNA bases	Polycyclic aromatic hydrocarbon like benzo[a]pyrene



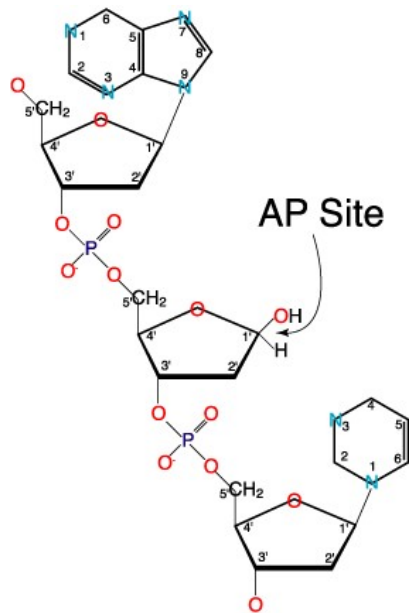
https://commons.wikimedia.org/wiki/File:Benzopyrene_DNA_adduct_1JDG.png (10.11.20)

DNA-Damage	Mechanism	Example
Base-Modifications	Reaction with DNA bases	Formation of 7,8-dihydro-8-oxoguanine (8-oxodG) from a reaction of reactive oxygen species with guanine bases

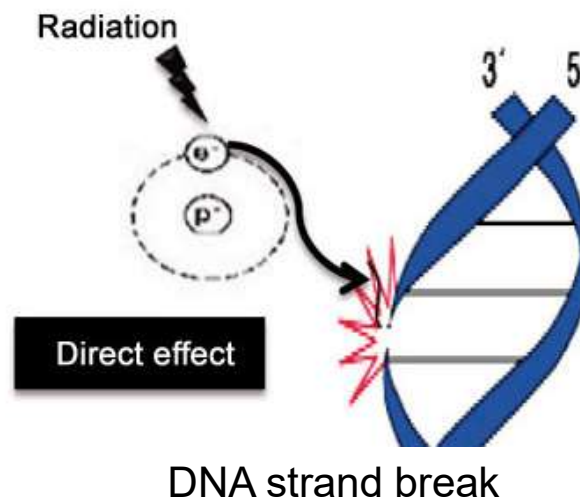


<https://de.wikipedia.org/wiki/8-Hydroxydesoxyguanosin> (10.11.20)

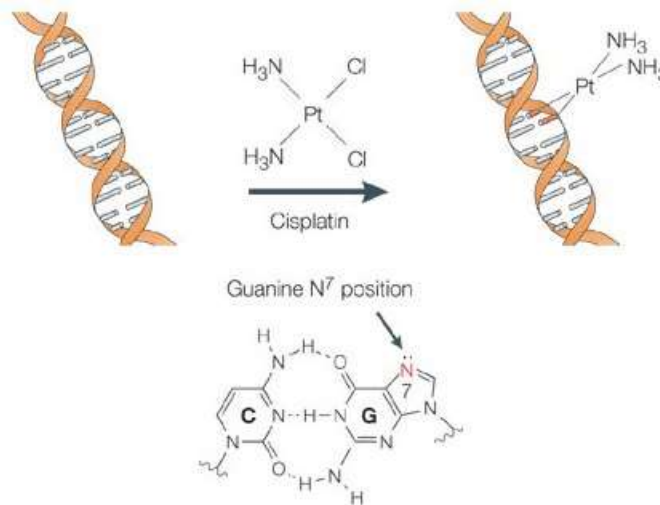
DNA-Damage	Mechanism	Example
AP-Lesion	Loss of a purine (apurinic) or pyrimidin (apyrimidinic) base	Alkylating substances facilitate the hydrolysis of the base-suger binding



DNA-Damage	Mechanism	Example
DNA-strand break	Loss of desoxyribose-phosphate-binding	Topoisomerase inhibitors and reactive oxygen species



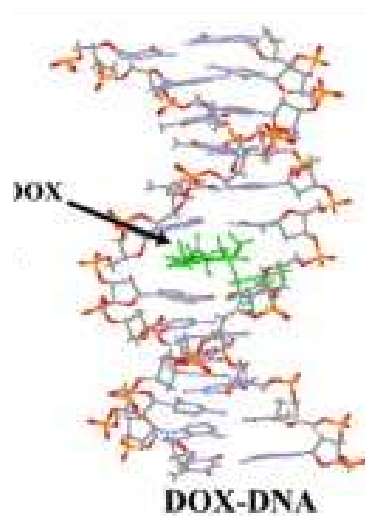
DNA-Damage	Mechanism	Example
crosslink	Connection base-base or base-protein	Bifunctional agents like cisplatin or mitomycin C



Crosslinker cisplatinum

<https://www.researchgate.net/publication/221920821>
 Antioxidants in Cancer Treatment (11.11.20; cropped)

