OPCW

Organisation for the Prohibition of Chemical Weapons

Chemical Action on Life Processes

An exploration of the systems biology of toxic chemicals and a hands on DNA experience

Science for Diplomats at EC-92
The Hague, 8 October 2019

Dr Christophe Curty, 2019 Scientific Advisory Board Vice-Chair/2020 Chair

Ms Andrea Dymytrova, Special Guest

Dr Jonathan E. Forman, Science Policy Adviser/Secretary to the SAB

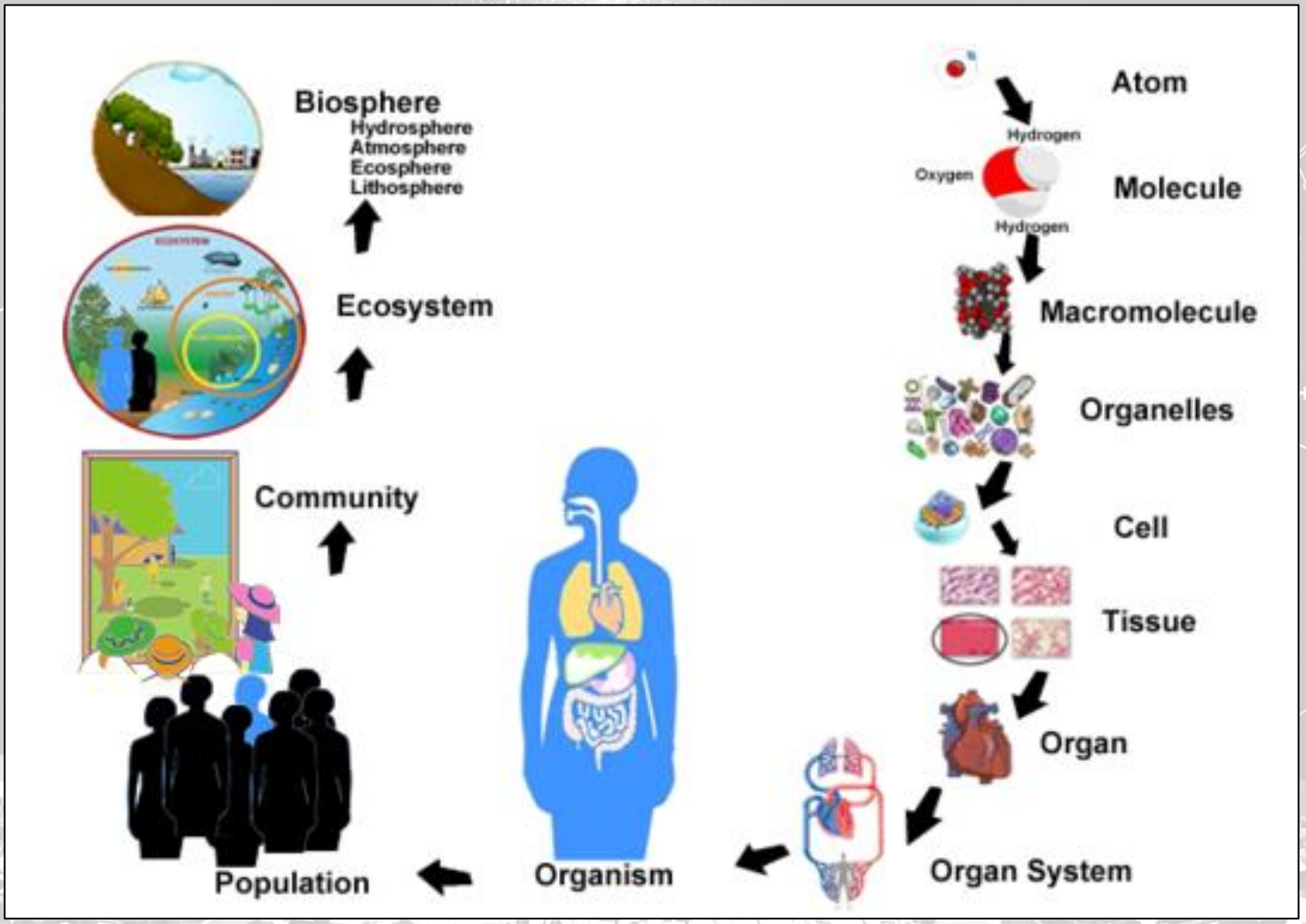
Mr Bernhardt Fourie, Office of Confidentiality and Security

Ms Giovanna Pontes, Office of Strategy and Policy

Ms Julieta Schneider, Office of Strategy and Policy

Mr Cheng Tang, 2019 Scientific Advisory Board Chair

How Do Atoms and Molecules Connect to our Priorities?



http://cms.gavirtualschool.org/Shared/Science/Biology17/WelcomeToBiology/Biology_WelcomeToBiology_Shared4.html

Toxicology

"The study of the adverse effects of chemicals on living organisms"

GHS hazard pictograms

Basic assumption of toxicology

"The dose makes the poison"
(Latin: ***sola dosis facit venenum***)

"Alle Ding' sind Gift und nichts ist ohn' Gift; allein die Dosis macht, dass ein Ding kein Gift ist."

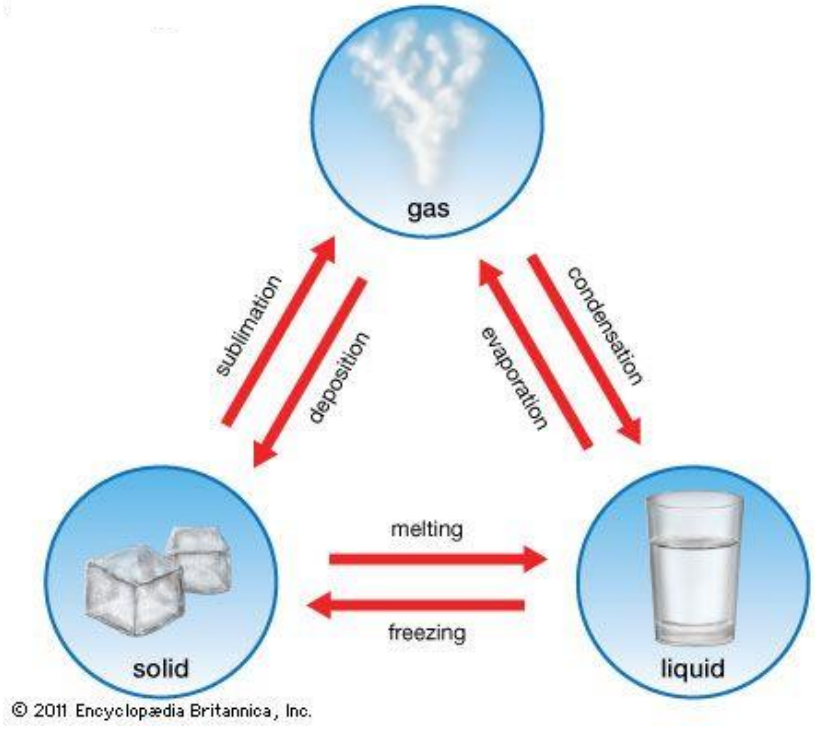
All things are poison, and nothing is without poison, the dosage alone makes it so a thing is not a poison.

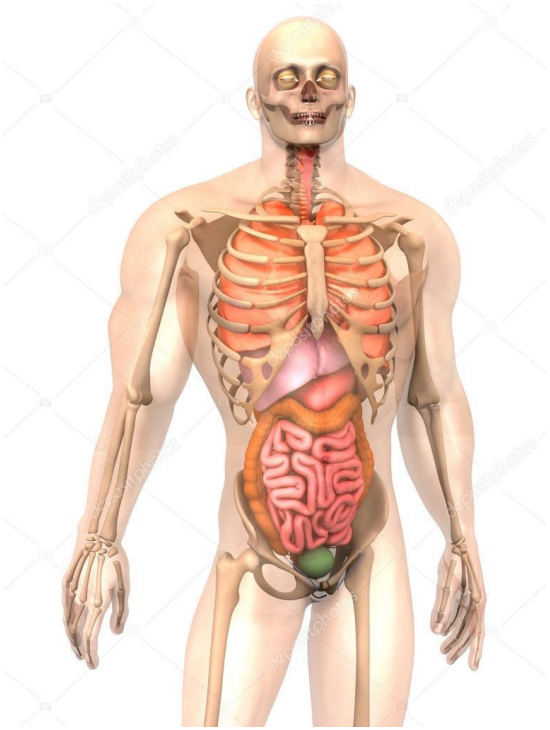
Paracelsus (1493-1541)

Individual Response to Exposure

Individual sensitivity

Routes of Exposure





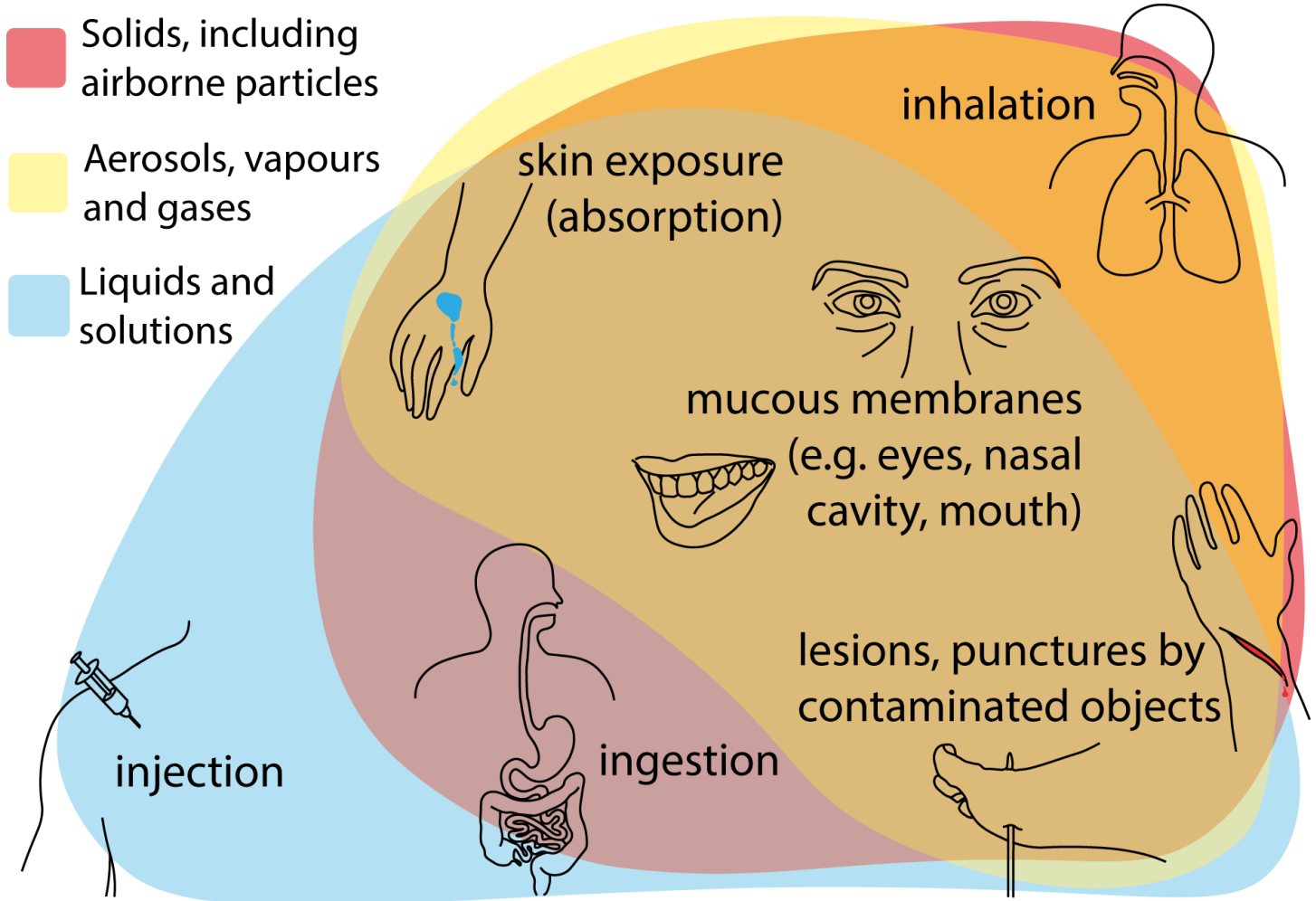
Inhalation

Ingestion

Skin absorption

Duration of exposure

Routes of Exposure and Physical State of Chemical Agent



Routes of Exposure

Acute

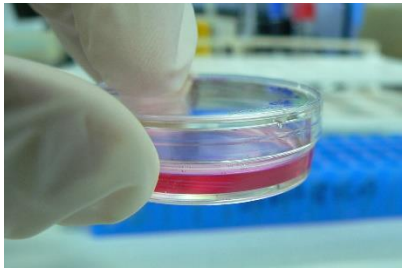
Single short-term exposure

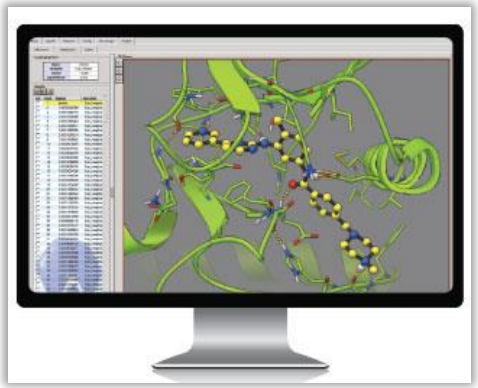
Chronic

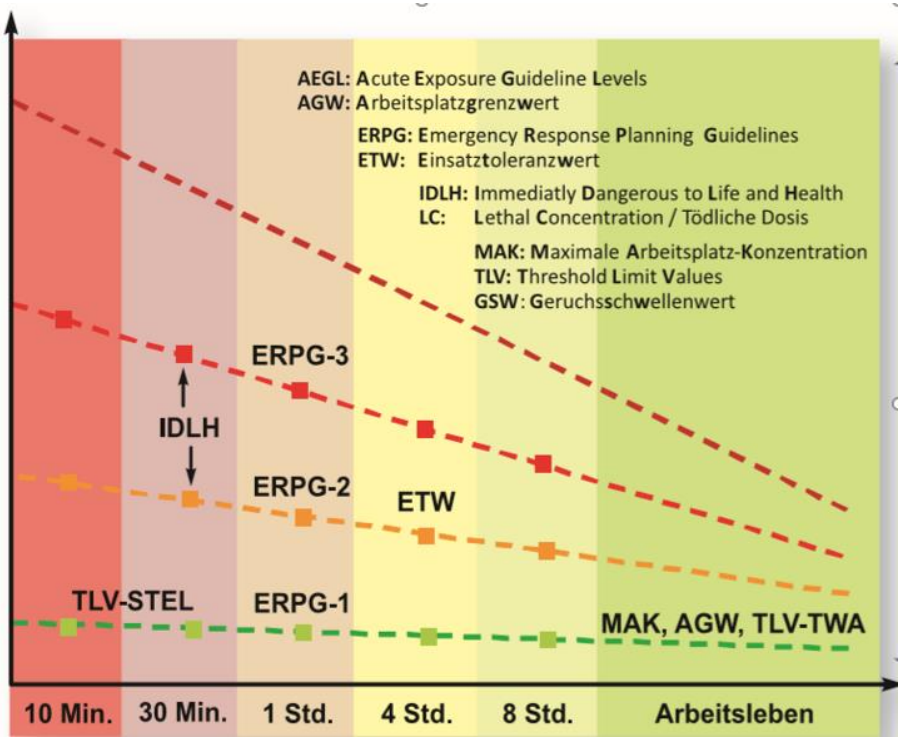
Repeated or continuous exposure

How much of a chemical is required to cause death?

Testing for Toxicity







Dosage Units

- **Median Lethal Dose** (LD_{50})

  The "dose of a chemical expected to be lethal to 50% of the members of an exposed population."

