The Most Common Chemical Toxicants Measured at GPL

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Overview

The Most Common Chemical Toxins at GPL
For each toxin

1. Sources
2. Prevalence
3. Mechanism of Damage
4. Diseases Caused
5. Assessment of Body Load
6. Elimination

Agency for Toxic Substances and Disease Registry Priority List

2019 Rank	Substance Name
1	ARSENIC
2	LEAD
3	MERCURY
4	VINYL CHLORIDE
5	POLYCHLORINATED BIPHENYLS
6	BENZENE
7	CADMIUM
8	BENZO(A)PYRENE
9	POLYCYCLIC AROMATIC HYDROCARBONS
10	BENZO(B)FLUORANTHENE
11	CHLOROFORM
12	AROCLOR 1260
13	DDT, P,P'-
14	AROCLOR 1254
15	DIBENZO(A,H)ANTHRACENE
16	TRICHLOROETHYLENE

Substance Priority List | ATSDR (cdc.gov)
Accessed 2021-10

Most Common Chemical Toxins at GPL

Most Common
- Acrolein
- Acrylamide
- Bromopropane
- MTBE
- Perchlorate

Second Most Common
- Phthalates
- Styrene
- Xylene

Why The Difference?!

Possibilities

- CDC includes in their prioritization toxic waste dumps
- These chemical toxins have limited disease associations
- GPL primarily testing sick people
- The conventional standards are distorted by the pervasive nature of these chemical toxins—no healthy/low toxin control groups
- Transgenerational effects virtually unstudied

5

Chemical Toxins

Non-Persistent

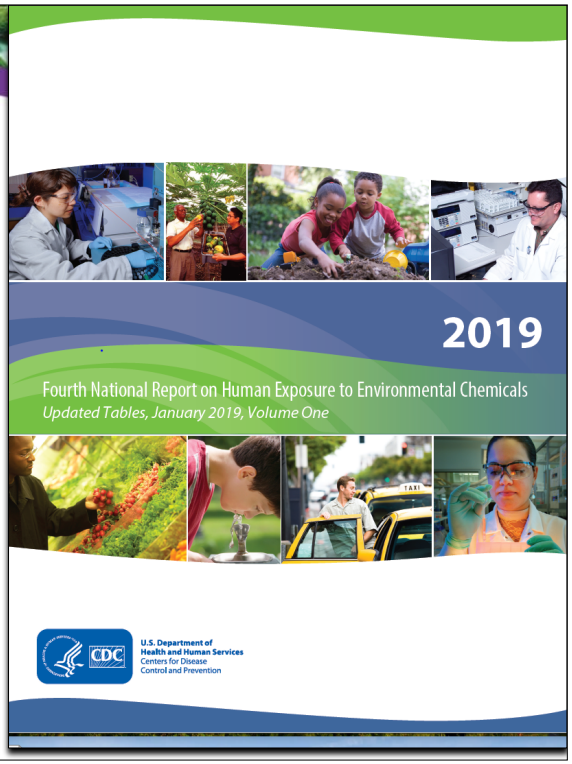
- Bisphenols (BPx)
- Glyphosate
- Polycyclic aromatic hydrocarbons (PAHs)
- Parabens
- Phthalates
- Solvents

MANY more!

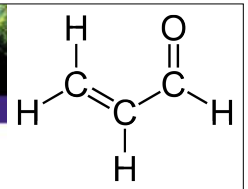
Persistent

- (Typically halogenated)
- Organochlorine pesticides
- Organophosphate pesticides
- Perfluorocarbons
- Polybrominated diphenyl ethers (PBDEs)
- Polychlorinated biphenyls (PCBs)
- Pyrethroid pesticides

Source of US Population Toxicant Load



Increased Disease Risk



Acrolein

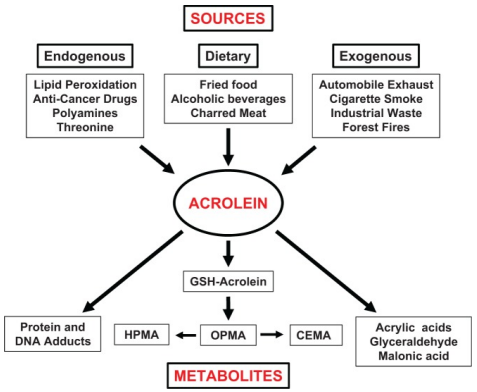
Acrolein

- Modest persistence
- Simplest unsaturated aldehyde
- Smell of burnt fat
- Ubiquitous; an EPA high-priority air and water toxin
- Main Sources:
  - Released into the environment when manufactured
  - Emitted from combustion processes (smoking, fossil fuels)
  - Contact herbicide/biocide (in 2001, CA alone used 120 tons)
  - Found in beverages & foods: coffee, alcohol, cheese, donuts, etc
  - Heating and cooking of fats, oils, and sugars increases levels

DeJarnett N, et al. Acrolein exposure is associated with increased cardiovascular disease risk. J Am Heart Assoc. 2014 Aug 6;3(4):e000934. PMID: 25099132
Faroon O, et al. Acrolein environmental levels and potential for human exposure. Toxicol Ind Health. 2008 Sep;24(8):543-64. PMID: 19039083

Sources & Metabolism

- Detoxified by glutathione, and also depletes it
- Forms protein adducts, which disrupt function
- Impairs mitochondrial & endoplasmic reticulum function
- Forms adducts with DNA, but role in cancer controversial



Moghe A, et al. Molecular mechanisms of acrolein toxicity: relevance to human disease. Toxicol Sci. 2015 Feb;143(2):242-55. PMID: 25628402

Mechanisms of Respiratory Toxicity

- Protein–acrolein adducts accumulate at sites of inflammation
- Cellular oxidative stress, including compromise of glutathione
- Necrotic cell death
- Loss of lung elasticity and enlarged lung airspaces

Yeager RP, et al. Proposed Mode of Action for Acrolein Respiratory Toxicity Associated with Inhaled Tobacco Smoke. Toxicol Sci. 2016 Jun;151(2):347-64. PMID: 26969371

Cardiovascular Toxicity

- Oxidative damage
  - Acrolein-modified proteins have been detected in oxidized low-density lipoprotein and human atherosclerotic lesions, and the uptake of acrolein-modified low-density lipoprotein implicated in foam cell formation
- Endothelial dysfunction
  - Suppresses endothelial NOS activation, attenuates endothelial cell migration, blocks vascular endothelial growth factor and reduces circulating levels of angiogenic cells