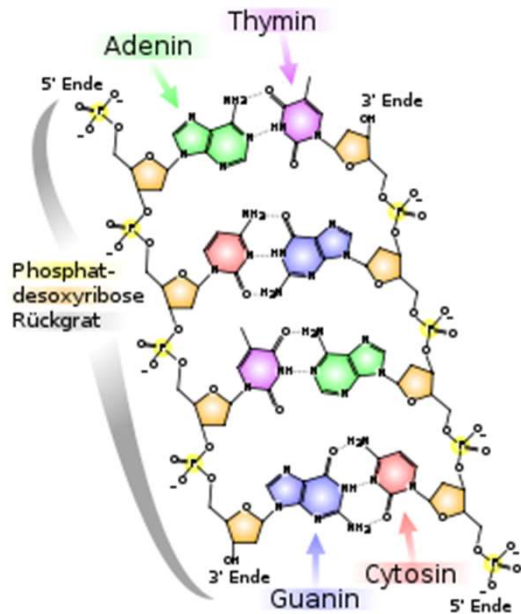
DNA-Damage	Mechanism	Example
Intercalation/ non-covalent binding	Placement between DNA bases or on DNA-helix-windings (minor/major groove)	Flat molecules like doxorubicin



Intercalating doxorubicin

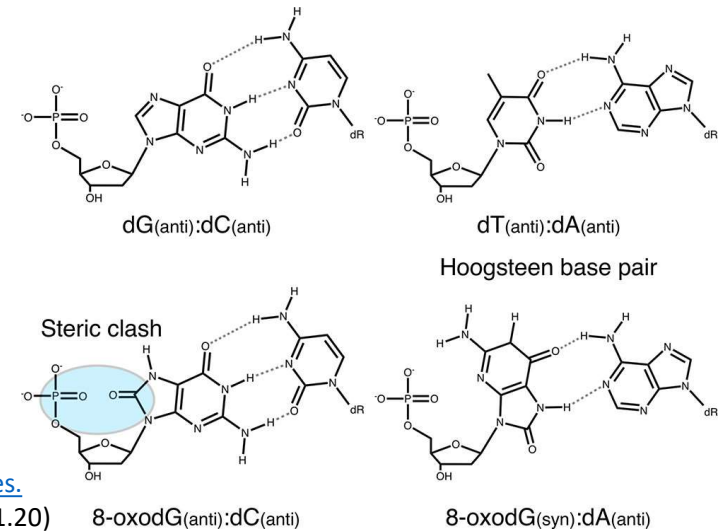
<https://ars.els-cdn.com/content/image/1-s2.0-S0141813014001123-fx1.jpg> (11.11.20; cropped)

Consequences of DNA damage: Manifestation of mutations

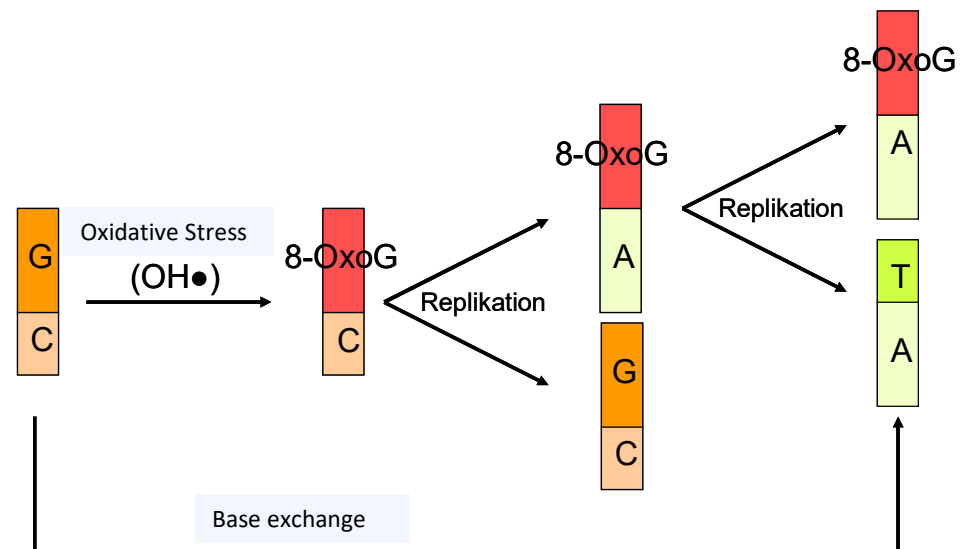


source: <https://de.wikipedia.org/wiki/Desoxyribonukleins%C3%A4ure> (11.11.20)