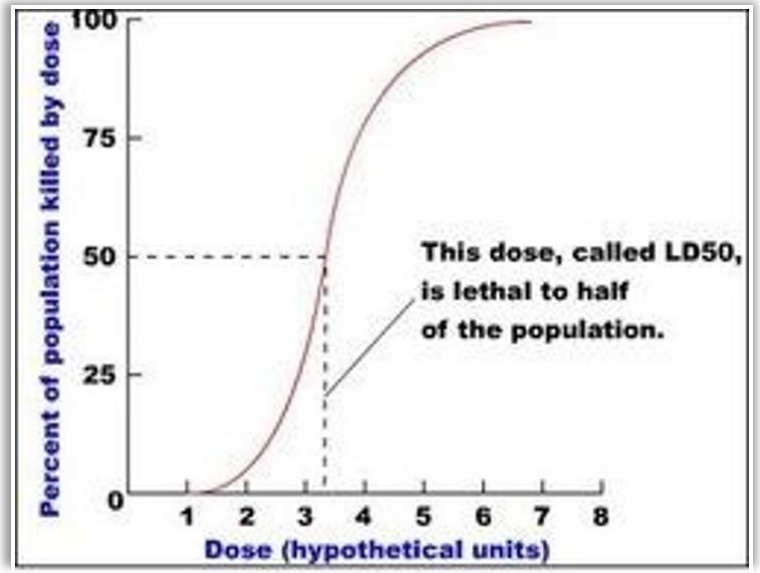
  [mg/kg body weight]

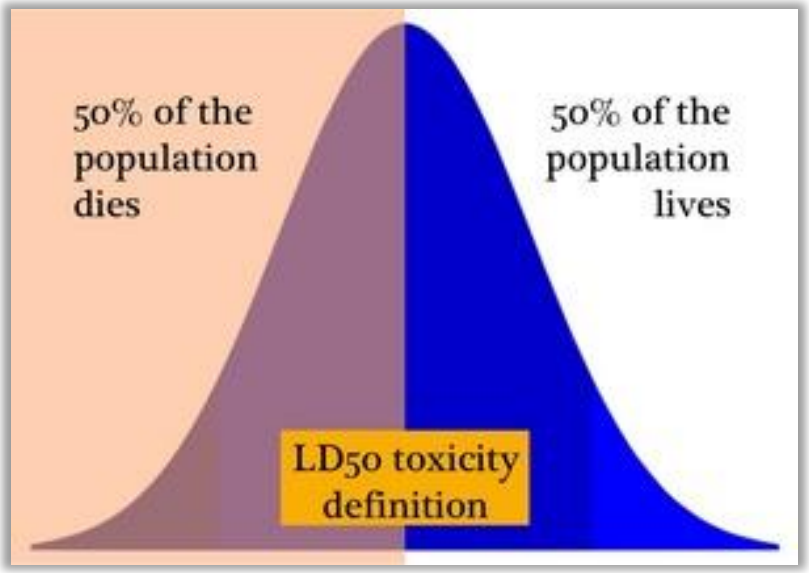
- **Median Lethal Concentration as a function of time** (LCt_{50})

  The "concentration of a chemical (in vapor phase) expected to be lethal to 50% of the members of an exposed population for a specified period of time."

  [mg·min/m³]

Dosage Units





Example: Dichlorovos

Insecticide commonly used in household pesticide strips

- Oral LD_{50} (rat): 56 mg/kg
- Dermal LD_{50} (rat): 75 mg/kg
- Intraperitoneal LD_{50} (rat): 15 mg/kg
- Inhalation LC_{50} (rat): 1.7 ppm (15 mg/m3); 4-hour exposure
- Oral LD_{50} (rabbit) 10 mg/kg
- Oral LD_{50} (pigeon:): 23.7 mg/kg

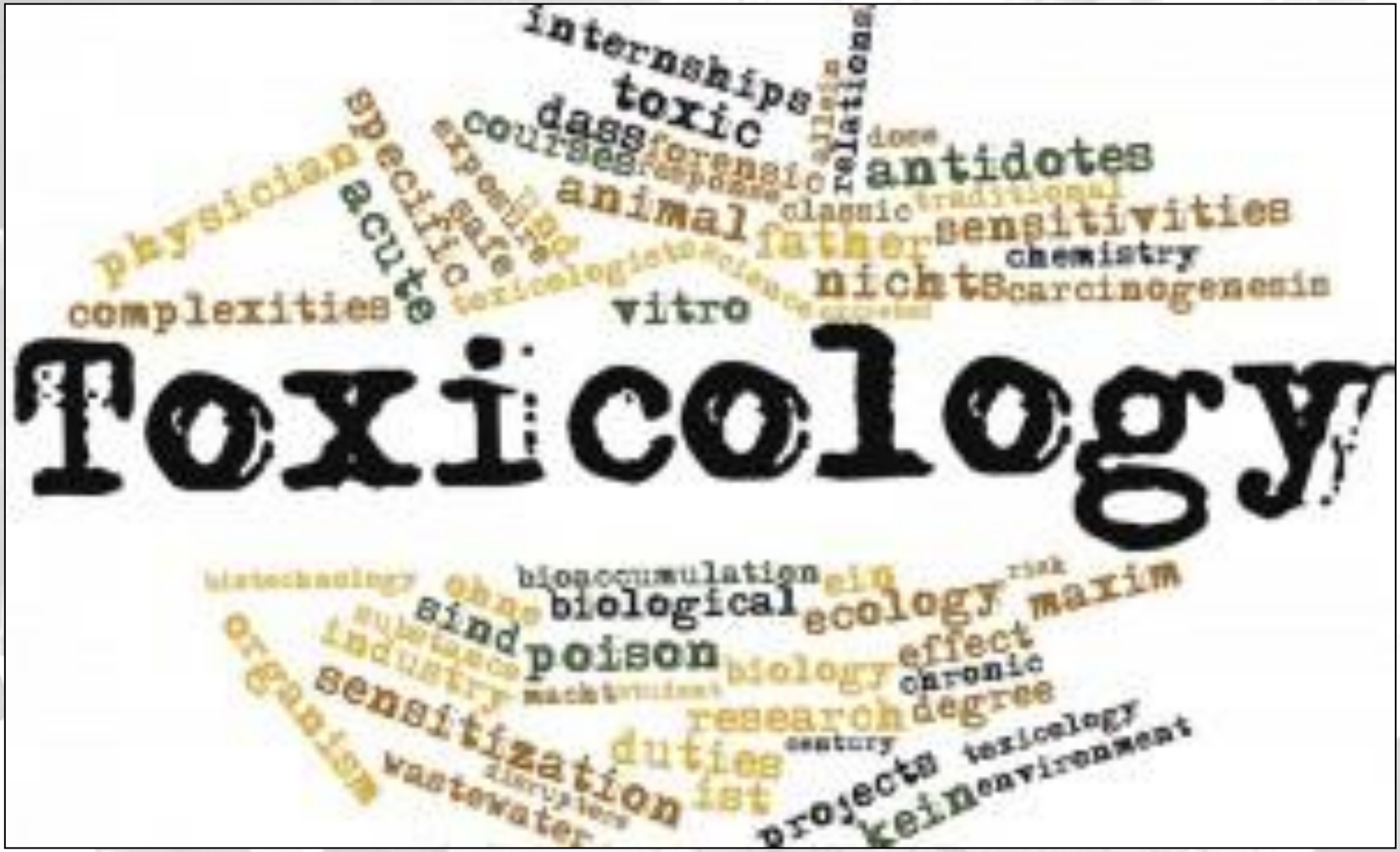
Toxicity classes



Toxicity Classes: Hodge and Sterner Scale					
		Routes of Administration			
		Oral LD_{50}	Inhalation LC_{50}	Dermal LD_{50}	
Toxicity Rating	**Commonly Used Term**	**(single dose to rats) [mg/kg]**	**(exposure of rats for 4 hours) [ppm]**	**(single application to skin of rabbits) [mg/kg]**	**Probable Lethal Dose for Man**
1	Extremely Toxic	1 or less	10 or less	5 or less	1 grain (a taste, a drop)
2	Highly Toxic	1-50	10-100	5-43	4 ml (1 tsp)
3	Moderately Toxic	50-500	100-1000	44-340	30 ml (1 fl. oz.)
4	Slightly Toxic	500-5000	1000-10,000	350-2810	600 ml (1 pint)
5	Practically Non-toxic	5000-15,000	10,000-100,000	2820-22,590	1 litre (or 1 quart)
6	Relatively Harmless	15,000 or more	100,000	22,600 or more	1 litre (or 1 quart)

For what?

- Emergency procedures
- Safety clothing and equipment guidelines
- Transportation regulations
- Occupational exposure limits



Environmental Toxicology: https://www.slideshare.net/misteraugie/hlth104chapter03

What is a LD_{50} and LC_{50}? https://www.ccohs.ca/oshanswers/chemicals/ld50.html

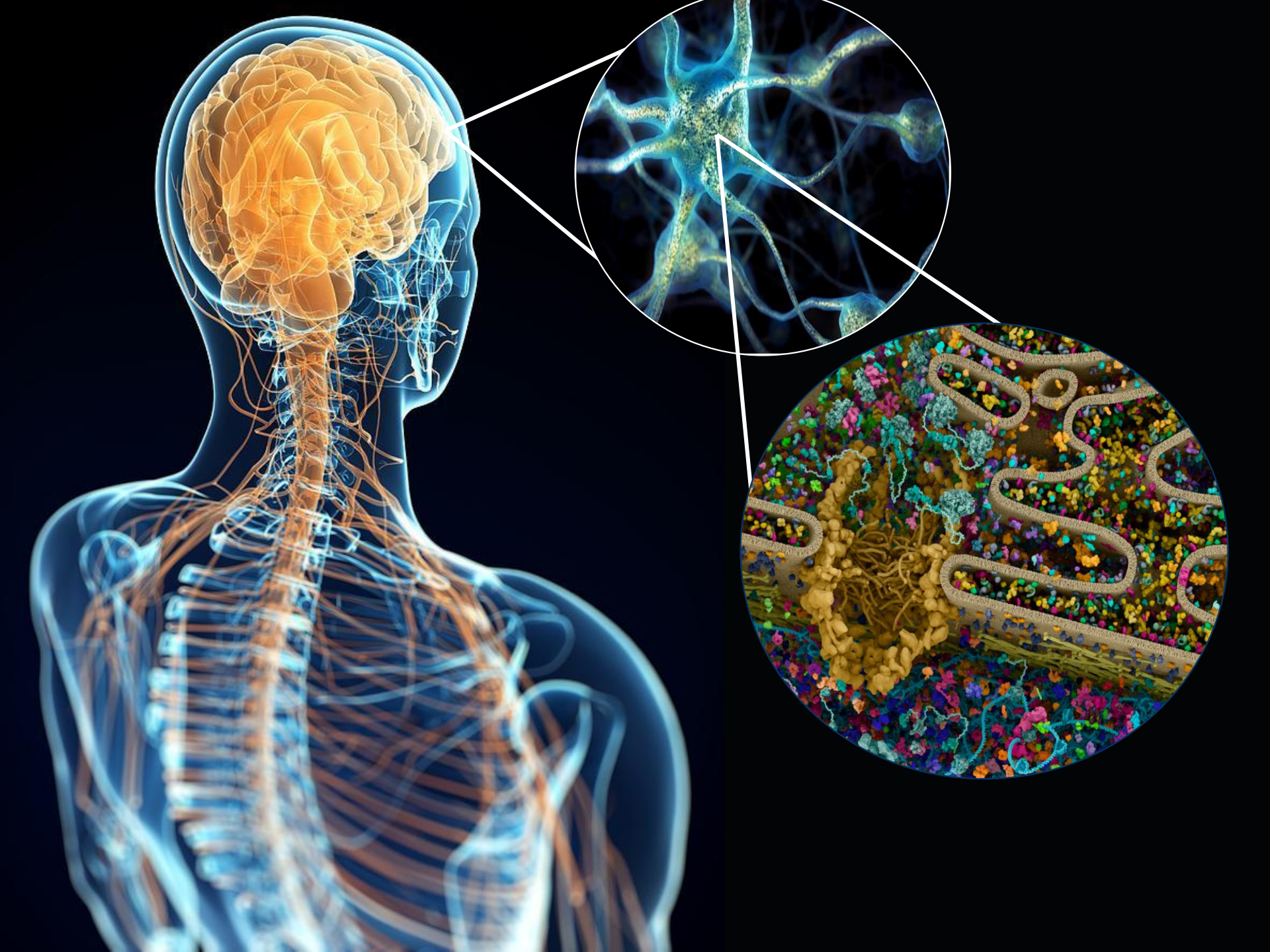
What is the definition of a "toxic chemical“?

Any chemical which through its ***chemical action on life processes*** can cause death, temporary incapacitation or permanent harm to humans or animals. This includes all such chemicals, regardless of their origin or of their method of production, and regardless of whether they are produced in facilities, in munitions or elsewhere

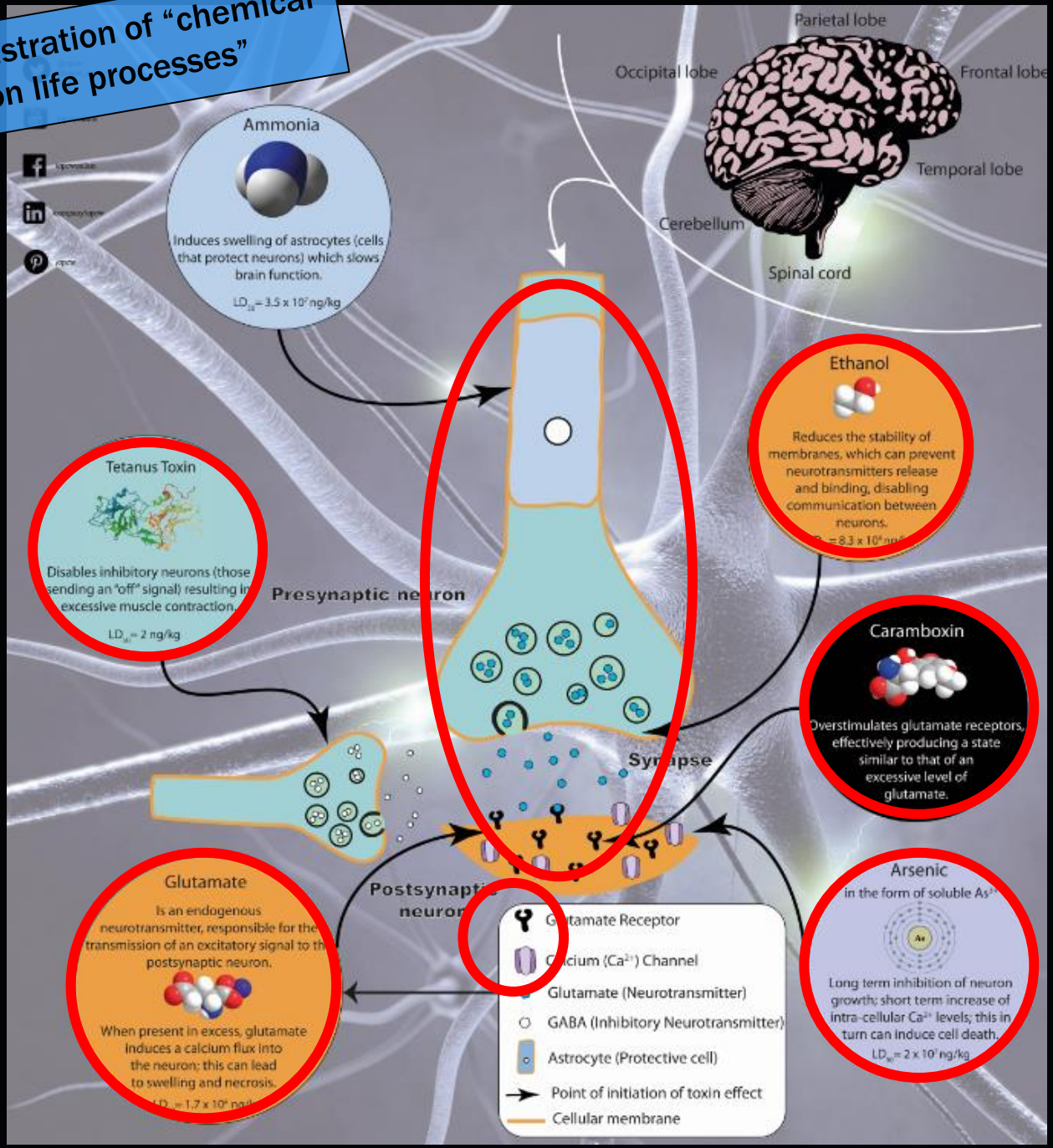
- Chemical Weapons Convention Article II, Paragraph 2