DeJarnett N, et al. Acrolein exposure is associated with increased cardiovascular disease risk. J Am Heart Assoc. 2014 Aug 6;3(4):e000934. PMID: 25099132
McGraw KE, et al. Exposure to volatile organic compounds - acrolein, 1,3-butadiene, and crotonaldehyde - is associated with vascular dysfunction. Environ Res. 2021 May;196:110903. PMID: 33636185

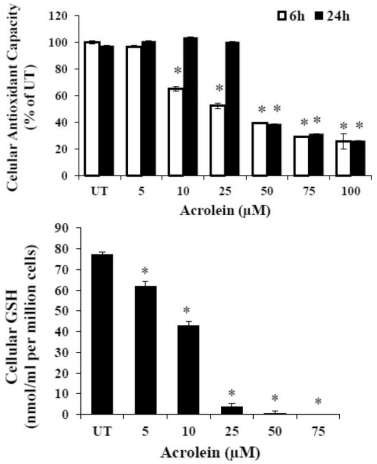
Mitochondrial Dysfunction

- One of most reactive aldehydes in tobacco smoke
- Thought to be responsible for ~90% of the non-cancer disease risk associated with smoking
- In vitro and in vivo data for mitochondrial dysfunction – animal model demonstrates decrease in abundance of key regulators involved in the process of mitochondrial biogenesis
  - Decreased transcript levels of Ppargc1a, nuclear respiratory factor 1 (Nrf1) and peroxisome proliferator-activated receptor alpha (Ppara)

Tulen CBM, et al. Acrolein inhalation acutely affects the regulation of mitochondrial metabolism in rat lung. Toxicology. 2022 Mar 15;469:153129. PMID: 35150775

Depletes Glutathione Levels

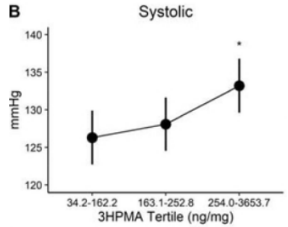
- Acrolein is primarily metabolized via rapid reaction with sulfhydryl groups of glutathione forming mercapturic acid
- In vitro, hepatocytes exposed to acrolein at increasing levels show glutathione depletion, and decreased cellular antioxidant capacity, which does not recover at high levels
- Attenuated by NAC

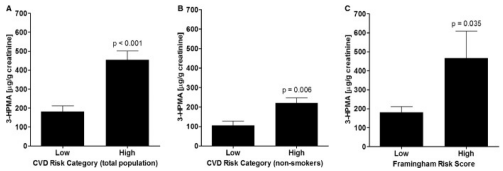


Mohammad MK, et al. Acrolein cytotoxicity in hepatocytes involves endoplasmic reticulum stress, mitochondrial dysfunction and oxidative stress. Toxicol Appl Pharmacol. 2012 Nov 15;265(1):73-82. PMID: 23026831

Cardiovascular Disease Risk

- 3-hydroxypropylmercapturic acid (3-HPMA) is major urine metabolite
- Does-dependent increased SBP
- 3-HPMA levels positively associated with increased levels of platelet-leukocyte aggregates and Framingham Risk Score





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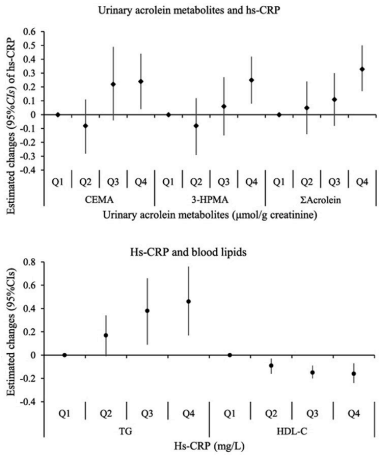
NHANES – CVD Risk CRP-mediated

- Significantly higher triglycerides (TG), hsCRP, and lower HDL-C
  - Each 1-unit increment in acrolein increased TG 0.06 mmol/L and decreased HDL-C 0.02 mmol/L
  - A positive dose-response relationship between urinary ∑acrolein and dyslipidemia risk
  - hs-CRP significantly mediated the associations



Feng X, et al. Urinary acrolein metabolites, systemic inflammation, and blood lipids: Results from the National Health and Nutrition Examination Survey. Chemosphere. 2022 Jan;286(Pt 2):131791. PMID: 34371361

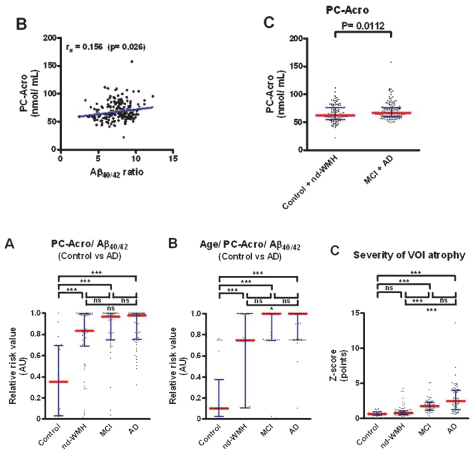
∑Acrolein & Diabetes

- Diabetes as well as insulin resistance positively associated with the 3-HPMA, CEMA and ΣAcrolein with evidence of a dose-response relationship ($p < 0.05$)
- Non-monotonic association of urinary 3-HPMA with HOMA-IR, HOMA-β, and fasting insulin
- ΣAcrolein: OR = 3.36 for diabetes

Feroe AG, et al. Acrolein metabolites, diabetes and insulin resistance. Environ Res. 2016 Jul;148:1-6. PMID: 26991531