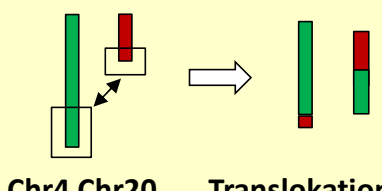
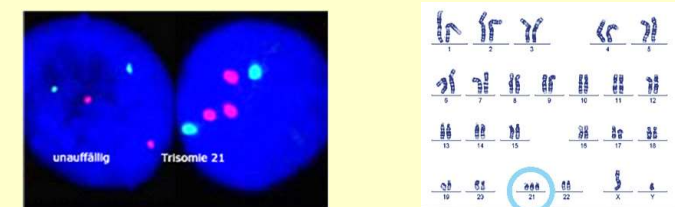
Incorporation of wrong DNA base opposite to oxidized guanine leads to manifestation of damage as mutation



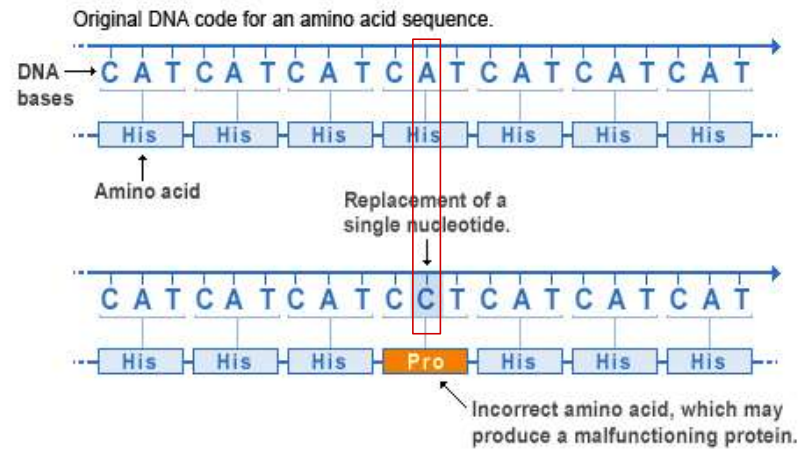
Source: <https://elifesciences.org/articles/45320#C1> (11.11.20)



Types of Mutations

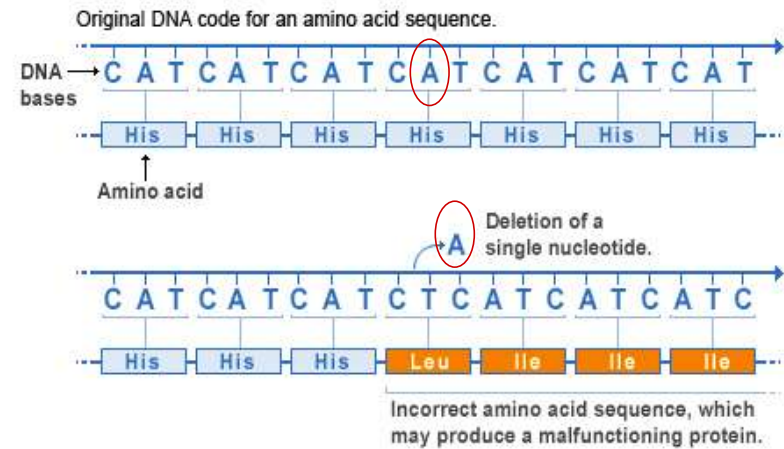
Category	Description
Gene mutation	Alteration of DNA-sequence within a gene e.g. sequence - CAT- = histidine; - CCT- = proline
Chromosomal mutation	Structural alteration of a chromosome, e.g.: 
Genome mutation	Alteration of copy number of chromosome/s, e.g.:  <p> Bildquellen: https://www.gentest-embryo.eu/genetik-kinderwunsch.php?c=genetische-erkrankungen; https://www.humangenetik.uk-erlangen.de/aerzte-und-zuweiser/klinische-zytogenetik/ (11.11.20) </p>

Missense mutation



U.S. National Library of Medicine

Deletion mutation



U.S. National Library of Medicine

Is there a threshold of a „non-carcinogenic amount“
of a chemical?

Relevance of threshold for cancer risk assessment

Lutz WK. Toxicol Lett. 2009 Nov 12;190(3):239-42.