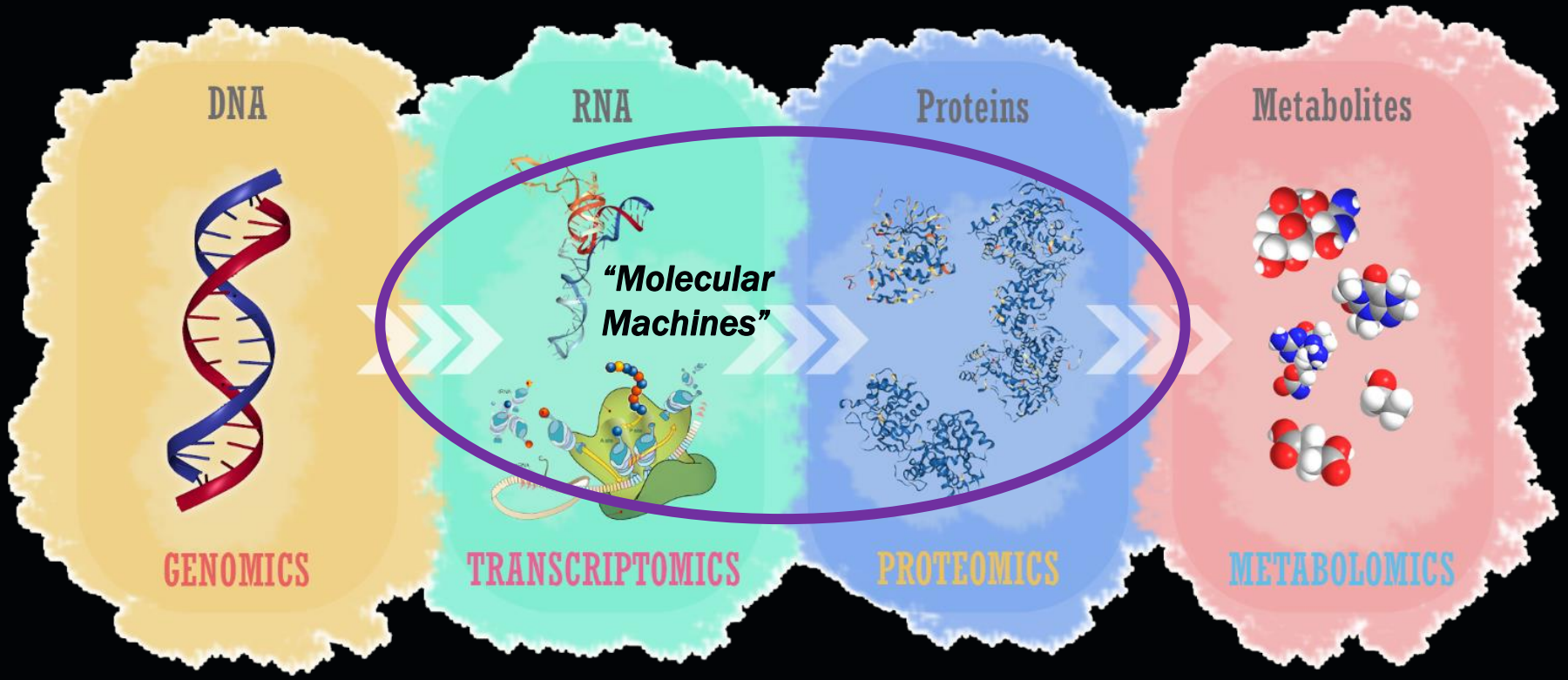
What is a “Life Process”?

(*this is not defined in the Convention*)



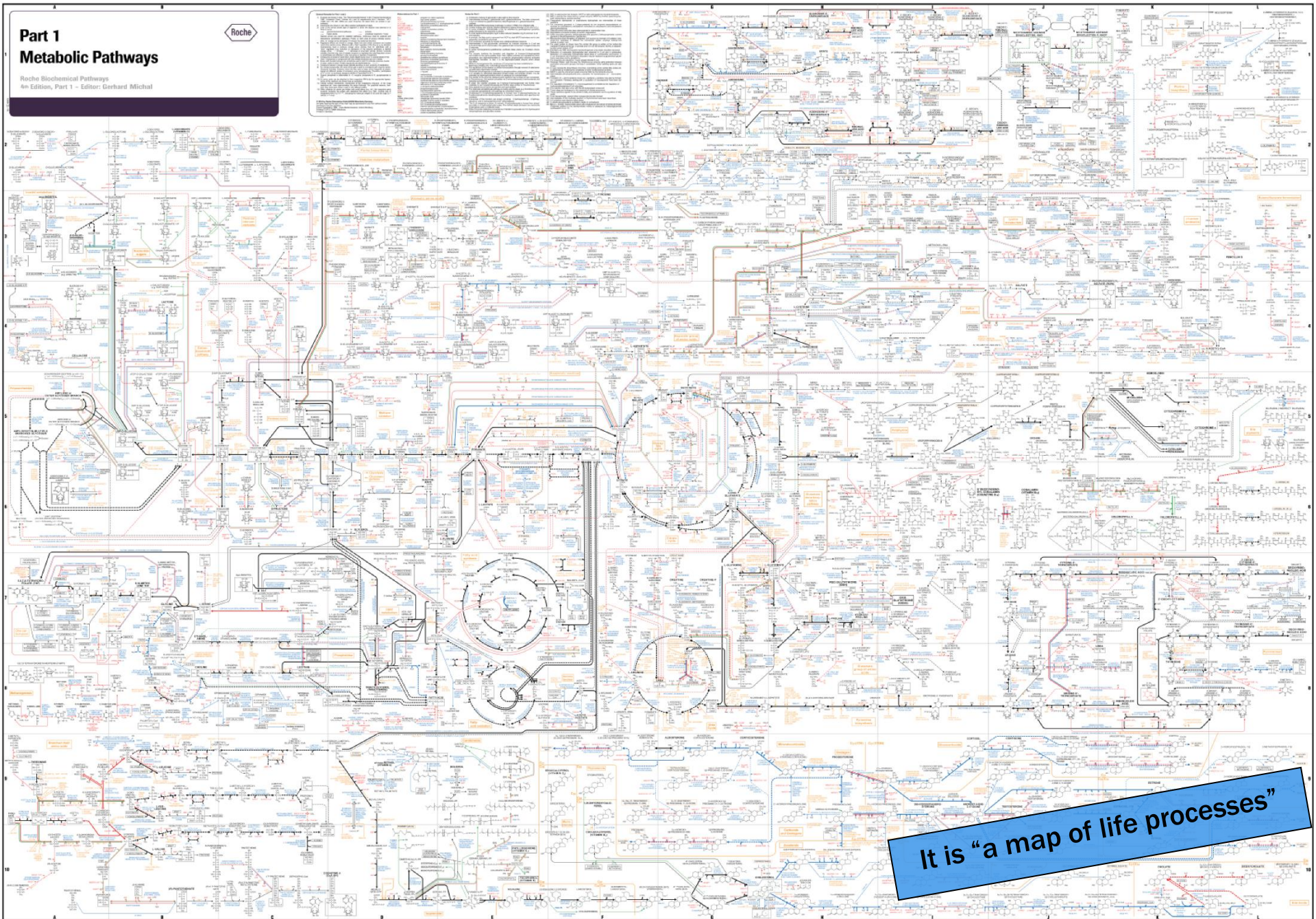
This is an illustration of "chemical action on life processes"




DNA
RNA
Proteins
Metabolites
"Molecular Machines"
GENOMICS
TRANSCRIPTOMICS
PROTEOMICS
METABOLOMICS

https://www.cellsignal.com/contents/science-cellular-landscapes/cellular-landscapes-vesicle-trafficking/science-landscapes-vesicle-trafficking#

This is NOT a UN Org Chart!



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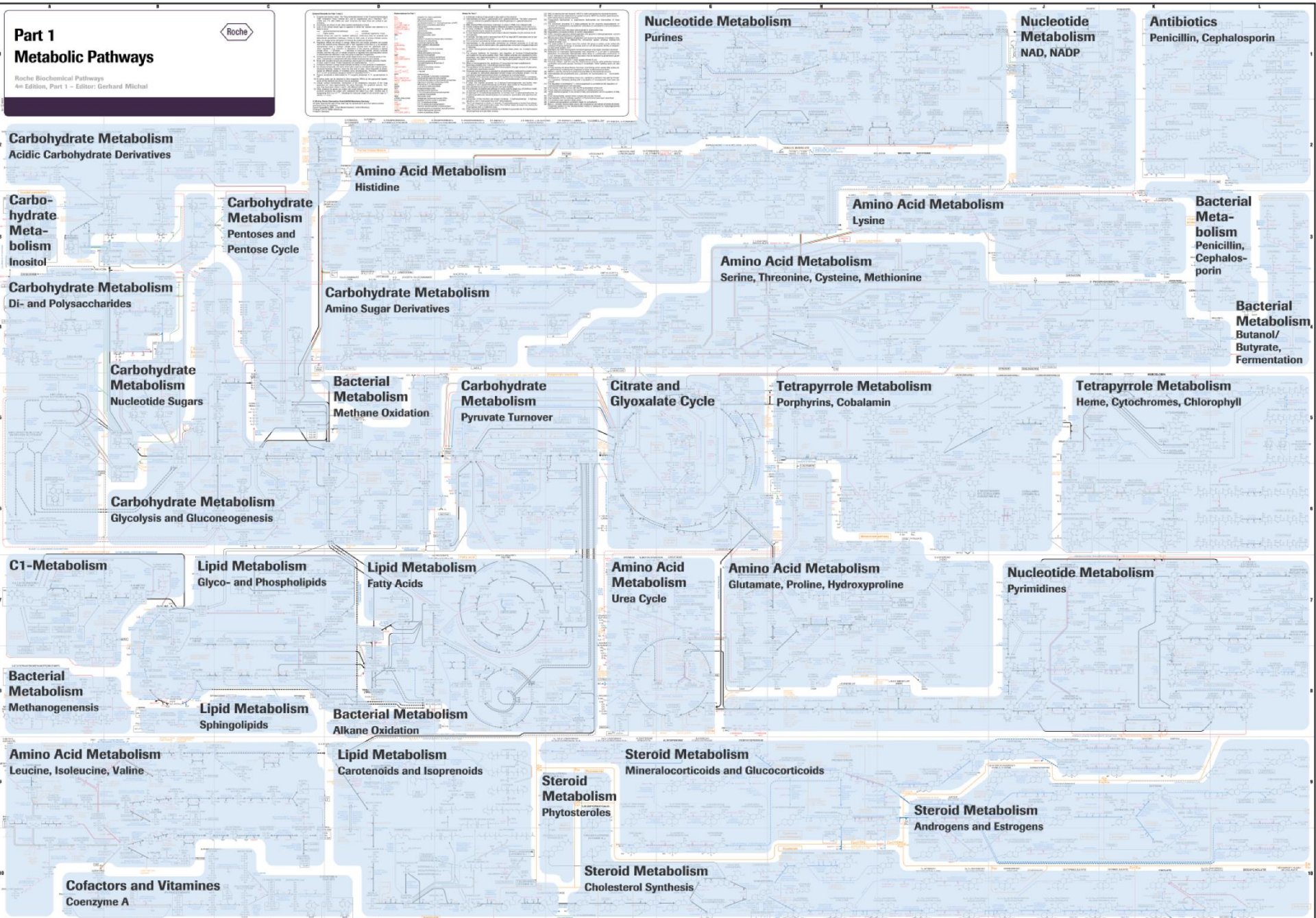

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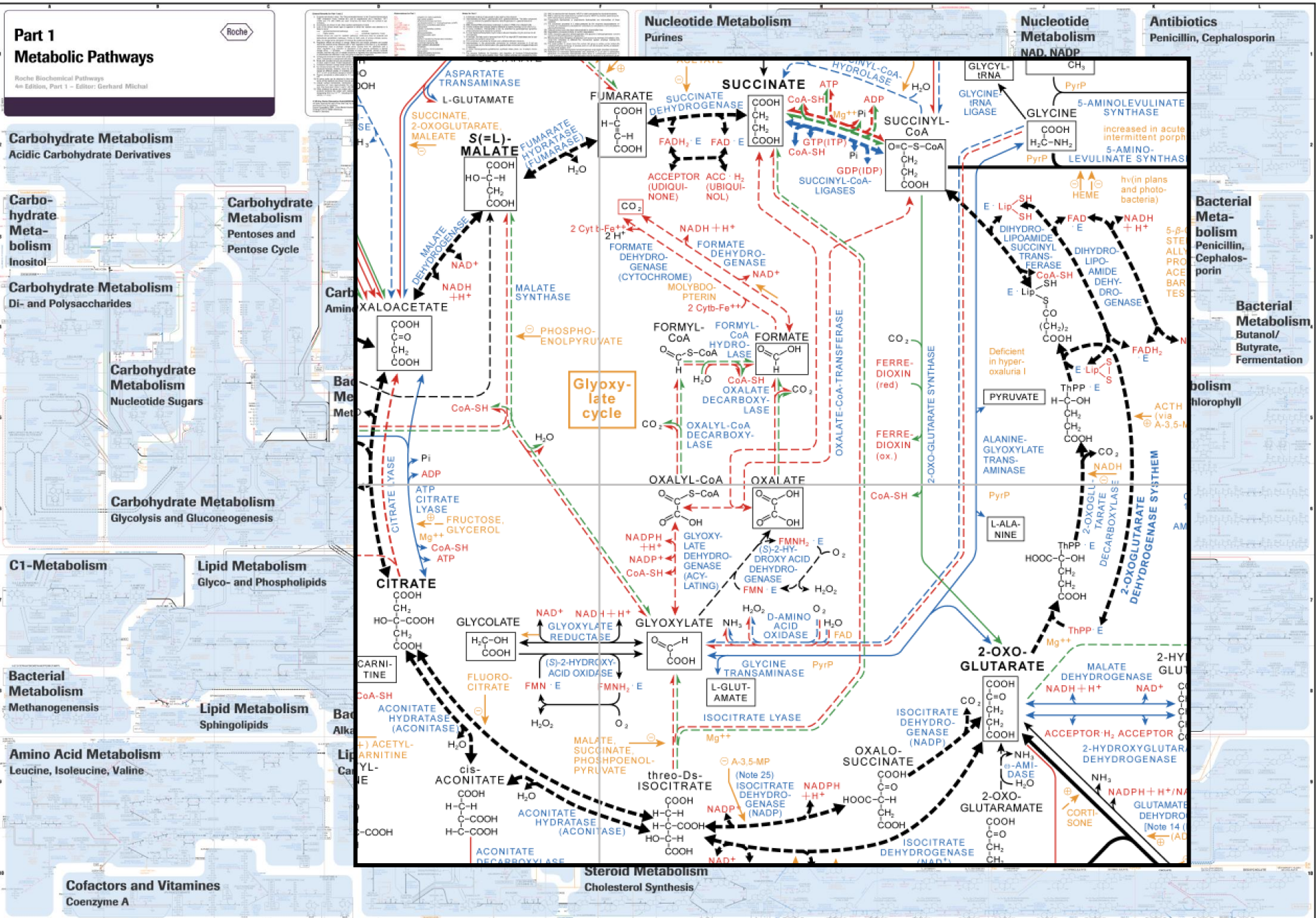
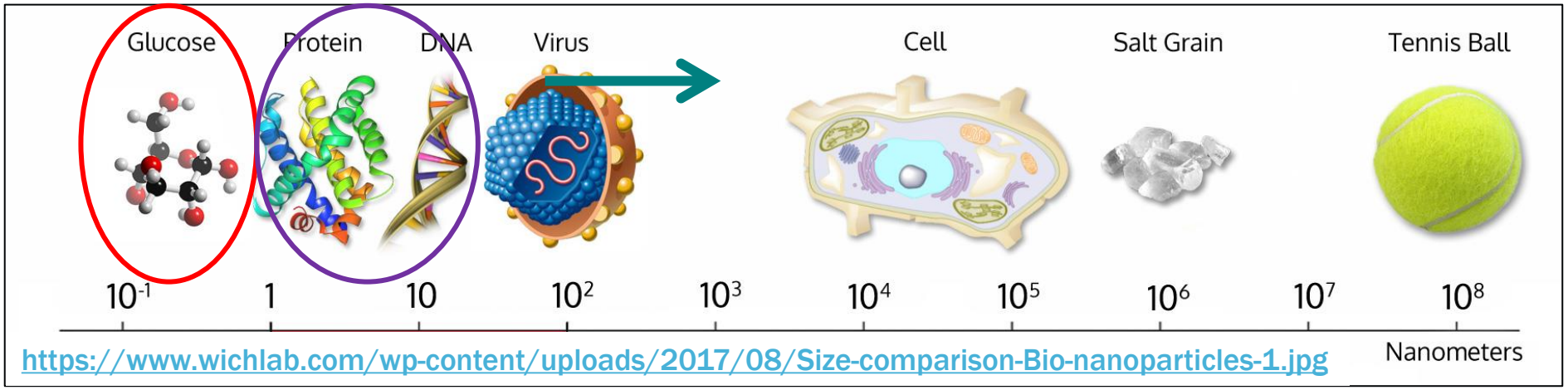