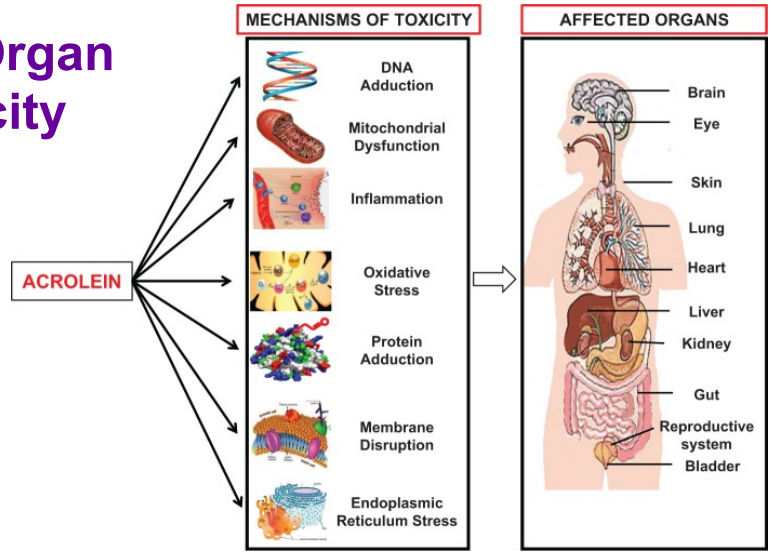
Neurological Disease

- Protein-conjugated acrolein (PC-Acro)
- 120 MCI/AD patients, and 101 elderly controls
- PC-Acro significantly correlated with amyloid beta 40/42 (Aβ40/42)
- When PC-Acro & Aβ40/42 combined, predictive of AD, MCI, as well as white matter hyperintensity



Waragai M, et al. Increased protein-conjugated acrolein and amyloid-β40/42 ratio in plasma of patients with mild cognitive impairment and Alzheimer's disease. J Alzheimers Dis. 2012;32(1):33-41. PMID: 22751175

Multi-Organ Toxicity

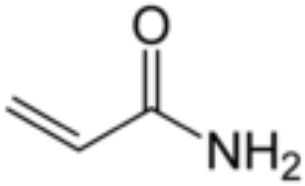


Moghe A, et al. Molecular mechanisms of acrolein toxicity: relevance to human disease. Toxicol Sci. 2015 Feb;143(2):242-55. PMID: 25628402

Clinical Takeaways

Acrolein

- Major disease: Cardiovascular disease, lipid abnormalities, diabetes, cognitive impairment, mitochondrial dysfunction
- Primary sources: Smoking, foods cooked at high temperature, exposure to combustion products
- Best measure: Urinary
- Best intervention: Avoidance, glutathione support



Acrylamide

Acrylamide

- Non-persistent
- Precursor to polyacrylamides which form soft gels when hydrated: thickeners and flocculation agents
- Acrylamide forms in burnt areas of food, particularly starchy foods like potatoes and grains
- Neurotoxic; small risk of a few cancers
- Mainly detoxed by glutathione conjugation
- Found in 99.9% of population; levels 2x in smokers

Acrylamide Factsheet | National Biomonitoring Program | CDC (Accessed 2022-10)

Acrylamide Production in Food

- Forms in foods from a chemical reaction between asparagine and reducing sugars (e.g., glucose and fructose).
- Part of the Maillard reaction which leads to color, flavor, and aroma changes in cooked foods.
- Forms at elevated temperatures when frying or baking (above 120 C) and low moisture
- About 1/3 of calories come from foods contaminated with acrylamide

Reducing Acrylamide in Cereal-based Foods: Fact Sheet (fda.gov) (Accessed 2022-10)

Acrylamide Content of Foods

Sweet Potato Chips with Sea Salt Crinkle Cut	8440
Popchips Potato Sea Salt	3060
Popchips Potato Sea Salt	2890
House of Herbs Blackstrap Molasses	2160
House of Herbs Blackstrap Molasses	2110
MiCostenita Papitas Casera Homemade Potatoes	1770
Nabisco Ginger Snaps	1450
Colton's Steak House Trail Potatoes Potato Skins	1440
Lay's Classic Potato Chips	1410
Better Made Potato Chips Original	1370
Nathan's Famous Jumbo Crinkle Cut French Fries! (fried)	1330
Logan's Road House Loaded Potato Skins	1330
Giant Brand O'Brien Style Hash Browns (fried)	1290
MiCostenita Papitas Casera Homemade Potatoes	1280
Woody's Grille Seasoned Waffle Fries	1260
Michael Season's Thin & Crispy Lightly Salted Potato Chips	1230
Nathan's Famous Jumbo Crinkle Cut French Fries! (fried)	1220
General Mills Corn Chex	1210
General Mills Corn Chex	1200
Ore Ida Mini Tater Tots (fried)	1170
IHOP Hash Browns	1090
Price First 100% Instant Coffee	1080
Nabisco Ginger Snaps	1060
Good Health Veggie Chips Sea Salt	1050
Red Robin Sweet Potato Fries	1030
Grub Burger Bar Sweet Potato Fries	1020

Survey Data on Acrylamide in Food | FDA (Accessed 2022-10)

Acrylamide Toxic to Fetus

Acrylamide - Clinical

- Acrylamide toxic, but supposedly only human exposure is to “non-toxic” polyacrylamide
- So why is GPL finding so much of it in humans?
- Likely due to being formed from food the way it is cooked
- Neurotoxicity at high dosages
- Most recent research finally documenting the problems

Clinical Correlations with Acrylamide

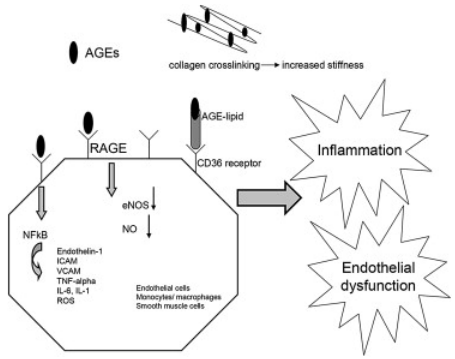
- Statistically significant “J” shaped curve in children with disabilities
- Top to bottom quartile: OR = 2.07 for cancer
- Top to bottom quartile: OR = 1.61 for CHD death
- Strong linear correlation with all-cause mortality

Meng F, Qi Y, Wu Y, He F. Association between acrylamide exposure and the odds of developmental disabilities in children: A cross-sectional study. Front Public Health. 2022 Sep 30;10:972368. PMID: 36249258
Gu W, Zhang J, Ren C, Et al. The association between biomarkers of acrylamide and cancer mortality in U.S. adult population: Evidence from NHANES 2003-2014. Front Oncol. 2022 Sep 28;12:970021. PMID: 36249016
Wu H, Sun X, Jiang H, et al. The Association Between Exposure to Acrylamide and Mortalities of Cardiovascular Disease and All-Cause Among People With Hyperglycemia. Front Cardiovasc Med. 2022 Jul 18;9:930135. PMID: 35924219.
Huang M, Jiao J, Wang J, Chen X, Zhang Y. Associations of hemoglobin biomarker levels of acrylamide and all-cause and cardiovascular disease mortality among U.S. adults: National Health and Nutrition Examination Survey 2003-2006. Environ Pollut. 2018 Jul;238:852-858. PMID: 29627755.