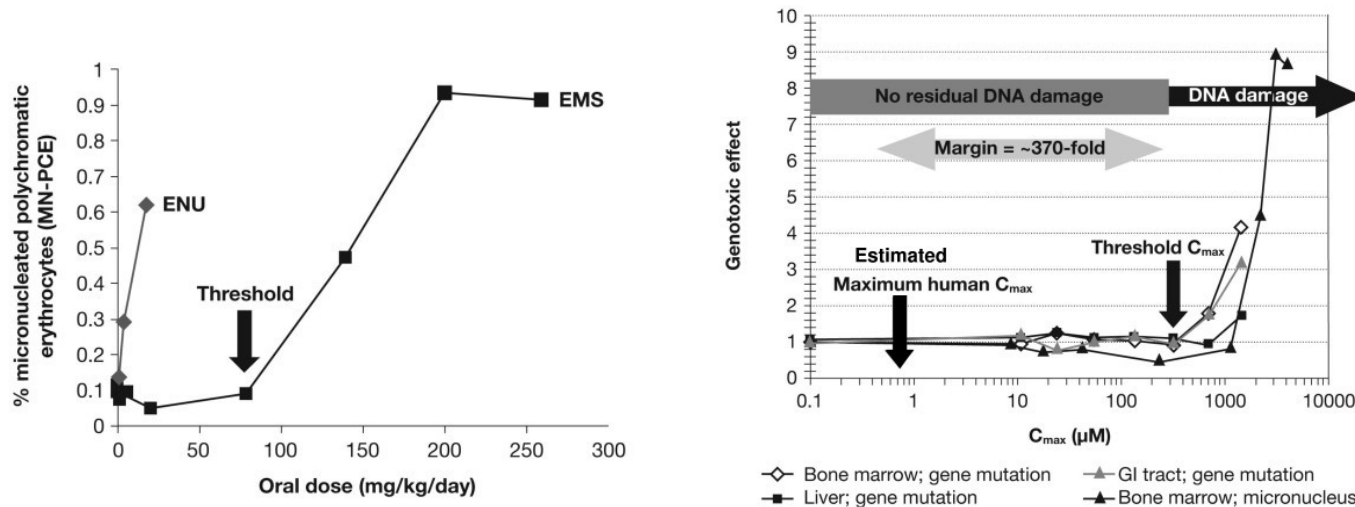
The Viracept (nelfinavir)--ethyl methanesulfonate case: a threshold risk assessment for human exposure to a genotoxic drug contamination?

- In May 2007, the F. Hoffmann-La Roche Company became aware of a contamination of Viracept (nelfinavir) tablets by the mutagenic DNA-ethylating agent ethyl methanesulfonate (EMS) as a result of a production incident
- HIV-patients could have been exposed for 3 months to daily doses of up to 2.75 mg EMS, i.e., about 50 microg/kg per day
- traditional cancer risk assessment for an alkylating agent is based on a linear dose-response

→ patients would be assumed to suffer from increased cancer risk due to the exposure

Relevance of threshold for cancer risk assessment

A standard 4-week toxicity study with EMS in the rat indicated an NOAEL of 20mg/kg per day. Extensive studies on the genotoxicity showed threshold-like dose responses for chromosome damage (bone marrow micronucleus test; left side) and gene mutations (right side)



Using a threshold risk assessment based on estimated c(max) of EMS, a safety factor of 370 was derived for maximum doses ingested by Viracept patients

→ No increased cancer risk!

Which chemicals cause cancer ?

The International Agency for Research on Cancer (IARC) have devised a system of categories to evaluate the carcinogenicity of an agent to humans.

An agent is classified based on scientific evidence derived from human and experimental animal studies and from mechanistic and other relevant data

Agents Classified by the IARC Monographs, Volumes 1-134

Group 1	Carcinogenic to humans	127 agents
Group 2A	Probably carcinogenic to humans	95 agents
Group 2B	Possibly carcinogenic to humans	323 agents
Group 3	Not classifiable as to its carcinogenicity to humans	500 agents

Group 1: Infectious conditions, Chemical substances, Radiations and physical agents thereof, Complex mixtures/agents, Exposure circumstances

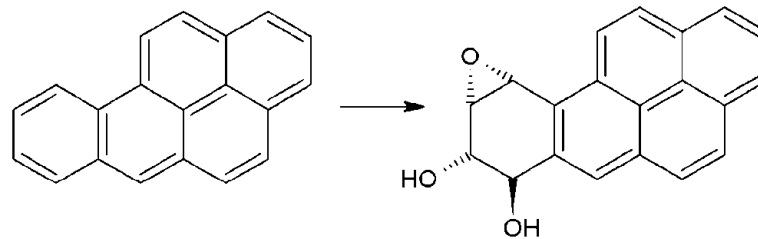
Chemicals: 54 substances or substance classes are listed

<https://monographs.iarc.who.int/agents-classified-by-the-iarc/> (7.11.23)

https://en.wikipedia.org/wiki/IARC_group_1_Carcinogens#Chemical_substances (7.11.23)

Examples for carcinogenic substances or substance groups: polycyclic aromatic hydrocarbons

- Form during incomplete combustion of organic material like coal, gasoline, wood, tobacco
- Most well known example is benz[a]pyrene
- Benzo[a]pyrene is oxidized to a diol-epoxid, which forms a DNA-adduct

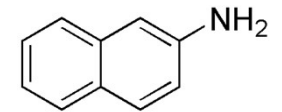


- Ubiquitous substances, carcinogenic
- May occur in foodstuff, for example via contact with smoke (barbecue)