Just Like Chemistry, Molecular Biology is also About Molecules…

The molecules are just very large…



https://www.wichlab.com/wp-content/uploads/2017/08/Size-comparison-Bio-nanoparticles-1.jpg

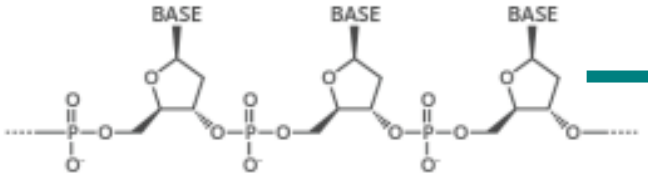
Similar size to a number of classical chemical warfare agents

Proteins and DNA can be ~10 – 100 times larger

THE CHEMICAL STRUCTURE OF DNA

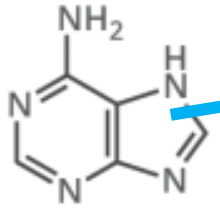
"Shape"

THE SUGAR PHOSPHATE 'BACKBONE'

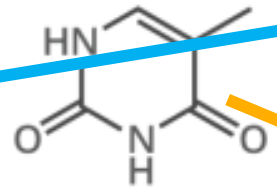


DNA is a polymer made up of units called nucleotides. The nucleotides are made of three different components: a sugar group, a phosphate group, and a base. There are four different bases: adenine, thymine, guanine and cytosine.

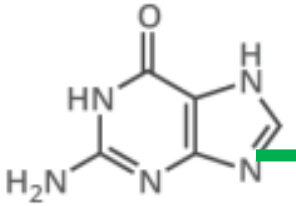
A ADENINE



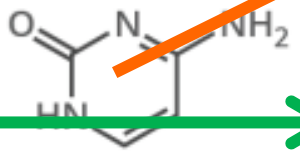
T THYMINE

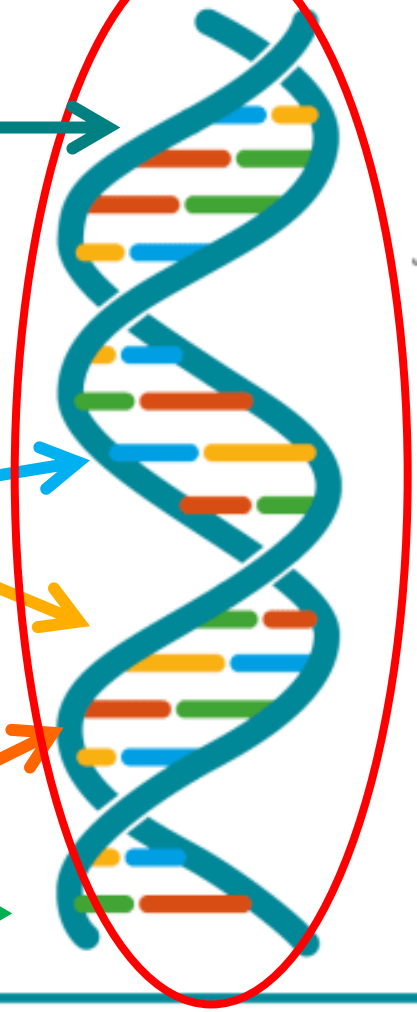


G GUANINE



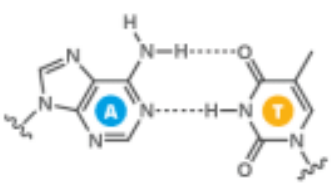
C CYTOSINE

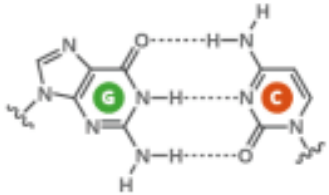




WHAT HOLDS DNA STRANDS TOGETHER?

DNA strands are held together by hydrogen bonds between bases on adjacent strands. Adenine (A) always pairs with thymine (T), while guanine (G) always pairs with cytosine (C). Adenine pairs with uracil (U) in RNA.





FROM DNA TO PROTEINS

The bases on a single strand of DNA act as a code. The letters form three letter codons, which code for amino acids - the building blocks of proteins.

DNA → (TRANSCRIPTION) → RNA → (TRANSLATION) → PROTEIN

An enzyme, RNA polymerase, transcribes DNA into mRNA (messenger ribonucleic acid). It splits apart the two strands that form the double helix, then reads a strand and copies the sequence of nucleotides. The only difference between the RNA and the original DNA is that in the place of thymine (T), another base with a similar structure is used: uracil (U).

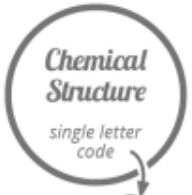
"Short-hand"

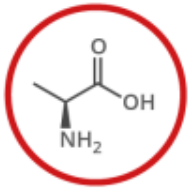
In multicellular organisms, the mRNA carries genetic code out of the cell nucleus, to the cytoplasm. Here, protein synthesis takes place. 'Translation' is the process of turning the mRNA's 'code' into proteins. Molecules called ribosomes carry out this process, building up proteins from the amino acids coded for.

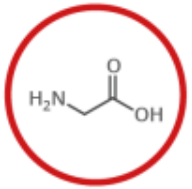
A GUIDE TO THE TWENTY COMMON AMINO ACIDS

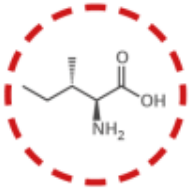
AMINO ACIDS ARE THE BUILDING BLOCKS OF PROTEINS IN LIVING ORGANISMS. THERE ARE OVER 500 AMINO ACIDS FOUND IN NATURE - HOWEVER, THE HUMAN GENETIC CODE ONLY DIRECTLY ENCODES 20. 'ESSENTIAL' AMINO ACIDS MUST BE OBTAINED FROM THE DIET, WHILST NON-ESSENTIAL AMINO ACIDS CAN BE SYNTHESISED IN THE BODY.

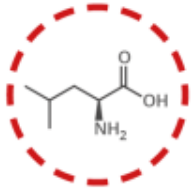
Chart Key: ALIPHATIC · AROMATIC · ACIDIC · BASIC · HYDROXYLIC · SULFUR-CONTAINING · AMIDIC · NON-ESSENTIAL · ESSENTIAL

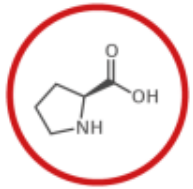


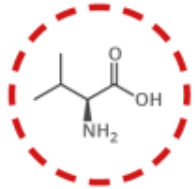

ALANINE A
Ala
GCT, GCC, GCA, GCG

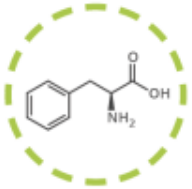

GLYCINE G
Gly
GGT, GGC, GGA, GGG

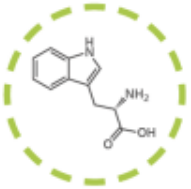

ISOLEUCINE I
Ile
ATT, ATC, ATA

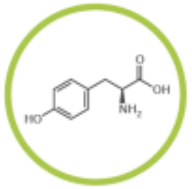

LEUCINE L
Leu
CTT, CTC, CTA, CTG, TTA, TTG

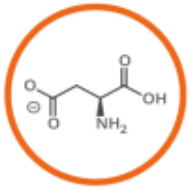

PROLINE P
Pro
CCT, CCC, CCA, CCG

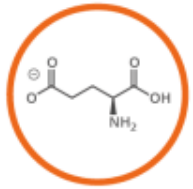

VALINE V
Val
GTT, GTC, GTA, GTG

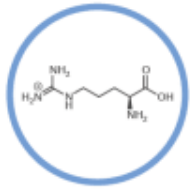

PHENYLALANINE F
Phe
TTT, TTC

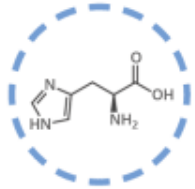

TRYPTOPHAN W
Trp
TGG

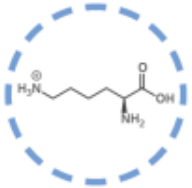

TYROSINE Y
Tyr
TAT, TAC

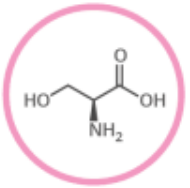

ASPARTIC ACID D
Asp
GAT, GAC

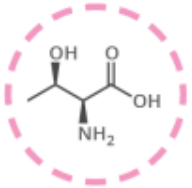

GLUTAMIC ACID E
Glu
GAA, GAG

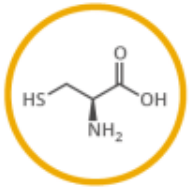

ARGININE R
Arg
CGT, CGC, CGA, CGG, AGA, AGG

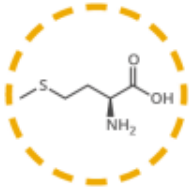

HISTIDINE H
His
CAT, CAC

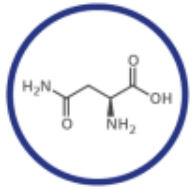

LYSINE K
Lys
AAA, AAG

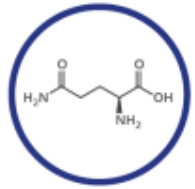

SERINE S
Ser
TCT, TCC, TCA, TCG, AGT, AGC


THREONINE T
Thr
ACT, ACC, ACA, ACG


CYSTEINE C
Cys
TGT, TGC

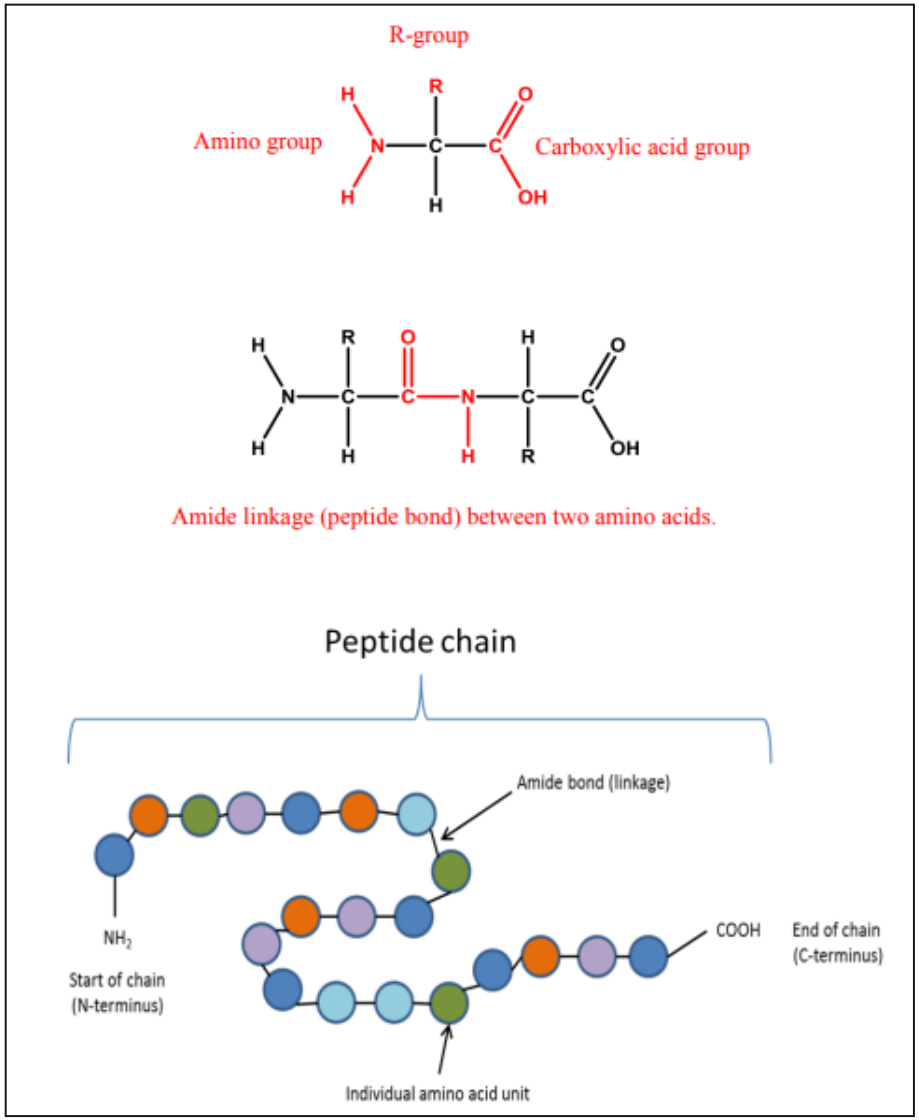

METHIONINE M
Met
ATG


ASPARAGINE N
Asn
AAT, AAC


GLUTAMINE Q
Gln
CAA, CAG

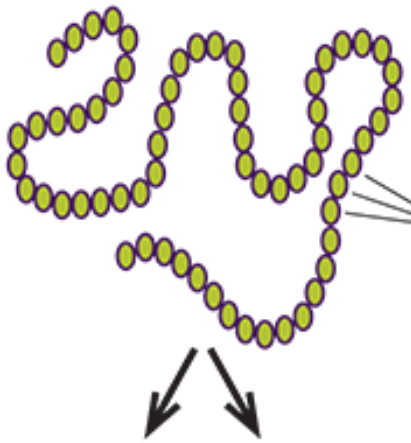
Note: This chart only shows those amino acids for which the human genetic code directly codes for. Selenocysteine is often referred to as the 21st amino acid, but is encoded in a special manner. In some cases, distinguishing between asparagine/aspartic acid and glutamine/glutamic acid is difficult. In these cases, the codes asx (B) and glx (Z) are respectively used.