Vitamin D Ameliorates the Damage

The Damage of AGEs

- AGEs
  - Advanced glycated end-products
  - Non-enzymatic glucose adducts with proteins, lipids, nucleic acids
  - Induce cross-linking of collagen, elastin, proteins
  - Bind to AGE-specific receptors (RAGEs) increasing release of inflammatory mediators



⇒Tissue thickening, scarring and dysfunction in skin, heart, vessels, kidneys, eyes, brain, etc.

Meerwaldt R, et al. Clinical relevance of advanced glycation end products for vascular surgery. Eur J Vasc Endovasc Surg. 2008;36(2):125-31

The Damage of AGEs

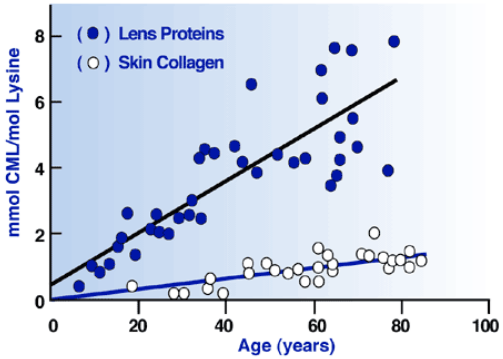
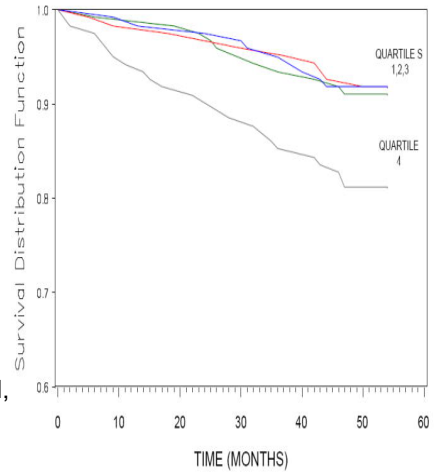


Fig. 2. Increased accumulation of AGEs (CML) with age in human lens protein and skin collagen. (Dyer, et all. The Maillard reaction in vivo, 1991.)

AGEs & Cardiovascular Aging

- Women's Health and Aging Study I (WHAS I), a population-based study
  - Measured serum carboxymethyl-lysine (CML)
  - Approximately 2-fold increase in cardiovascular mortality risk for those in highest tertile
- Glycation of LDL cholesterol
  - Leads to its delayed receptor-mediated clearance and
  - Subsequent deposition in the vessel wall, contributing to atherosclerosis



Semba RD, et al. Advanced glycation end products and their circulating receptors predict cardiovascular disease mortality in older community-dwelling women. Aging Clin Exp Res. 2009 Apr;21(2):182-90.

Ways to Decrease Acrylamide Production in Food

Strategies to Decrease Exposure

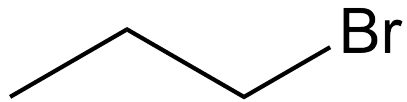
- Limit all fried potato products
- Limit cooking color changes to tan, not brown
- Do not refrigerate potatoes before cooking
- Optimize vitamin D status

You Can Help Cut Acrylamide in Your Diet | FDA (accessed 2022-10)

Clinical Takeaways

Acrylamide

- Major disease: Neurological, some cancers, infertility
- Primary sources: Browed foods
- Best measure: Urinary
- Best intervention: Cooking techniques which do not brown food, glutathione support, vitamin D



Bromopropane

1-Bromopropane

- Non-persistent
- 1-bromopropane (1-BP), also known as n-propyl bromide
- An ozone-depleting halogenated solvent
- Widely used as an organic solvent
  - Cleaning of precision instruments, hardware and electronics, dry cleaning, and in other industries.
  - Synthesis of pharmaceuticals, pesticides, asphalt, etc.
- EPA reported in 2015 that 25.9 million pounds of 1-BP were manufactured in or imported into the United States
- Animal studies suggest possible metabolic, reproductive & neurological toxicity and cancer risk
- Surprisingly limited human data

Yang G, et al. 1-Bromopropane-induced apoptosis in OVCAR-3 cells via oxidative stress and inactivation of Nrf2. Toxicol Ind Health. 2021 Feb;37(2):59-67. PMID: 33305700

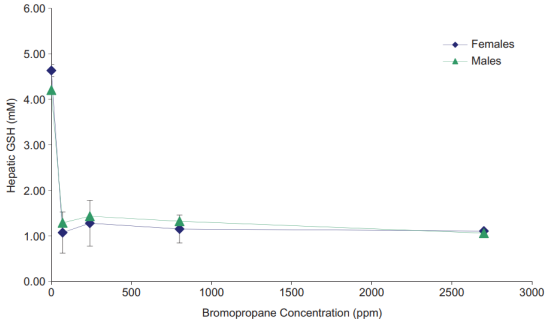
Occupational Exposure & Metabolism

- 1-BP median concentrations > 4x higher in hairdressers in NHANES
  - Higher among those using chemical straighteners or relaxers
  - Several VOCs were up to 5-fold higher in hairdressers
- Workers that spray 1-BP (furniture)
- Routes of metabolism not clear in humans
- N-acetyl-S-(n-propyl)-L-cysteine (AcPrCys) found to be effective biomarker

Louis LM, et al. Biomonitoring of volatile organic compounds (VOCs) among hairdressers in salons primarily serving women of color: A pilot study. Environ Int. 2021 Sep;154:106655. PMID: 34090205

Metabolism – GSH Depleted

- Lacking good human data for pathways
- In rats, hepatic GSH levels drop dramatically, 80% lower relative to control regardless of 1-BP exposure
- Metabolism also modulated by CYP2E1 activity



Garner CE, et al. Species and sex-dependent toxicokinetics of 1-bromopropane: the role of hepatic cytochrome P450 oxidation and glutathione (GSH). Xenobiotica. 2014 44:644-56. PMID: 24438363

Neurological Toxicity

- Lacking large human studies – despite inclusion of 1-BP in NHANES
- Very little research looking at possible associations!
- Neurotoxicity largely based on clinical reports of human cases and animal studies
  - Clinical signs reported included muscle weakness, paresthesia, numbness, urinary incontinence and memory disturbances
- Animal studies find 1-BP produces S-propyl cysteine adducts, within the nervous system on neurofilaments, may be responsible for neurotoxicity