Aromatic amines

Aromatic carbohydrates with an amino group

- In industrial production processes, e.g. dye or rubber production
- Also in tobacco smoke
- Model compounds: benzidine, 2-naphtylamine, 4-aminodiphenyl



2-Naphtylamine

Heterocyclic aromatic amines

- Form during preparation of meat and fish from creatinine, amino acids and sugar at temperatures > 130 °C

PhIP 2-amino-1-methyl-6-phenylimidazo[4,5-b']pyridine

IQ 3-Methyl-3H-imidazo[4,5-f]chinolin-2-amine

DiMeIQx 3,4,8-Trimethyl-3H-imidazo[4,5-f]chinoxalin-2-amien

MeIQ 3,8-Dimethyl-3H-imidazo[4,5-f] chinolin-2-amine

MeIQx 3,8-Dimethyl-3H-imidazo[4,5-f] chinoxalin-2-amine



Carcinogenic agents are not always man-made
chemicals

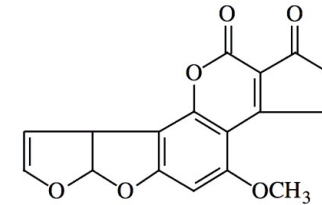
Carcinogenic natural compounds/agents

Chinese herb nephropathy

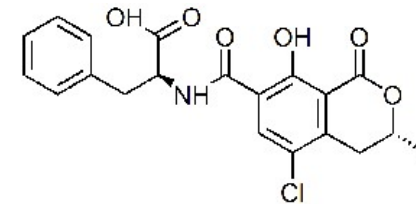
- Weight loss herb mixture with accidental addition of wrong chinese herbs
- 39 patients (mostly in Belgium) suffered from terminal kidney insufficiency
- 18 cases (46 %) urothelial carcinomas, another 19 patients dysplasia
- Only 2 patients without pathological alterations
- Compound-specific (aristolochic acid) DNA adducts in tissues, even though the exposure was more than 10 years before analysis

Mcyotoxins

- **Aflatoxin_{B1}** , warm and humid storage favors *Aspergillus flavus*
- In nuts, grains,...
- In some developing countries high exposure ,
in combination with hepatitis B major cause for liver cancer
- **DNA adduct formation**



- **Ochratoxin A** , *Aspergillus ochraceus* and *Penicillium verrucosum*
- In grains, legumes, coffee, beer, grape juice, raisins,
wine, cocoa products, nuts ,...
- Nephrotoxic, immune suppressive, carcinogenic
- **Mitotic disturbances, oxidative stress, etc**



Carcinogenic metals:

Some toxicologically important metals

• Aluminium	
• Arsenic	1
• Beryllium	1
• Lead	2A
• Cadmium	1
• Chrome	1 (some compounds)
• Copper	
• Manganese	
• Nickel	1 (as compounds)
• Platinum	
• Mercury	2B
• Thallium	
• Vanadium	1 (only V-pentoxid)
• Tin	

How are we exposed to metals?

Nutrition

- Meat (liver, kidney)
- Fish
- Grain from affected soil
- Drinking water

From the air

- Work place
- Dust sediments on food plants

Aluminium



<https://www.ugb.de/lebensmittel-im-test/aluminium-im-essen/> (9.6.22)

- Food (cereals, vegetables, tea leaves, herbs,)
- Food contact material
- Cosmetics
- In Germany through food about 0,5 mg/kg body weight per week
- Recommended tolerable weekly intake (1mg/kg body weight)
- Possible consequences: neurotoxicity and reprotoxicity, damage of kidney, liver, bones (but probably not carcinogenic)

Aluminium

Recommendation:

- Vary food choices
- Do not keep food in aluminium containers or foil which does not have a specific protective coating, especially not sour or salty food.

Arsenic

- exposure through drinking water in some regions of the world
- Leads to black foot disease (hyperpigmentation), hyperkeratosis, liver and kidney-damage, polyneuropathy, and cancer, mostly of the skin, bladder and kidney



Bildquelle: <https://de.wikipedia.org/wiki/Mees-Nagelb%C3%A4nder> CC BY-SA 3.0 (23.4.20)



Bildquelle: Reuters, von: https://www.liberation.fr/planete/2016/04/06/au-bangladesh-l-arsenic-empoisonne-toujours-les-habitants_1444091 (23.4.20)