Proteins are Sequences of Connected Amino Acids



OPCW

Proteins are Sequences of Connected Amino Acids



Primary protein structure
is sequence of a chain of amino acids.

Amino Acids

Pleated sheet

Alpha helix

Secondary protein structure
occurs when the sequence of amino acids are linked by hydrogen bonds.

Pleated sheet

Alpha helix

Tertiary protein structure
occurs when certain attractions are present between alpha helices and pleated sheets.

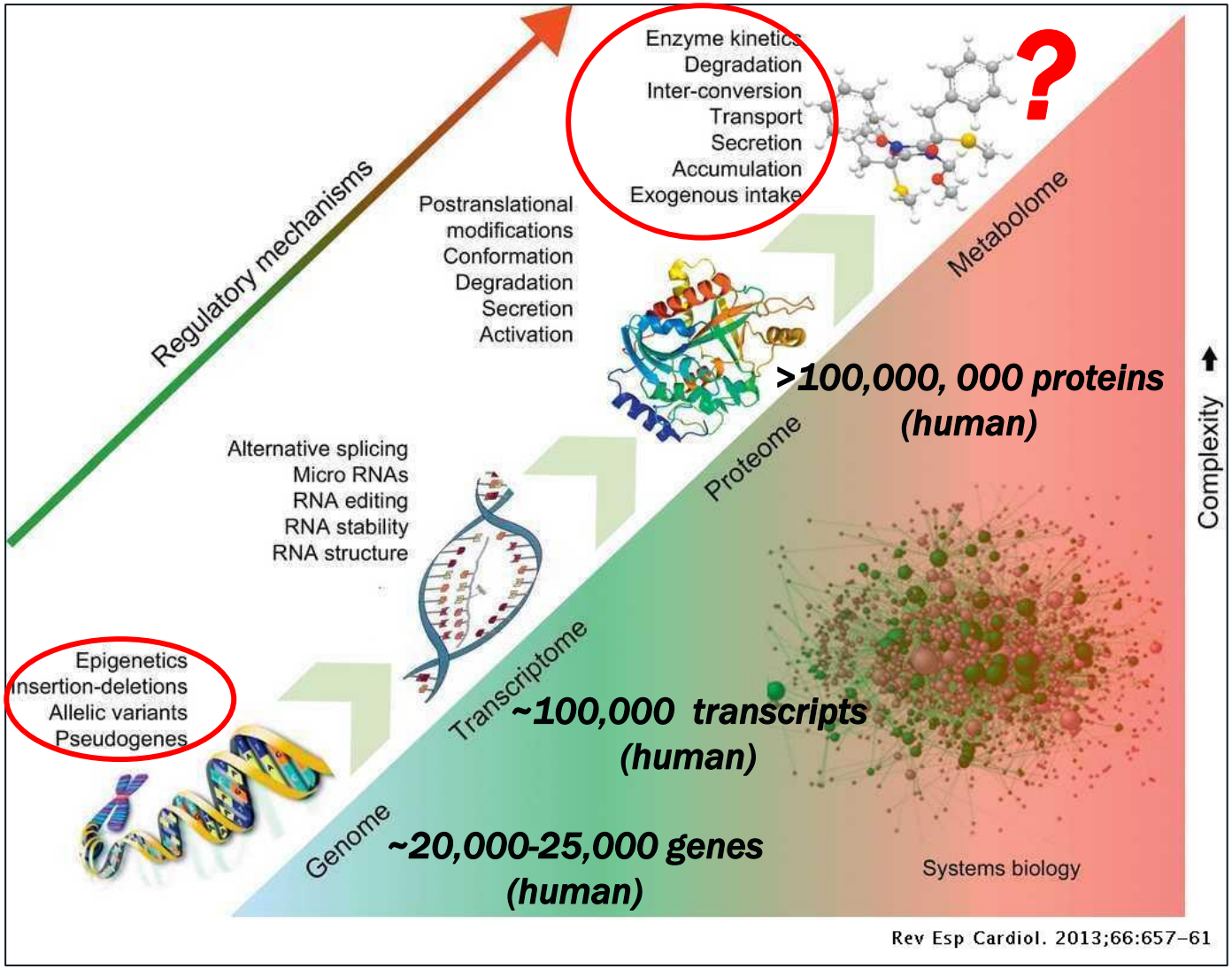
"Molecular Machines"
(these perform biological functions)

Quarternary protein structure
is a protein consisting of more than one amino acid chain.

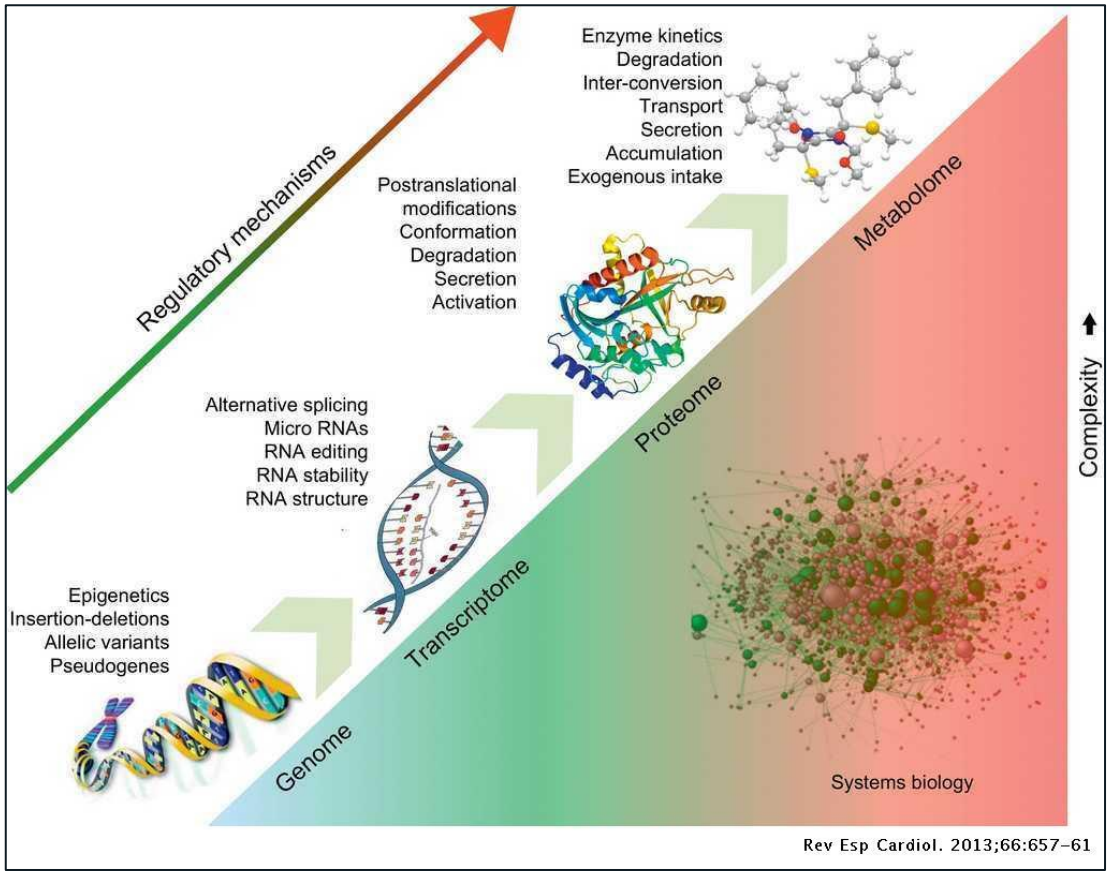
Proteins are Sequences of Connected Amino Acids

To Help Understand This, We Built a Model…

Living Systems Enjoy Broad Molecular Diversity



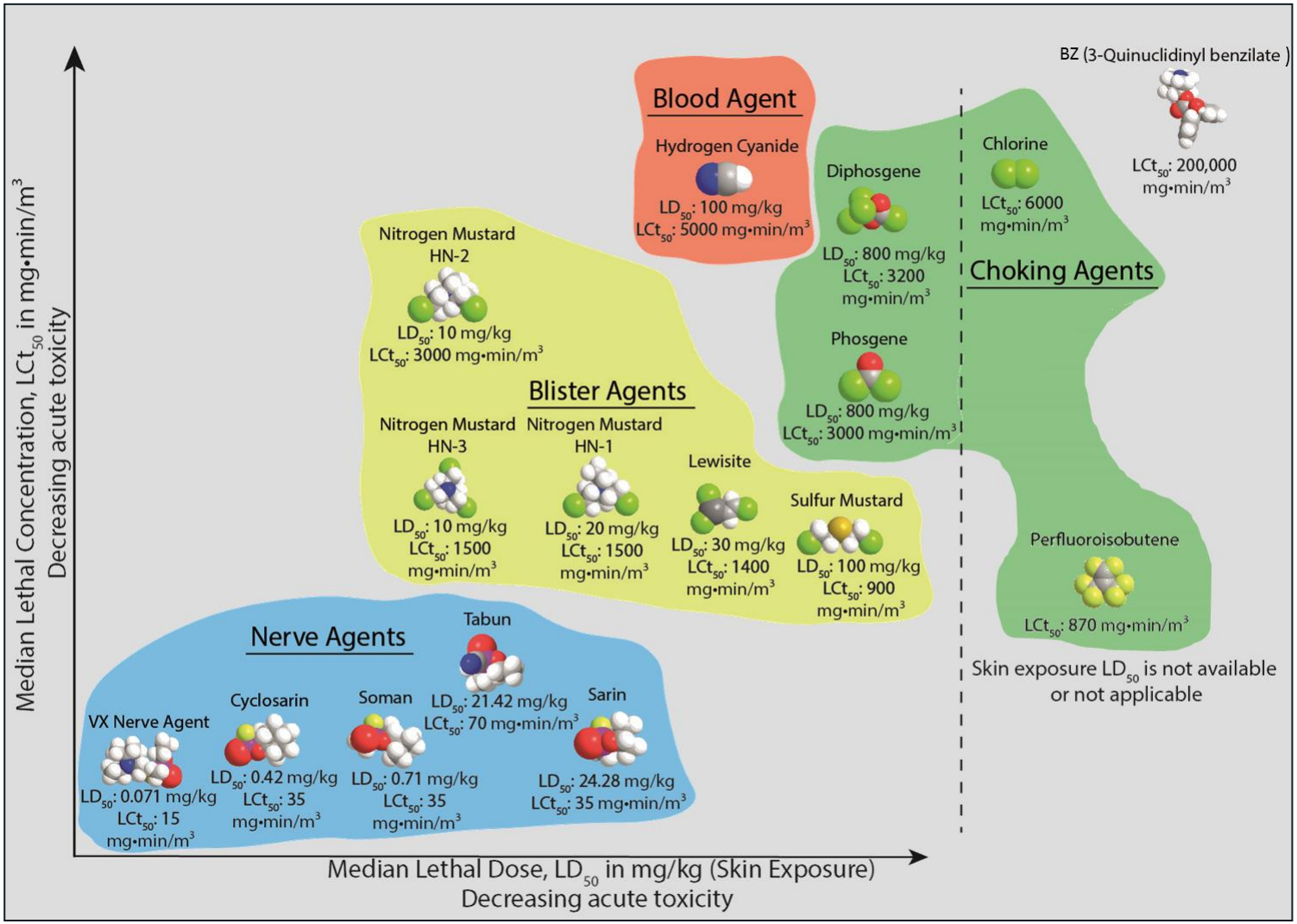
Living Systems Enjoy Broad Molecular Diversity



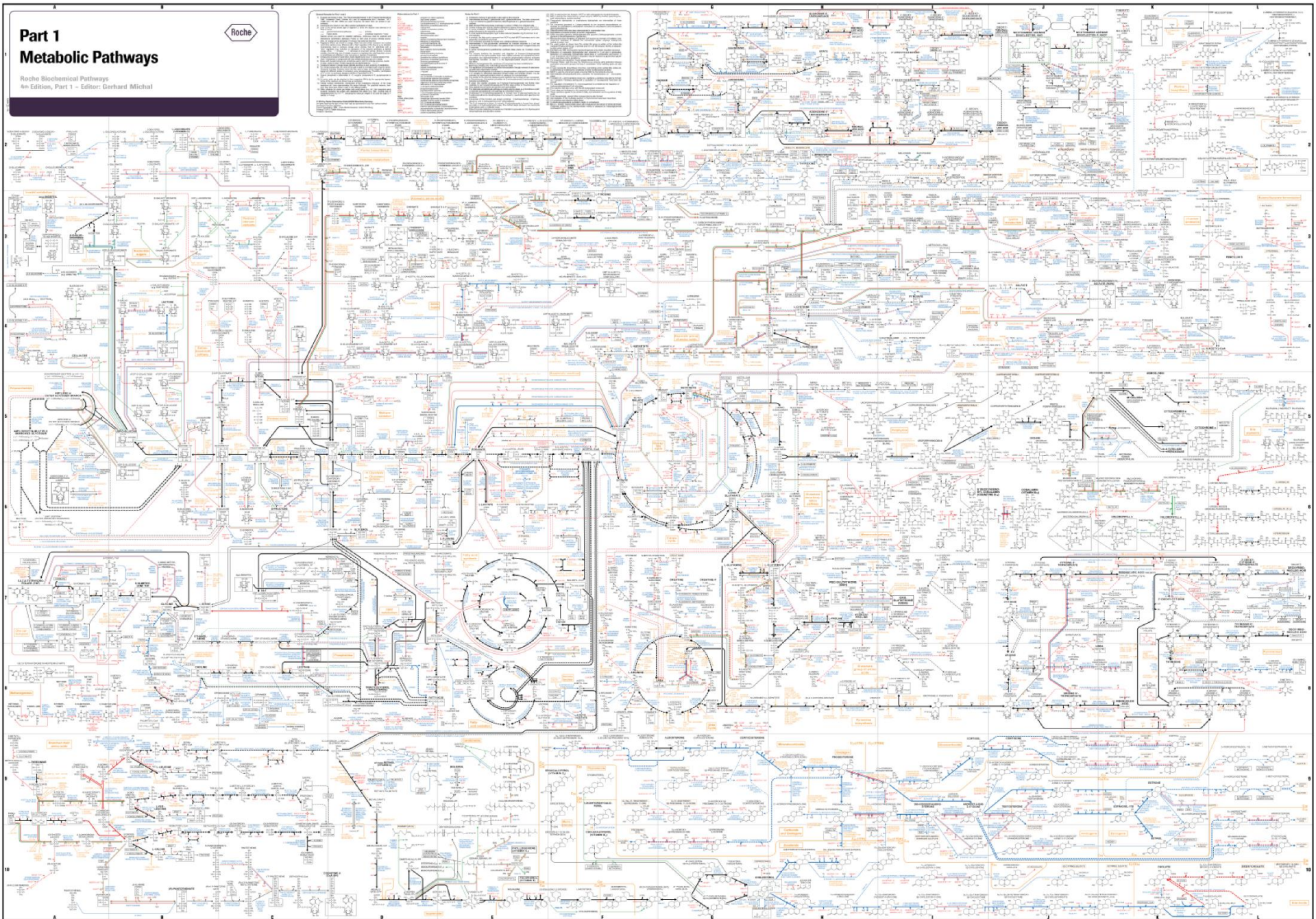
Biological systems are very complicated…
(a system of simultaneous and interacting processes)

Toxic chemicals can interfere with a multitude of life processes, and these can impact other life processes through interference in a "different" part of the "system"