Valentine WM. Toxic Peripheral Neuropathies: Agents and Mechanisms. Toxicol Pathol. 2020 Jan;48(1):152-173. PMID: 31181992

Reproductive Toxicity

- Lack of large studies in humans, with reproductive toxicity indicated by animal studies
- In animals, 1-BP associated with variety of problems, including spermiation failure, low epididymal sperm count and poor sperm motility
  - P450 activity implicated in toxicity, suggesting metabolite(s) have toxic effect
- Animal studies also suggest 1-BP associated with ovarian failure
  - May involve oxidative stress, as Nrf-2 inactivation implicated

Zong C, et al. Role of cytochrome P450s in the male reproductive toxicity of 1-bromopropane. Toxicol Res (Camb). 2016 Aug 4;5(6):1522-1529. PMID: 30090453
Yang G, et al. 1-Bromopropane-induced apoptosis in OVCAR-3 cells via oxidative stress and inactivation of Nrf2. Toxicol Ind Health. 2021 Feb;37(2):59-67. PMID: 33305700

Diabetes & Lung Function

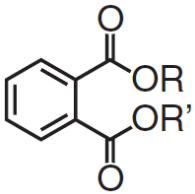
- Human data
  - 3678 adults in China cohort
  - Urinary metabolite, N-Acetyl-S-(n-propyl)-l-cysteine (BPMA)
- Significant dose–response relationship between BPMA and FPG levels
  - 32% mediated by 8-isoprostane
- Diabetes OR of 1.34
- Same cohort found impaired lung function with exposure, also partly mediated by 8-isoprostane

Yang S, et al. Lipid peroxidation mediated the association of urinary 1-bromopropane metabolites with plasma glucose and the risk of diabetes: A cross-sectional study of urban adults in China. J Hazard Mater. 2020 May 5;389:121889. PMID: 31859167
Wang B, et al. Cross-sectional and longitudinal relationships between urinary 1-bromopropane metabolite and pulmonary function and underlying role of oxidative damage among urban adults in the Wuhan-Zhuhai cohort in China. Environ Pollut. 2022 Nov 15;313:120147. PMID: 36096263

Clinical Takeaways

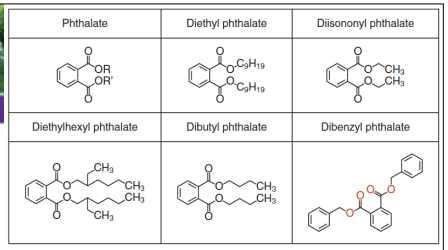
Bromopropane

- Major disease: Neurological damage, infertility (male and female), diabetes, loss of respiratory function, cancer
- Primary sources: Cosmetologists, industrial, dry cleaning
- Best measure: Urinary metabolites
- Best intervention: Avoidance, glutathione



Phthalates

Phthalates

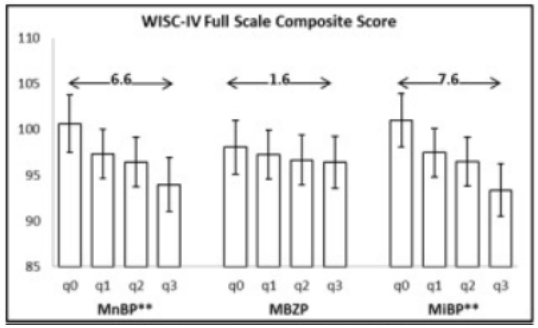


- Worldwide high-production chemicals used in many ways:
  - Make plastics more flexible and resilient
  - Solubilize fragrances in health and beauty aids
- Weakly bound to plastics and easily released into environment
- 2 categories: high-molecular-weight (HMW) or low-molecular-weight (LMW) compounds.
- In general:
  - HMW phthalates mainly from diet
  - LMW phthalates mainly from non-food sources

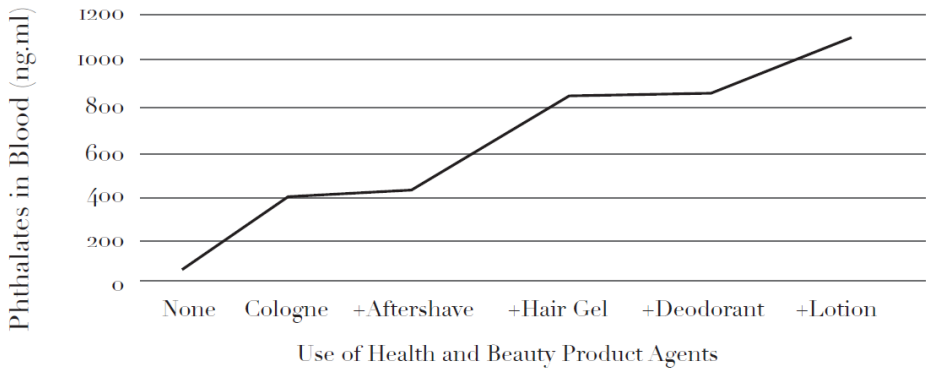
Phthalates and Disease

Disease	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
ADHD	Depends on phthalate	Depends on phthalate	2.1-12.7	>5%	24267794
Diabetes	17.5 ug/L	69.0%	1.5	25%	26119400
Infertility, male				FR = 0.8	24534276
Juvenile IQ	Maternal 19.4/5.0 ug/L (MnBP/MiBP)	25%		6.7-7.6 decrease	25493564

Maternal Prenatal Levels Inversely Correlate with Child IQ (Age 7)