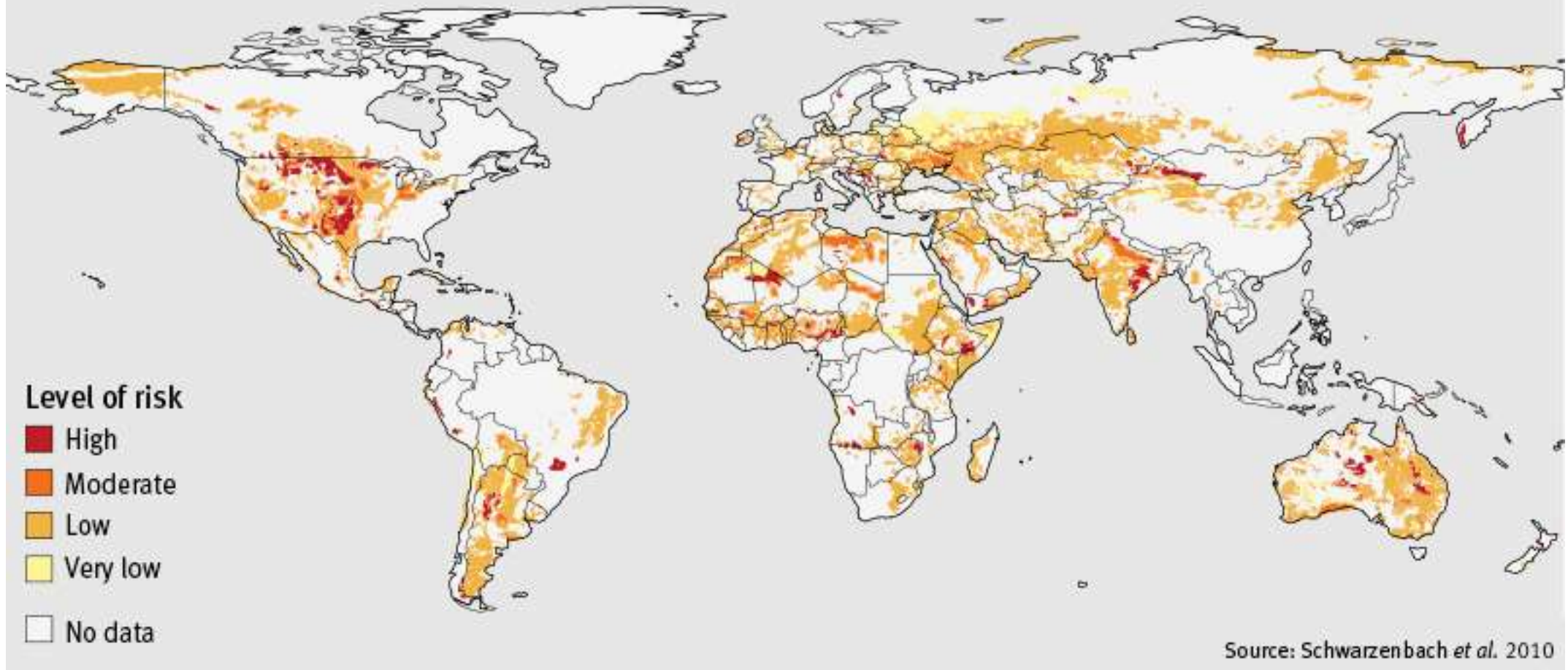
Bangladesh

- 1970th: many cholera-victims because no clean water was available
- Millions of water wells were built
- But: arsenic was mobilized and contaminated drinking water and is taken up by plants (rice)
- Hundreds of thousands developed cancer of the skin, bladder and kidney
- Estimation of WHO: 50 million people suffer from chronic arsenic poisoning

Worldwide:

- 200 millionen people drink water with more than 10 $\mu\text{g}/\text{ml}$ arsenic
- Asian countries like Bangladesh, Kambodscha, India, Nepal, Vietnam
- Latin American countries like Argentine, Bolivia, Chile, Mexico

Estimated Risk of Arsenic in Drinking Water



Quelle: https://serc.carleton.edu/integrate/teaching_materials/water_science_society/student_materials/648 (23.4.20); Modeled risk of As in drinking water at significant levels from Schwarzenbach *et al.*, 2010; Source: [United Nations Environment Programme \(UNEP\)](#)

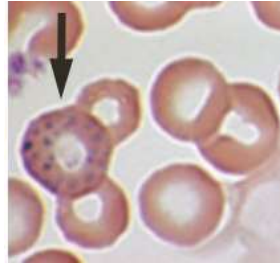
Environmental catastrophe in Brasil in 2015

November 2015

- Dam breakage in Brazilian mine
- 50 million tons of toxic mud reached the Atlantic ocean
- Arsenic, lead and copper in the river Rio Doce → biologically dead
- Supply of drinking water problematic even until today

Quellen: <http://www.zeit.de/wissen/umwelt/2015-11/bergbau-unglueck-brasilien-rio-doce> (23.4.20)
<https://www.domradio.de/themen/weltkirche/2016-04-28/nach-umweltkatastrophe-fordern-opfer-entschaedigung> (23.4.20)
https://de.wikipedia.org/wiki/Dammbruch_von_Brumadinho (23.4.20)

Lead



<https://de.wikipedia.org/wiki/Bleivergiftung> , CC-BY 2.0
<http://cnx.org/content/m15003/latest/> 23.4.20