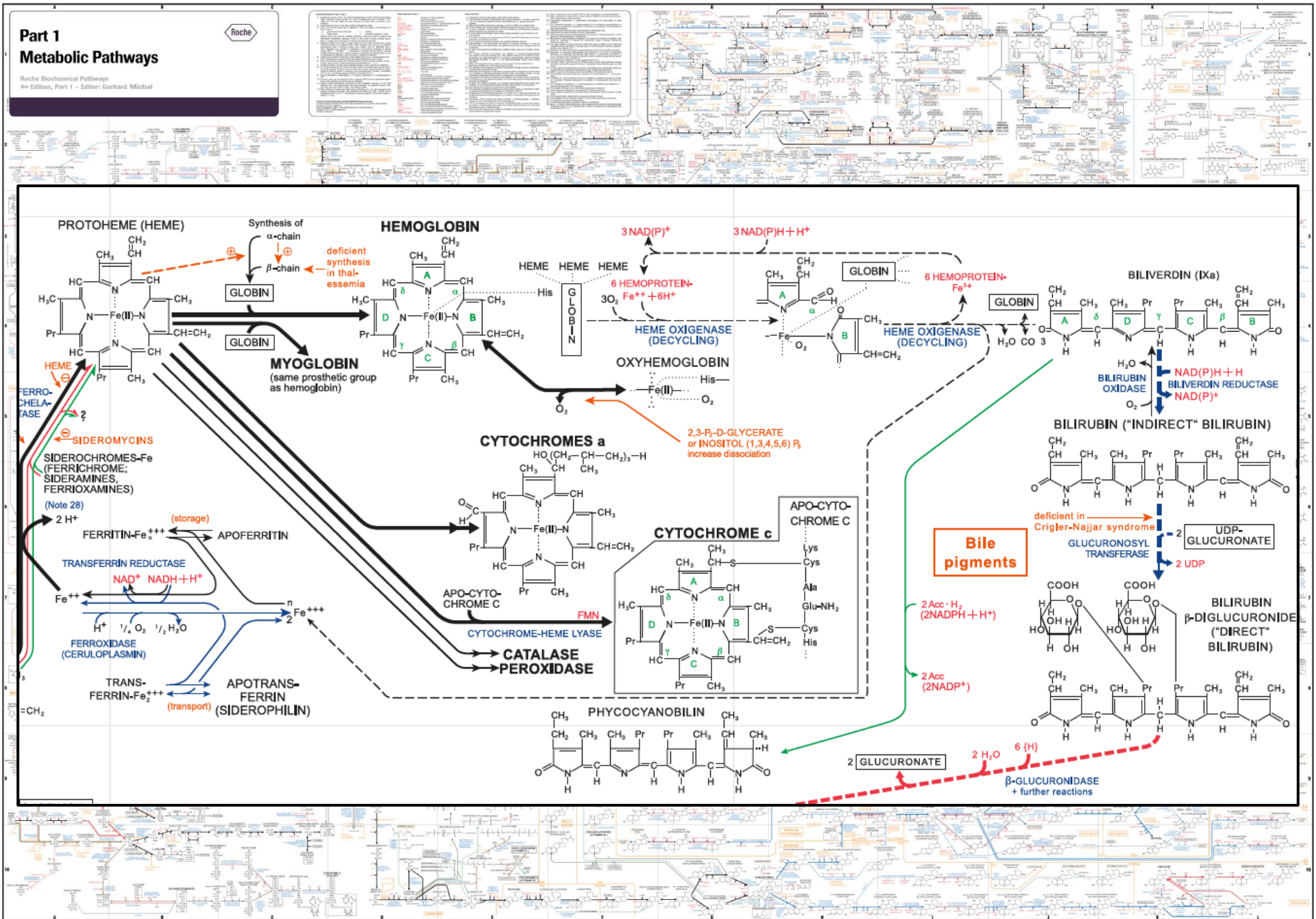
Why are Some Chemicals are “More Toxic” Than Others



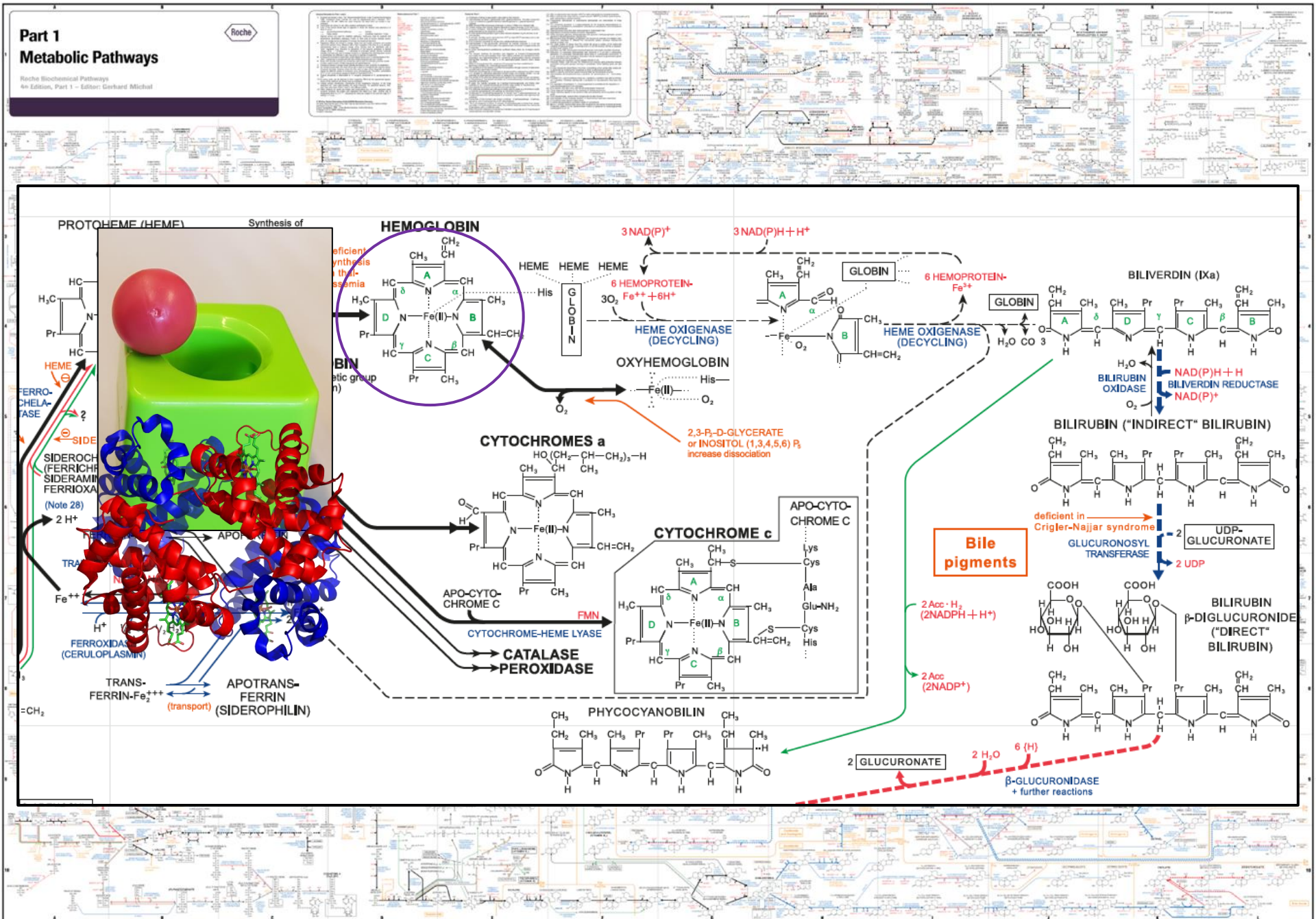
Chemical Action on Life Processes: Some Examples



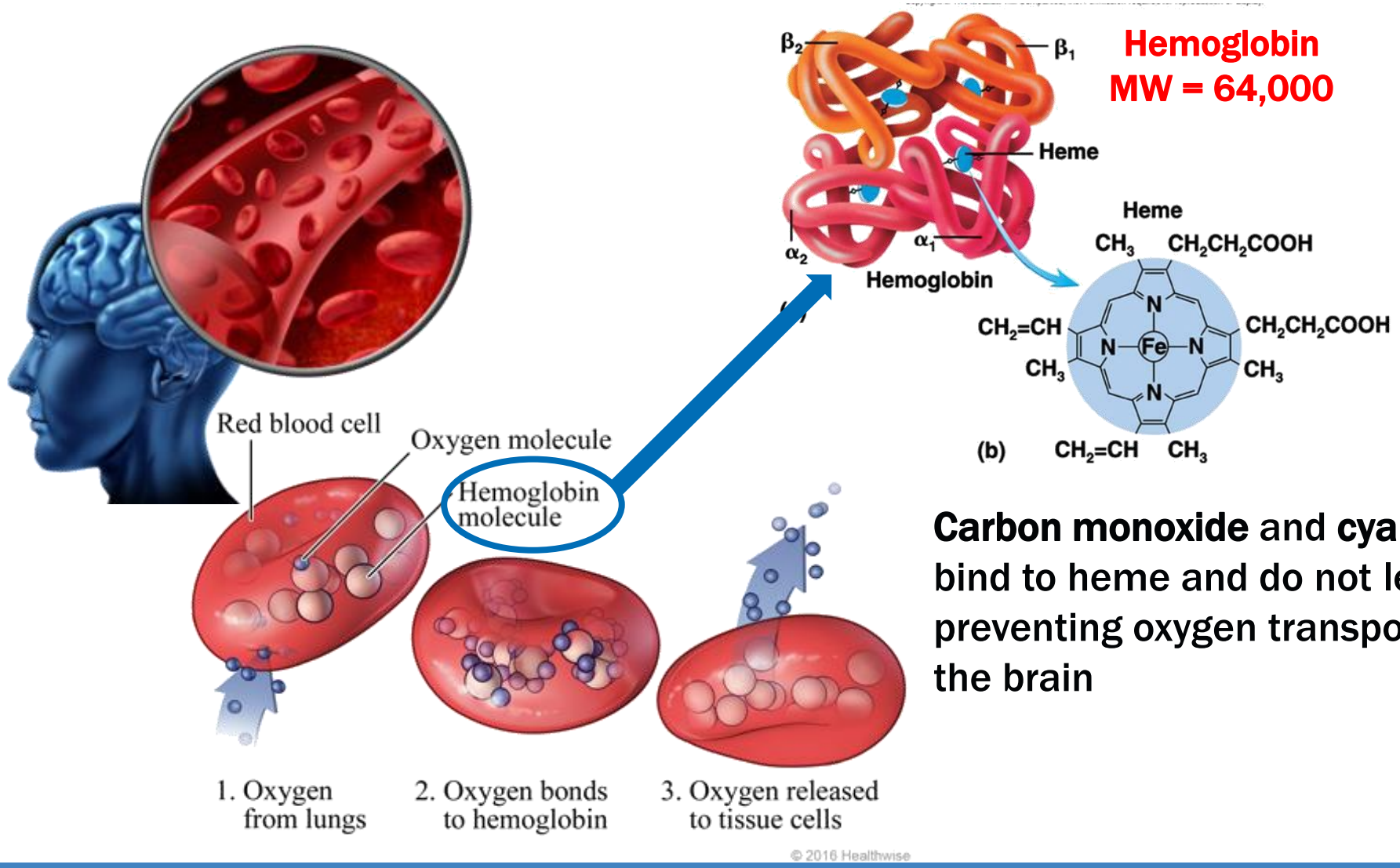
Chemical Action on Life Processes: Some Examples



Chemical Action on Life Processes: Some Examples



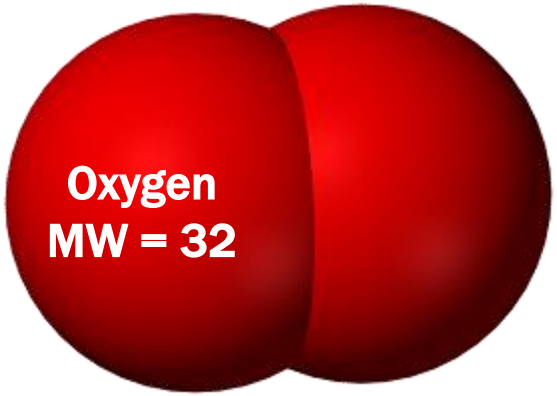
Bringing Oxygen to the Brain

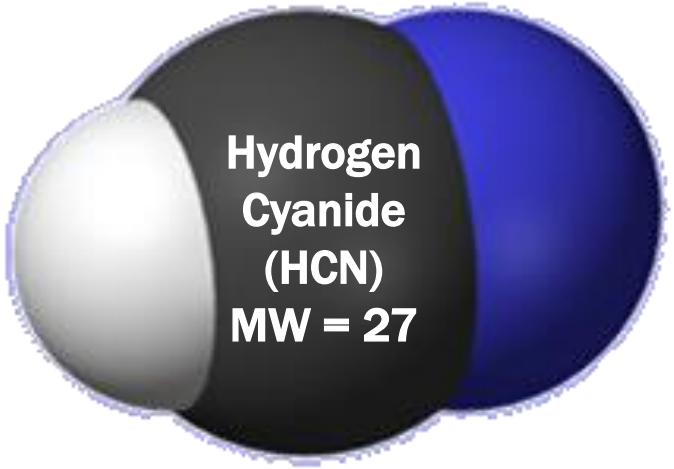


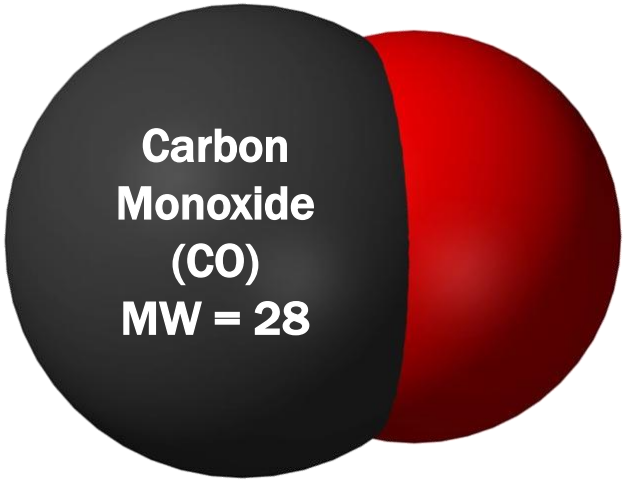
Hemoglobin
MW = 64,000

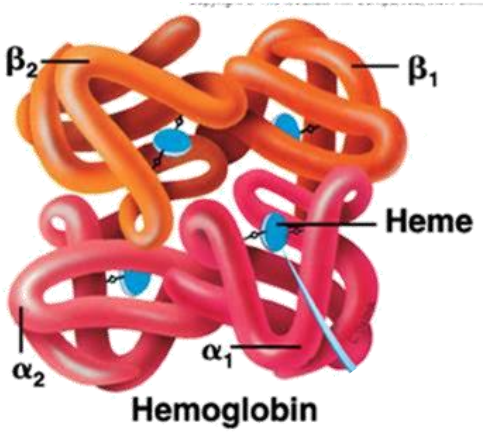
Carbon monoxide and **cyanide** bind to heme and do not let go, preventing oxygen transport to the brain