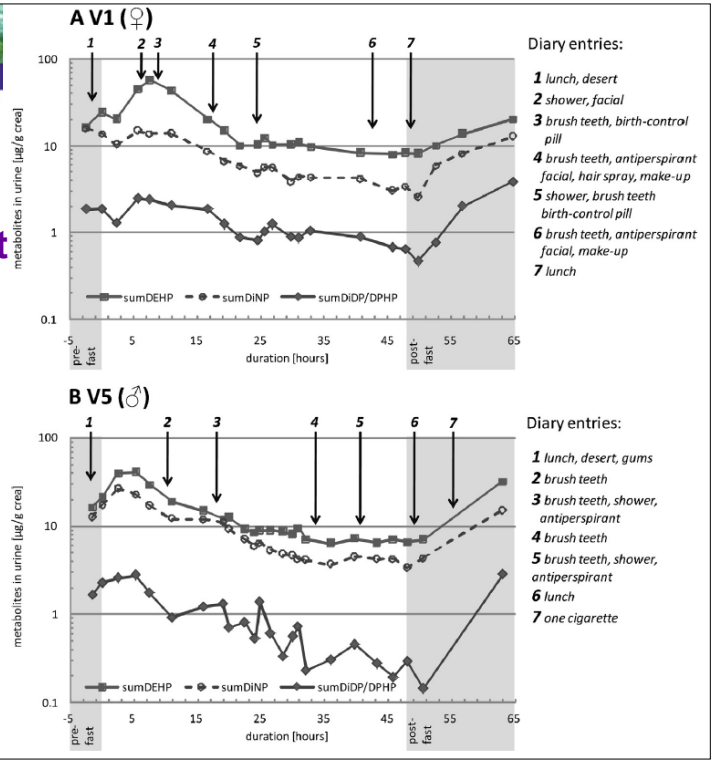


Health and Beauty Aids (HABAs) Significant Source of Phthalates

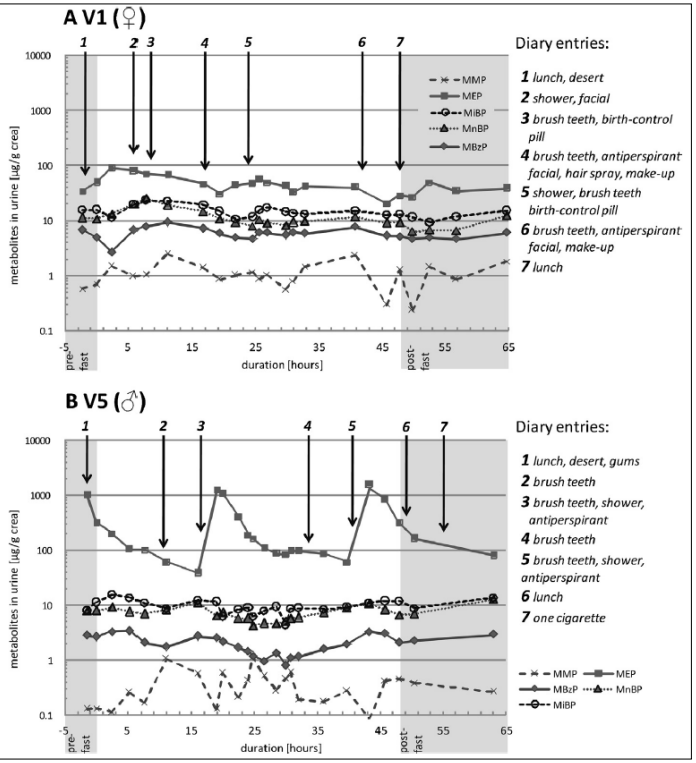


Duty SM, et al. Personal care product use predicts urinary concentrations of some phthalate monoesters. Environ Health Perspect. 2005 Nov;113(11):1530-5

HMW Phthalates Come From Diet



LMW Phthalates Come From Non-Dietary Sources



Fast Food = Lots of Phthalates

Edwards L, McCray NL, VanNoy BN, et al. Phthalate and novel plasticizer concentrations in food items from U.S. fast food chains: a preliminary analysis [published online ahead of print, 2021 Oct 27]. J Expo Sci Environ Epidemiol. 2021;10.1038/s41370-021-00392-8

Detoxification

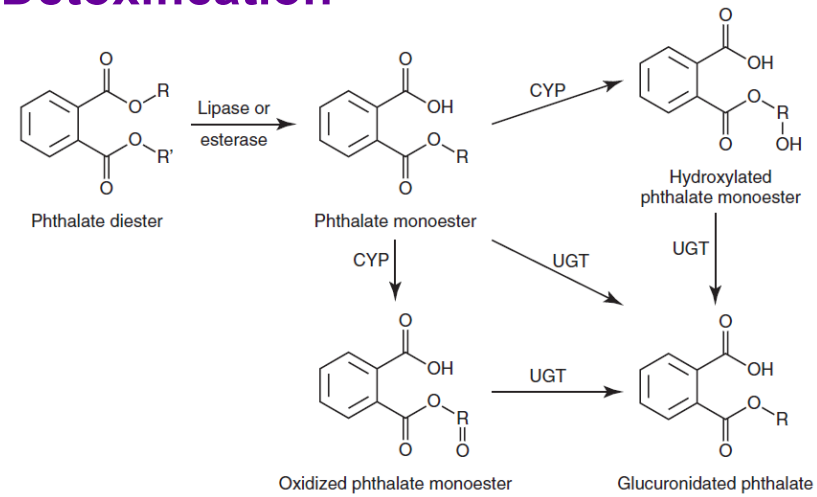
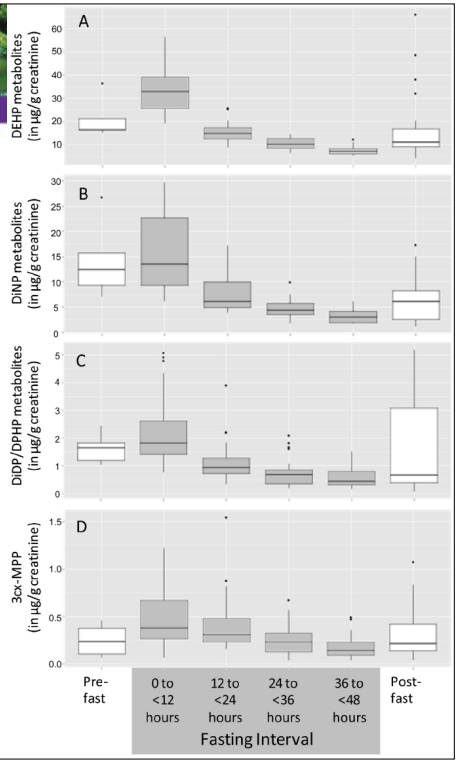


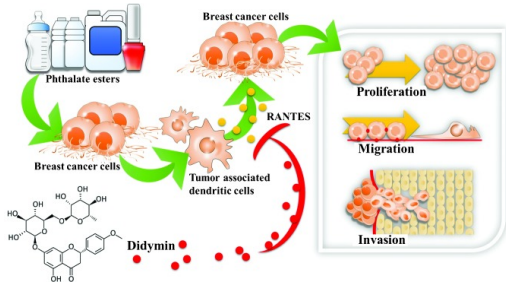
FIG. 26.2 Basic biotransformation of phthalates. (From North, M. L., Takaro, T. K., Diamond, M. L., & Ellis, A. K. [2014]. Effects of phthalates on the development and expression of allergic disease and asthma. *Annals of Allergy, Asthma & Immunology, 112*(6), 496–502.)