Busse et al., Deutsches Ärzteblatt 105, 757 2008



<http://www.befund.net/Neurologie/Fallhand/> (23.4.20)

- Neurotoxic, inhibition of hemoglobin synthesis, contraction of smooth muscles
- Classical symptoms (of very high exposure) like erythrocyte dotted pattern, gum deposits, falling hand are not common any more
- More common nowadays: stomach pain, tiredness, irritability, grey-yellowish skin, disturbed kidney function, neurotoxicity (concentration and memory-impairment)
- in children disturbed brain development may lead to intelligence reduction

Sources for exposure:

- Food: dust sedimentation on plant food, mushrooms
- Food kept in insuitable containers
- Exposure has decreased a lot
- But: half of US-american children show potentially harmful lead blood levels

(Source: PNAS 2020, <https://doi.org/10.1073/pnas.2202401111>)

UNICEF 2020:

- World wide, 800 million children have blood lead levels of $\geq 5\text{mg/dl}$
- One of the main reasons is the uncontrolled recycling of car lead- acid batteries

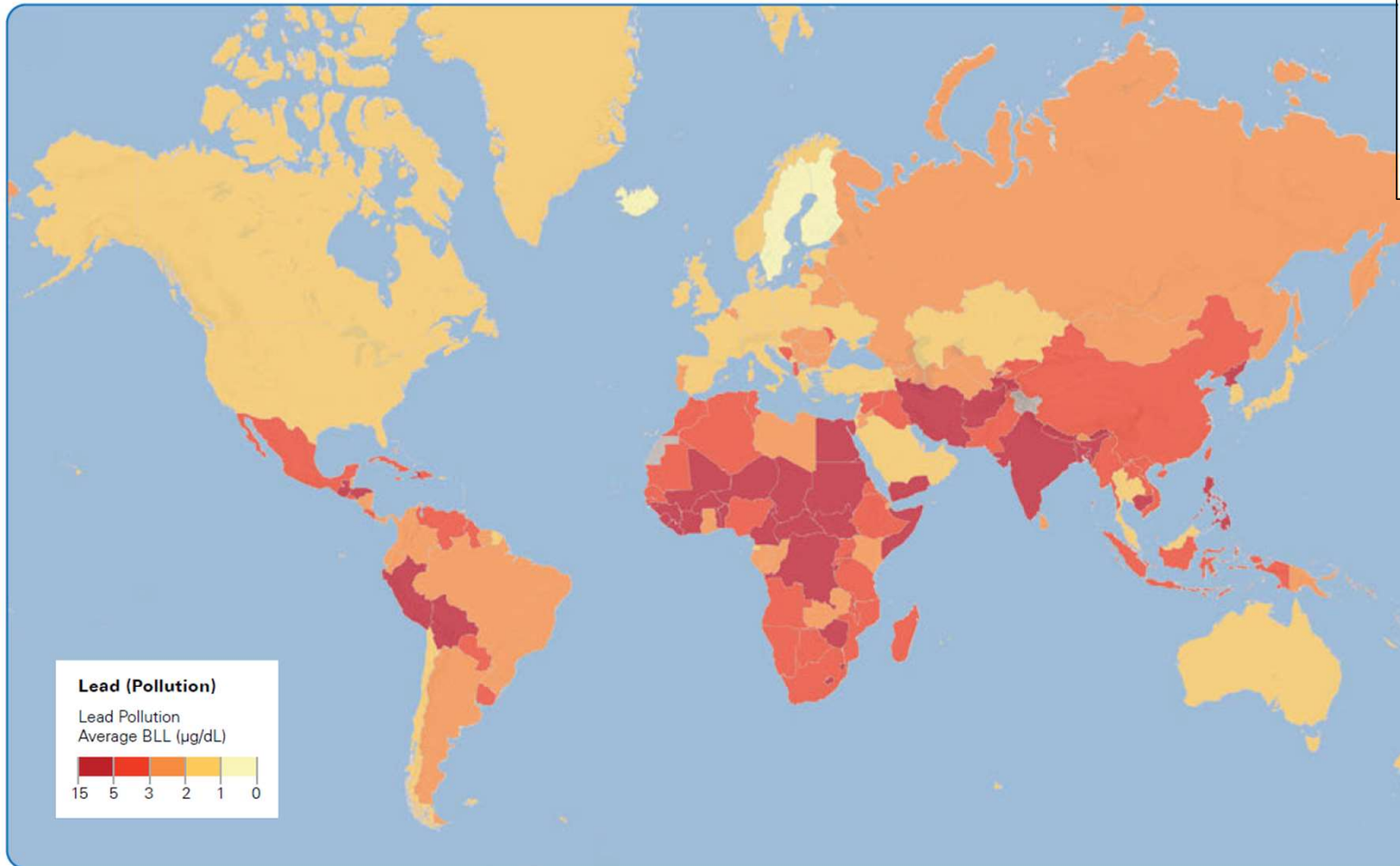
<https://www.unicef.org/reports/toxic-truth-childrens-exposure-to-lead-pollution-2020> (9.6.22)