Bringing Oxygen to the Brain





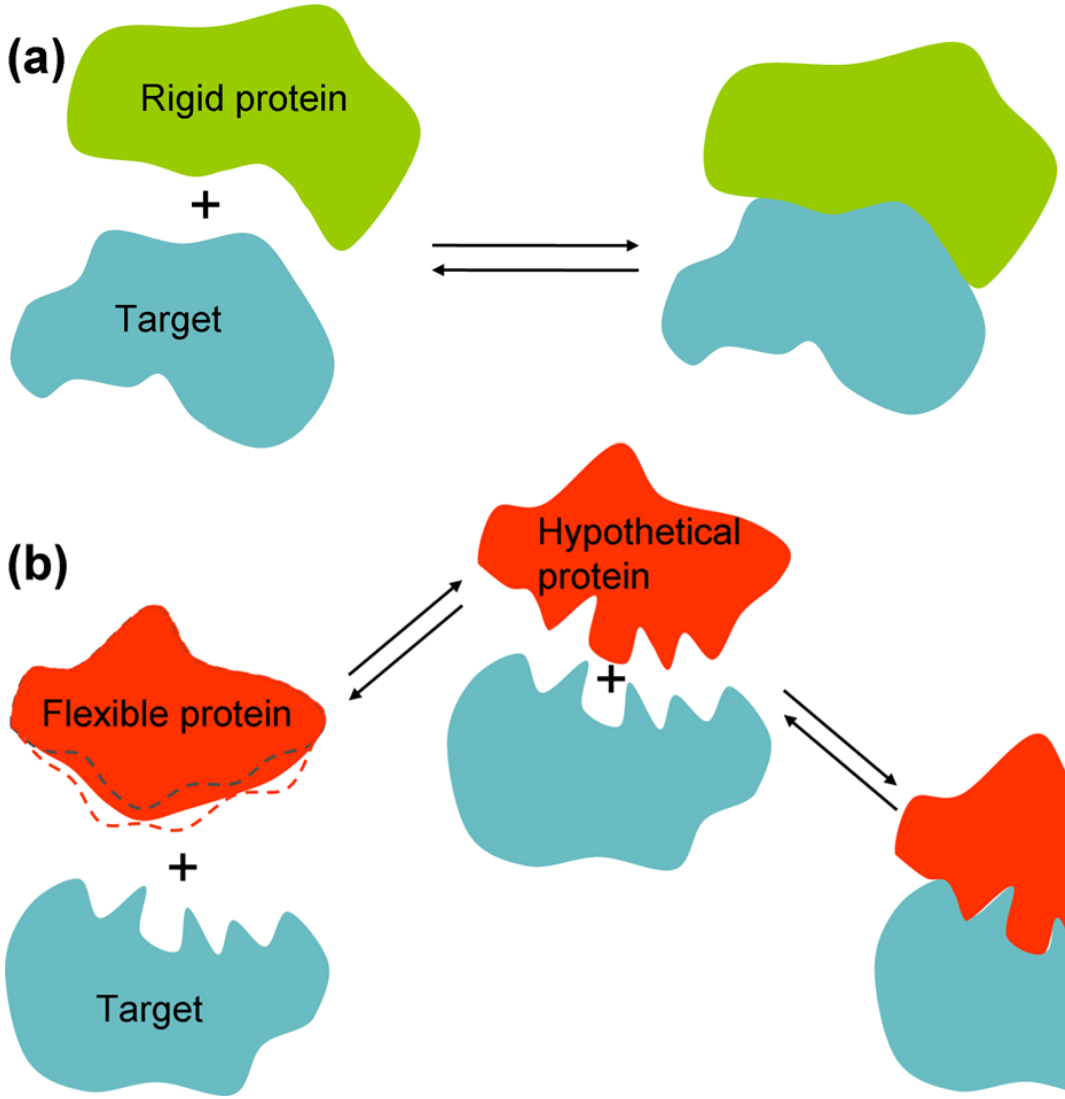




Hemoglobin
MW = 64,000

Toxic chemicals, ~ 2,000 times smaller than the hemoglobin transporter protein, shut down a vital life process

Molecule to Molecule Interactions

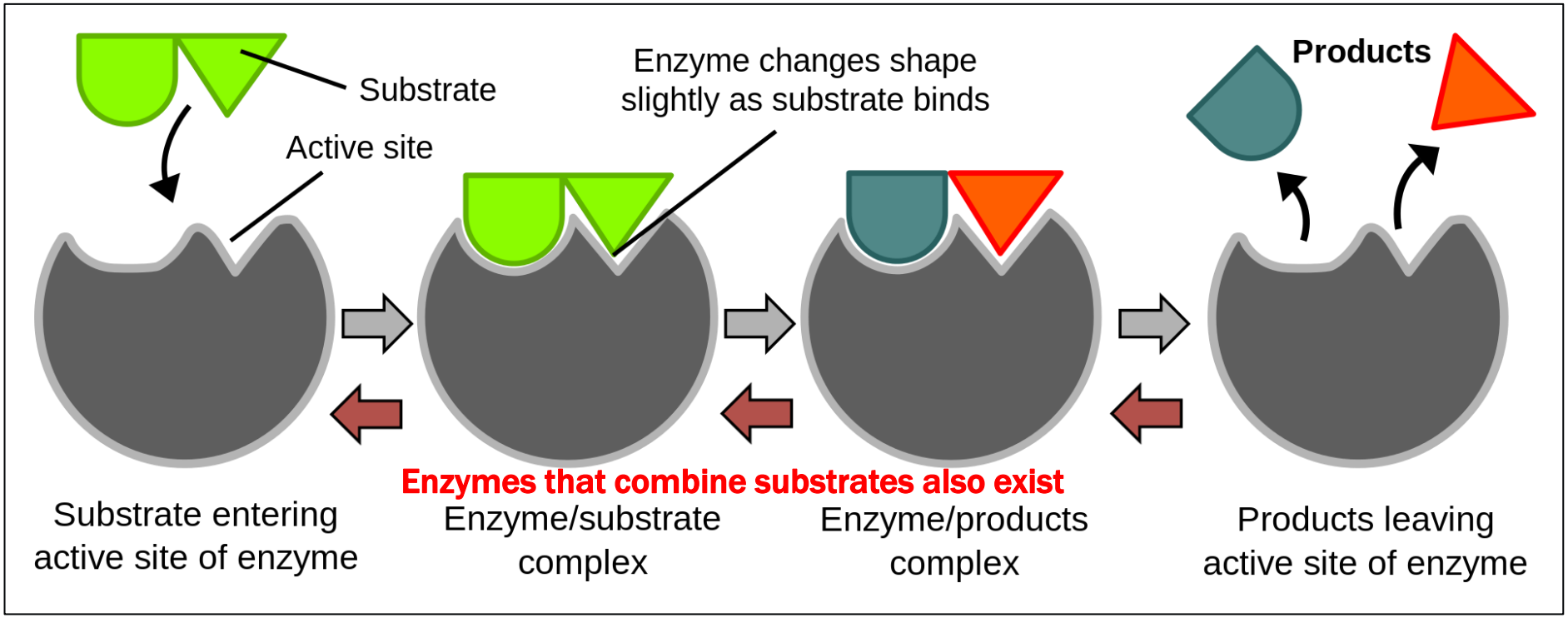


High Affinity
High Specificity

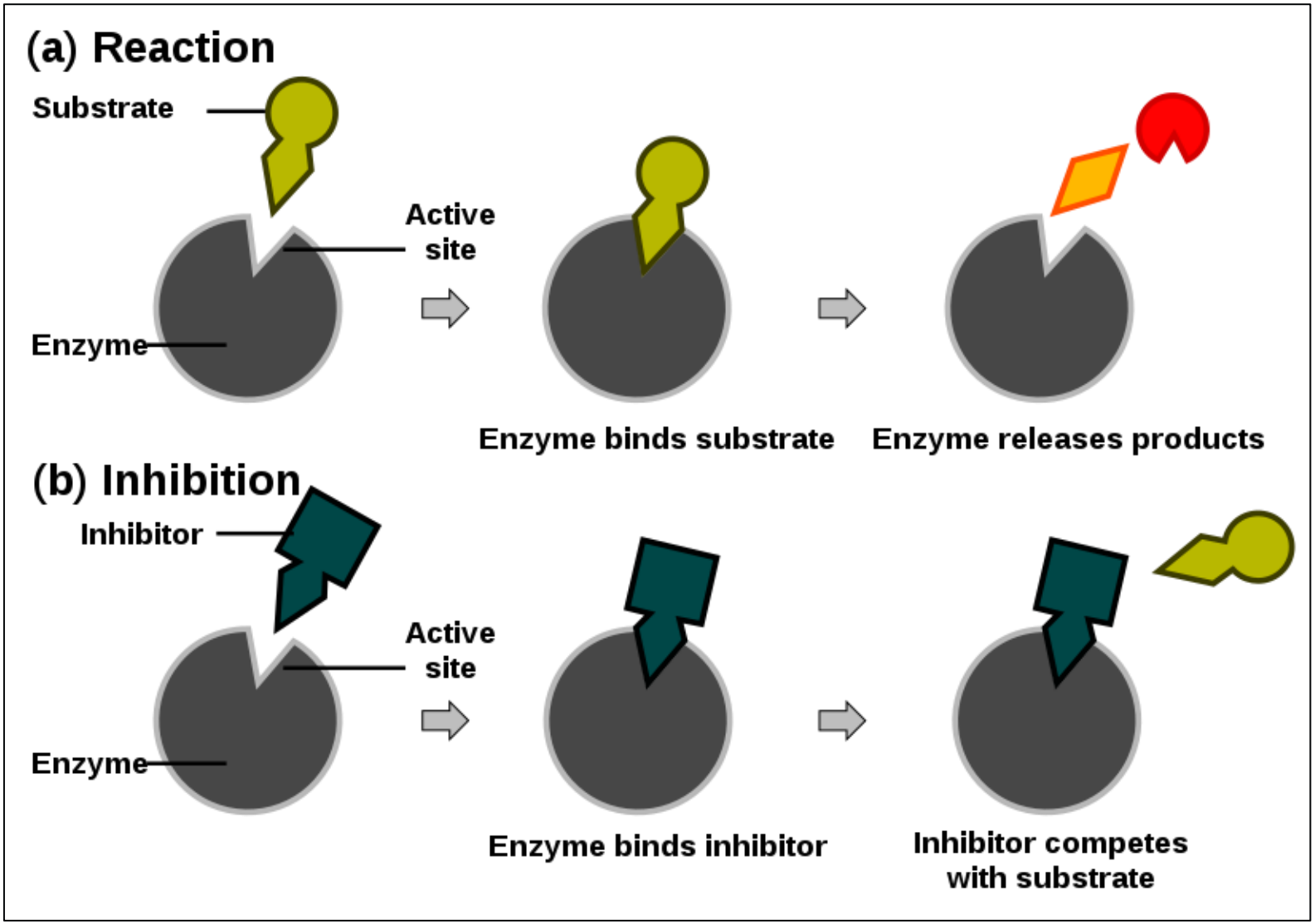
Low Affinity
High Specificity

Zhou, 2011; DOI:10.1016/j.tibs.2011.11.002

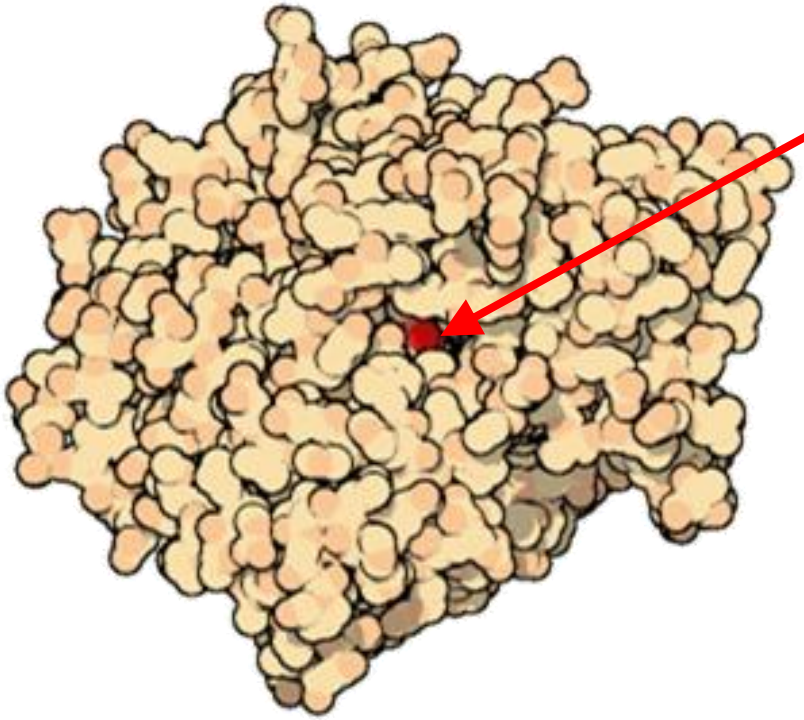
Molecule to Molecule Interactions



Enzyme Inhibition: “Turning off a Life Process”

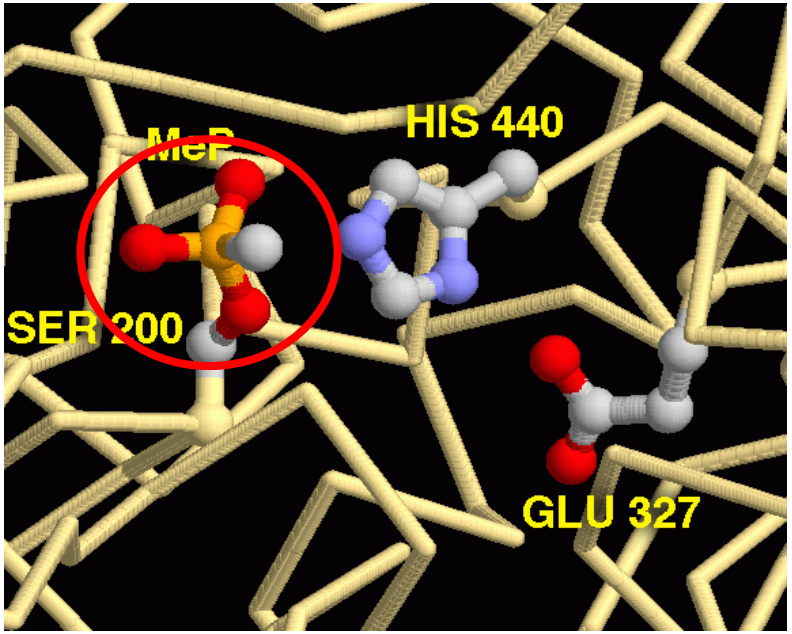


In Addition to Size and Shape – Chemical Functional Groups Still Matter



Binding pocket

Sarin adduct

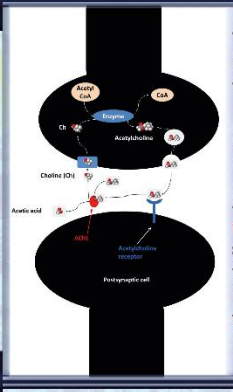


From PDB Molecule of the Month, 2004
https://pdb101.rcsb.org/motm/54

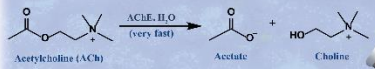
Acetylcholinesterase Inhibition

created by Sofía Sola Sancho and Maria Hemme

Acetylcholinesterase

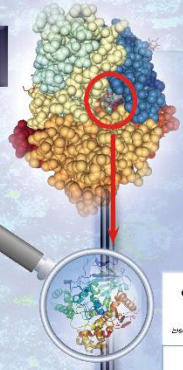


The primary **toxicity** of organophosphorus nerve agents results from the **inhibition** of the **enzyme Acetylcholinesterase (AChE)**.



AChE is responsible for breaking down the **neurotransmitter acetylcholine (ACh)**. This switches a nerve signal from on to off. If the enzyme is **inhibited**, ACh **accumulates** in the synapse and the signal **continues to transmit**.

Figure 1: Life Cycle of ACh.



Binding Site

The AChE **active site** is buried deep within the enzyme. It contains three amino acid residues **crucial for catalytic activity**: serine 200, histidine 440 and glutamate 327. The nerve agent binds to **serine 200**.

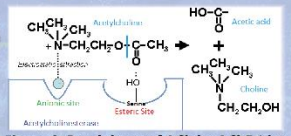


Figure 2: Breakdown of ACh by AChE (the normal function of the enzyme).