Dramatic Increase in HMW Excretion During Water Fasting



Flavonoids Mitigate Phthalate Toxicity

- Didymin, present mainly in Citrus fruits, reverted the cancerous effects induced by several phthalate esters (i.e., BBP, DBP, DEHP) in an *in vitro* experimental model targeting the CCL5 pathway



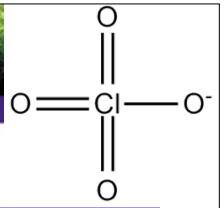
Hsu YL, et al. Didymin reverses phthalate ester-associated breast cancer aggravation in the breast cancer tumor microenvironment. Oncol Lett. 2016 Feb;11(2):1035-1042. PMID: 26893687

Clinical Takeaways

Phthalates

- Major disease: Infertility, low testosterone, obesity, diabetes, allergies, asthma, autism, mood disorder, reduced cognition
- Primary sources: Solid plastic products in the home, plastic-covered foods, personal care products, house dust
- Best measure: Review home for phthalate-containing products and urinary phthalate metabolites
- Best intervention: Avoidance, flavonoids, fasting

Physiological Dysfunction



Perchlorate

Perchlorate - Overview

- Non-persistent toxin
- ClO_4 (e.g., potassium perchlorate)
- Strong oxidant
- Uses:
  - Rocket fuel, fireworks, highway flares
  - To control static in food packaging
  - Graves disease
- Primary exposure through:
  - Inhalation: factory workers, cities with smog
  - Oral: water (historic) and food (current)

Perchlorate – Contamination

- Sources
  - Primary source industrial waste
  - MAY be created by chlorination of water
  - Naturally produced
- Widely contaminates the environment
  - Public water supply average: 1.16 PPM
  - Public water supplies above 4.1 PPM: 4%
  - Worse near military bases, manufacturing facilities

Steinmaus CM. Perchlorate in Water Supplies: Sources, Exposures, and Health Effects. Curr Environ Health Rep. 2016 Jun;3(2):136-43. PMID: 27026358

Perchlorate Metabolism/Detoxification

- Readily absorbed
- Little metabolism
- Mostly excreted unchanged in urine
- Excreted in breast milk
- Half-life: 8 hours

Steinmaus CM. Perchlorate in Water Supplies: Sources, Exposures, and Health Effects. Curr Environ Health Rep. 2016 Jun;3(2):136-43. PMID: 27026358

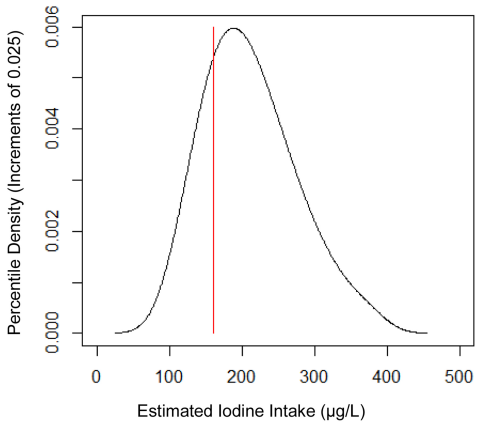
Perchlorate – Clinical Significance

- Binds to iodine
- Historically, potassium perchlorate was used to treat hyperthyroidism
- Human clinical research inconsistent
  - 59% of studies show clinical impact
- Inverse correlation thyroid hormone levels and perchlorate
  - But not reflected in hypothyroidism diagnosis
  - Positive correlation with TSH (women >> men)
- Dependent upon iodine status and goitrogen exposure

Niziński P, Błażewicz A, Kończyk J, Michalski R. Perchlorate - properties, toxicity and human health effects: an updated review. Rev Environ Health. 2020 Sep 4;36(2):199-222. PMID: 32887207.

Iodine Deficiency is Common in US

- RDI for adults:
  - 150 mcg/day
  - 220 for pregnant women
- Adequate to prevent goiter, not optimal
- Japan: 3-5 mg/d



Pregnant US women

Iodine Deficient Worldwide

WHO region[a]	Insufficient iodine intake (UI < 100 μg/l)			
	School-age children		General population	
	Proportion (%)	Total number (millions)[b]	Proportion (%)	Total number (millions)[b]
Africa	42.3	49.5	42.6	260.3
Americas	10.1	10.0	9.8	75.1
Europe	59.9	42.2	56.9	435.5
Eastern Mediterranean	55.4	40.2	54.1	228.5
South-East Asia	39.9	95.6	39.8	624.0
Western Pacific	26.2	48.0	24.0	365.3
Total	**36.5**	**285.4**	**35.2**	**1988.7**

[a] 192 WHO Member States.
[b] Based on population estimates in the year 2002.
Source (*16*).

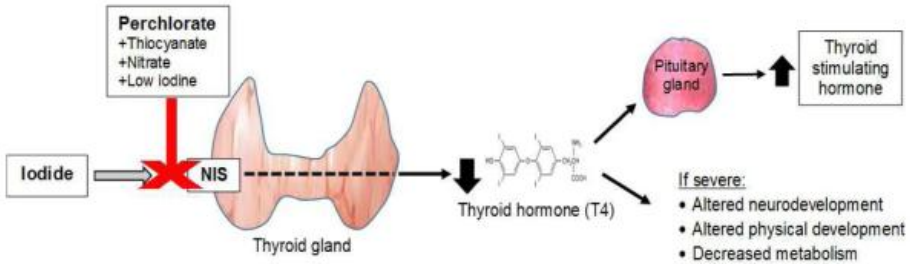
Table 5. **Change in total goitre prevalence (TGP) between 1993 and 2003, by WHO region**

WHO region[a]	General population TGP (%)		Percentage change
	1993	2003	
Africa	15.6	28.3	+81.4
Americas	8.7	4.7	–46.0
Eastern Mediterranean	22.9	37.3	+62.9
Europe	11.4	20.6	+80.7
South-East Asia	13.0	15.4	+18.5
Western Pacific	9.0	6.1	–32.2
Total	**12.0**	**15.8**	**+31.7**

[a] 192 WHO Member States.