The Toxic Truth:
Children's Exposure to Lead Pollution
Undermines a Generation of
Future Potential

unicef | for every child

PURE EARTH
RECYCLING

Figure 6 Children's Average Blood Lead Levels by Country ($\mu\text{g}/\text{dL}$)



The Toxic Truth:
Children's Exposure to Lead Pollution
Undermines a Generation of
Future Potential

unicef | for every child

PURE EARTH

Source: IHME 2019. See Annex for full list by country. Lead exposure and health data is also visualized at www.leadpollution.org

Note: The boundaries and names shown and the designations used on this map do not imply official endorsement or acceptance by the United Nations or UNICEF.

<https://www.unicef.org/reports/toxic-truth-childrens-exposure-to-lead-pollution-2020> (9.6.22)

Longitudinales Curriculum
Planetare Gesundheit



Notre-Dame 2019

- The roof construction consisted of large amounts of lead which melted
- Several hundred tons of lead into the environment
- Elevated lead levels measured in school and kindergarden children

Regional Health Agency reported on 14. October:

- 877 children analyzed
- 12 x lead poisoning $>50\mu\text{g/l}$
- 78 children were put under observation for possible health effects with $>25\mu\text{g/l}$
- Average of non-exposed children in the area was $13,5\mu\text{g/l}$
- Analysis done several months after the exposure – maximal blood levels not detected



Bildquelle: Thibault Camus/ AP, <https://www.spiegel.de/wissenschaft/technik/notre-dame-in-paris-warum-sich-das-feuer-so-schnell-ausbreitete-a-1263078.html> (23.4.20)

Quelle: <https://www.infosperber.ch/Gesundheit/Notre-Dame-de-Paris-Behorden-verharmlosen-Bleivergiftungen> (23.4.20)

Minamata-disease: 1950th in Japan

- Damage to the central nerve system
- Induced by chronic mercury poisoning due to sewage water of a chemical factory
- Sea algae and fish were contaminated, about 10.000 people poisoned and 3.000 deaths
- Children of survivors showed neurological damage (reduced IQ, movement disorders,...) and other teratogenic effects

Nowadays: Sources for mercury exposure: food, especially sea fish (methyl-mercury)

- no mining in Europe
- emission through burning of coal
- usage mostly for dental fillings

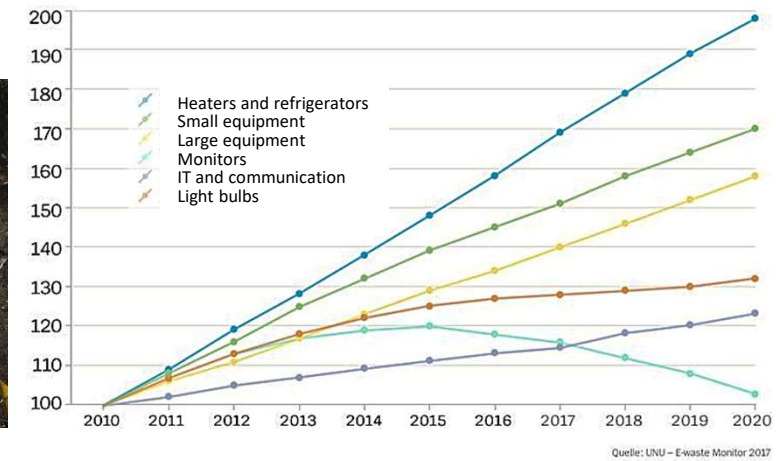
Worldwide: use and emission increasing with industrialization

Problem: gold mining in small private or illegal mines

Problem E-Waste



Increase of E-waste



- Hundreds of tons of used electric/electronic equipment is being shipped to african countries annually
- Although illegal, about 75% of these equipments end as e-waste
- Workers (often children) recycle materials without protection of any kind
- Exposure to toxic fumes endanger workers, but also families, because the toxic substances move into the soil and probably ground water of the area

<https://www.spiegel.de/wirtschaft/nigeria-wie-elektroschrott-aus-deutschland-das-land-verseucht-a-1155116.html> (25.11.21)

<https://www.spiegel.de/wirtschaft/soziales/nigeria-e-schrott-connection-stopft-autos-voll-a-1203561.html> (25.11.21)

Carcinogenic mechanisms of metals are indirect effects

- Inhibition of DNA-repair enzymes, or tumor suppressor genes, e.g. by binding to zinc-finger domains
- Modulation of gene expression, e.g. by influencing DNA-Cytosine-Methylation
- Inhibition of antioxidant defense, or induction of oxidative stress (e.g. by catalysing the Fenton-reaction, causing the formation of hydroxyl radicals), leading to more oxidized DNA bases