Andersson M, Takkouche B, Egli I, Allen HE, de Benoist B. Current global iodine status and progress over the last decade towards the elimination of iodine deficiency. Bull World Health Organ. 2005 Jul;83(7):518-25. PMID: 16175826

Seeing the Whole Picture



Perchlorate Summary

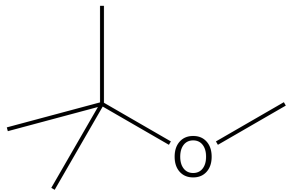
- Thyroid hormone levels decrease in proportion to body load
- Severity of clinical impact depends upon intake of iodine and goitrogens

Clinical Takeaways

Perchlorates

- Major disease: Decreased thyroid function
- Primary sources: Water and food
- Best measure: Urinary
- Best intervention: Avoidance, optimize iodine intake, decrease goitrogen intake

Only Susceptible Individuals



MTBE
(Methyl Tertiary-Butyl Ether)

MTBE

- Non-persistent (minutes!)
- Main use has been in gasoline to reduce knock—replaced lead for this purpose
  - Some water supplies, especially in cities, contaminate by leaking gasoline tanks
  - Supposedly no longer used in US so contamination **SHOULD** be low
- Used as solvent in industry and research
- Ubiquitous, measurable in virtually whole population
- Some medical use for dissolving gallstones

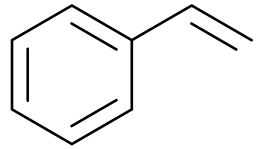
MTBE – Clinical

- Very difficult to separate MTBE effects from exposure to other constituents of gasoline
- Epidemiological research shows only limited acute symptomatology to workplace exposure
- Animal research shows increased risk for cancer at high and chronic exposure
- Virtually no research showing confirmed toxicity in humans
- Excreted unchanged in respiration and urine

Clinical Takeaways

MTBE

- Major disease: Transient symptoms with high expsosure
- Primary sources: Exposure to gasoline, transportation workers, industrial solvent exposure
- Best measure: Urinary metabolites
- Best intervention: Avoidance



Styrene

Styrene

- Used in many manufacturing processes:
  - Polystyrene (PS)
  - Acrylonitrile-butadiene-styrene (ABS)
  - Styrene-acrylonitrile (SAN)
  - Styrene-butadiene rubber (SBR)
  - Styrene-butadiene latex (SBL)
  - Unsaturated polyester resins (UPR) used in fiberglass
- Primary exposure:
  - Industrial exposure as well as those living nearby
  - Smoking (blood levels 4x higher than non-smokers)
  - Everyday life

Crinnion W, Pizzorno J. *Clinical Environmental Medicine*. 2019 Elsevier

Styrene Toxicity

- Causes oxidative damage:
  - Elevated malondialdehyde
  - Depleted glutathione
  - Results in DNA adducts and elevated 8-OHdG
- Carcinogenicity controversial

Sati, P. C., Khaliq, F., Vaney, N., et al. (2011). Pulmonary function and oxidative stress in workers exposed to styrene in plastic factory: Occupational hazards in styrene-exposed plastic factory workers. Human and Experimental Toxicology, 30(11), 1743–1750. PMID: 21382913
Wongvijitsuk, S., Navasumrit, P., Vattanasit, U., et al. (2011). Low level occupational exposure to styrene: Its effects on DNA damage and DNA repair. International Journal of Hygiene and Environmental Health, 214(2), 127–137. PMID: 21030303

Clinical Takeaways

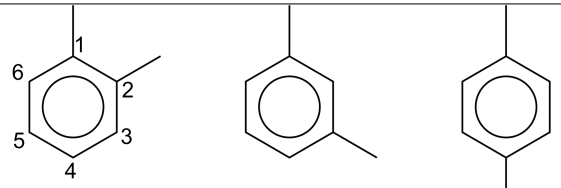
Styrene – Industrial exposure; smokers

- Major disease: Autism spectrum disorder (ASD) risk, reductions in vision and hearing, genotoxicity, increased cancer risk
- Primary sources: Smoking, vehicular exhaust, foods, memory foam mattresses
- Best measure: Urinary metabolites or blood styrene levels
- Best intervention: Avoidance, antioxidants, N-acetyl cysteine (NAC), garlic

Clinical Takeaways

Styrene – General Public

? ? ?

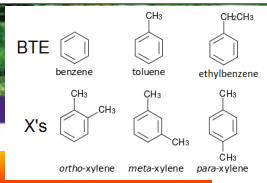


Xylene

Xylene

- Non-persistent
- Solvent with 3 variants of same formula
- Half of all xylenes used in production of polyethylene terephthalate (PET) plastic bottles and polyester clothing
- Printing and rubber industries
- Inhalation depresses neurological function
- Systematic reviews show little risk by itself.
- Pretty much all correlations with total solvent exposure

Clinical Takeaways



Xylenes (BTEX)

- Major disease: Mainly solvent exposure
- Primary sources: Plastics and industrial
- Best measure: Urine metabolites
- Best intervention: Avoidance

Conclusion

Conclusion

- The whole population is heavily exposed to many chemicals of varying toxicity
- Most disrupt physiology in proportion to load
- Disease associations/causes divergent
  - Hugely dependent on each person's unique biochemistry
- Waiting for overt disease is a poor strategy
- Optimal health depends upon minimizing chemical exposure and optimizing nutrients that facilitate detoxification and minimize damage
- Total chemical load appears a good measure of diet quality and lifestyle choices

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Patience!

Don't expect the speed of results seen with drug or even nutrition therapy

1. Identify and stop exposure
2. Greatly decrease body load
   - Some toxins become apparent only after others removed
3. For damaged enzymes to work:
   - Must displace enzyme poison with nutrient cofactor, or
   - Degrade and replace enzyme
     - **½ life MAO-B in baboon brain = 30 days**
4. Finally, the damage has to be repaired

Arnett CD, Fowler JS, MacGregor RR, et al. Turnover of brain monoamine oxidase measured in vivo by positron emission tomography using L-[11C]deprenyl. J Neurochem. 1987;49:522-7

Resources

- Consumer:
  - Pizzorno J. *The Toxin Solution*. HarperOne, 2017
  - Minich D. *Whole Detox: A 21-Day Personalized Program to Break Through Barriers in Every Area of Your Life*. HarperOne, 2016
- Practitioners:
  - Crinnon W, Pizzorno J. *Clinical Environmental Medicine*, Elsevier, 2018