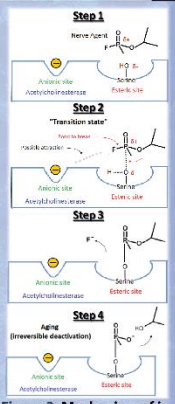
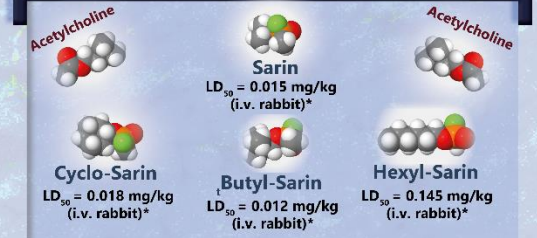
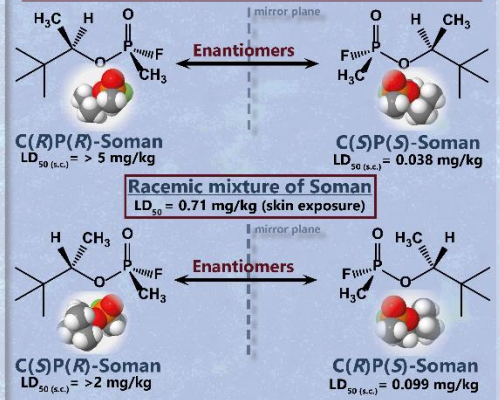


Figure 3: Mechanism of inhibition of AChE by Sarin.

Nerve Agent Molecular Shape and Size



Toxicity of an organophosphorus nerve agent depends on the ability to access the AChE binding site. **Size**, **shape** and **hydrophobicity** of the nerve agent exerts an effect. As alkyl substituents increase in size and degrees of freedom, toxicity decreases.



The **spatial orientation** (shape) of the molecule also matters, as illustrated by toxicity differences across the four stereoisomers of Soman.

* Black, R. M., & Harrison, J. M. (2009). The Chemistry of Organophosphorus Chemical Warfare Agents. PATAI'S Chemistry of Functional Groups. doi:10.1002/9780470682531.pat0070

Effects and Symptoms

Inhibition of AChE in muscarinic synapses (neuromuscular system) induces **cholinergic crisis**. Nicotinic synapses (central nervous system, e.g. brain) are also effected.

Symptoms include **sweating**, **salivation**, **miosis (pinpoint pupils)**, **paralysis**, **respiratory failure**, **seizures** and eventually **death**.

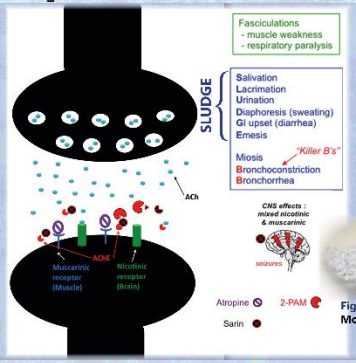
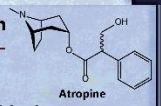


Figure 4: Inhibition of AChE by Sarin and Treatment with Atropine and 2-PAM.

Treatment

Atropine blocks the action of ACh at **muscarinic receptors** and treats **SLUDGE**.



Oximes such as **2-PAM** (pralidoxime) can reactivate inhibited AChE, but only before the aging process.
(Fig. 3, Step 3)

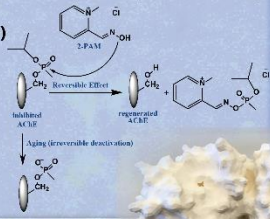


Figure 5: printed 3D Model of AChE

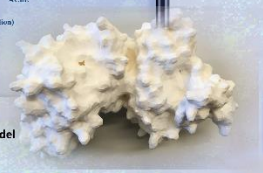
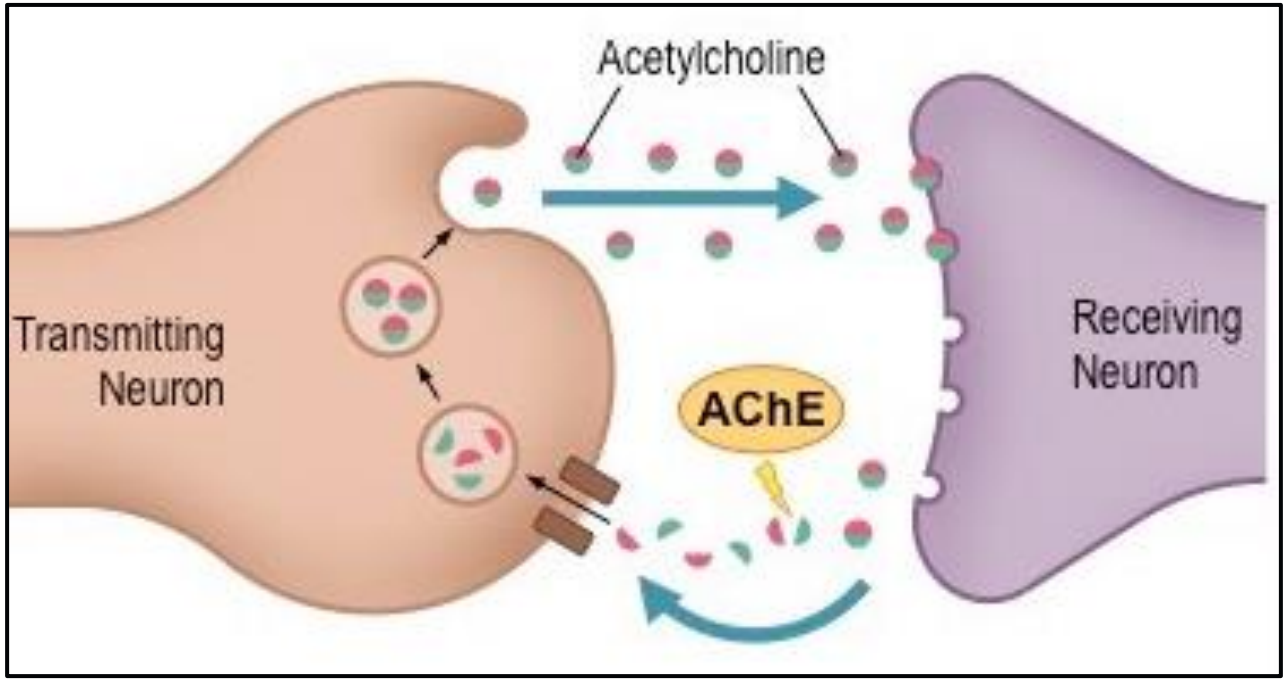
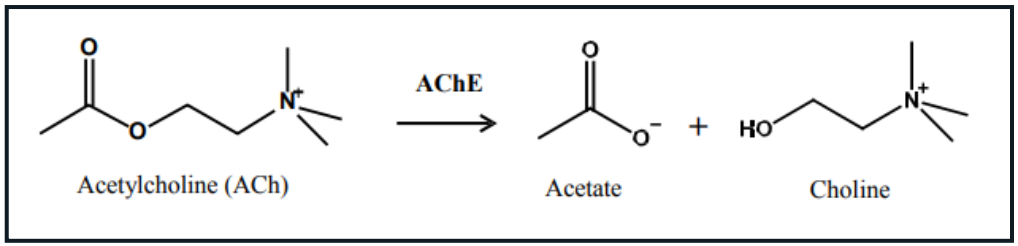


Figure 6: printed 3D Model of the AChE surface

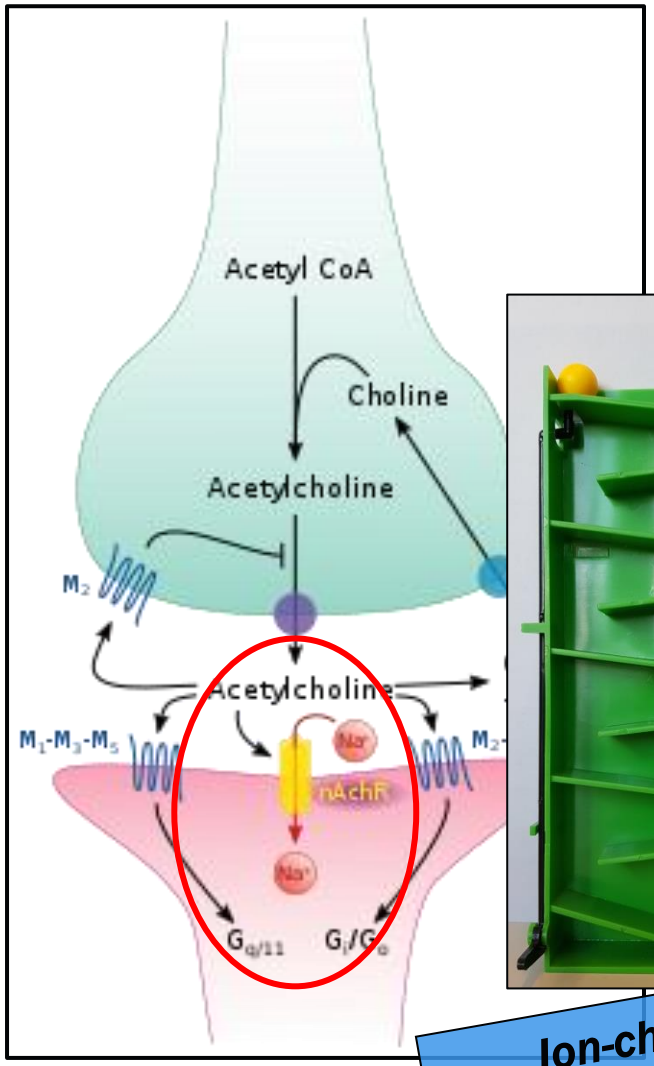
Normal Nerve Function



AChE = acetylcholinesterase

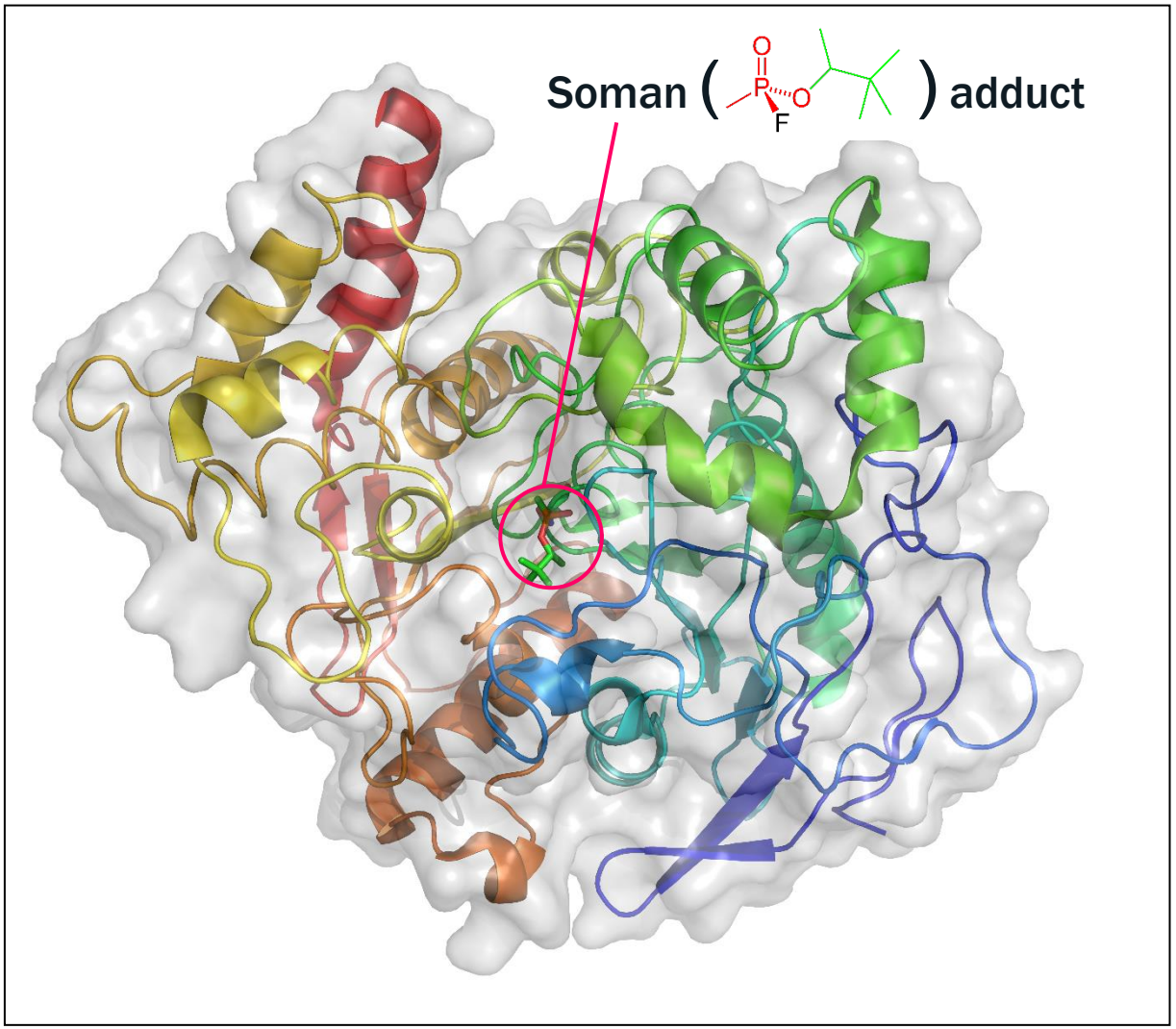


When Nerve Agent Inhibits Acetylcholinesterase

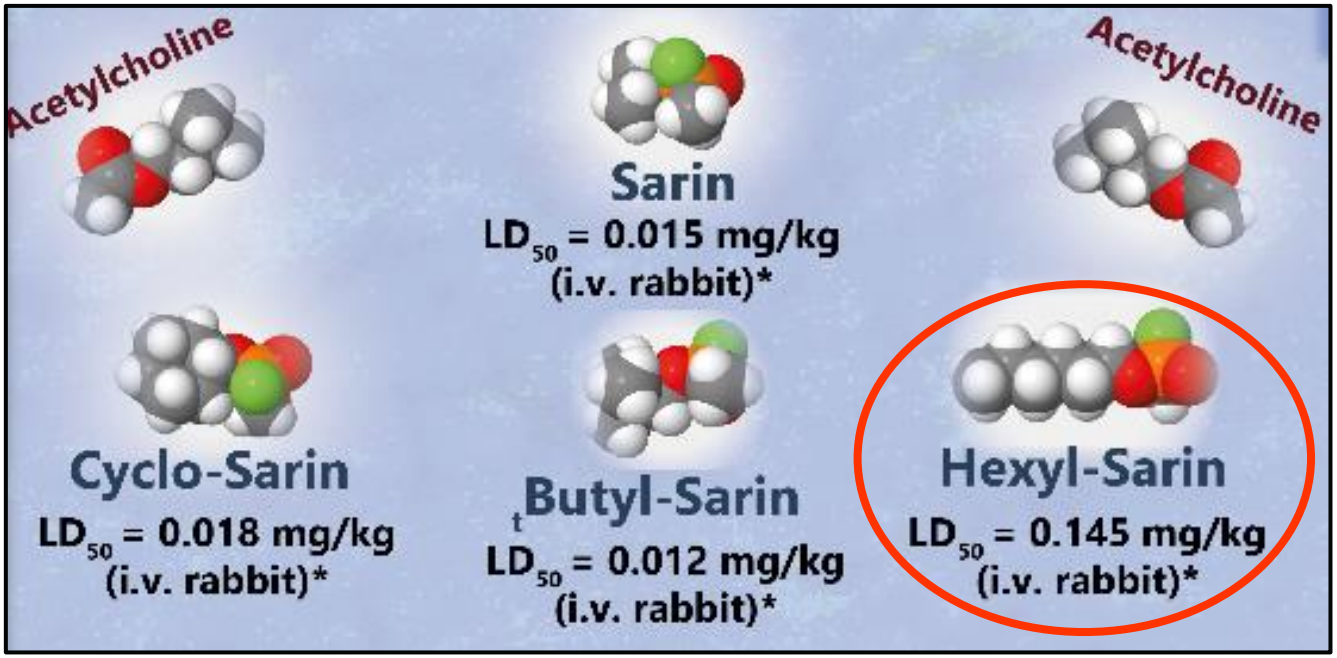


Ion-channel continually open: activates a cascade of "life processes"

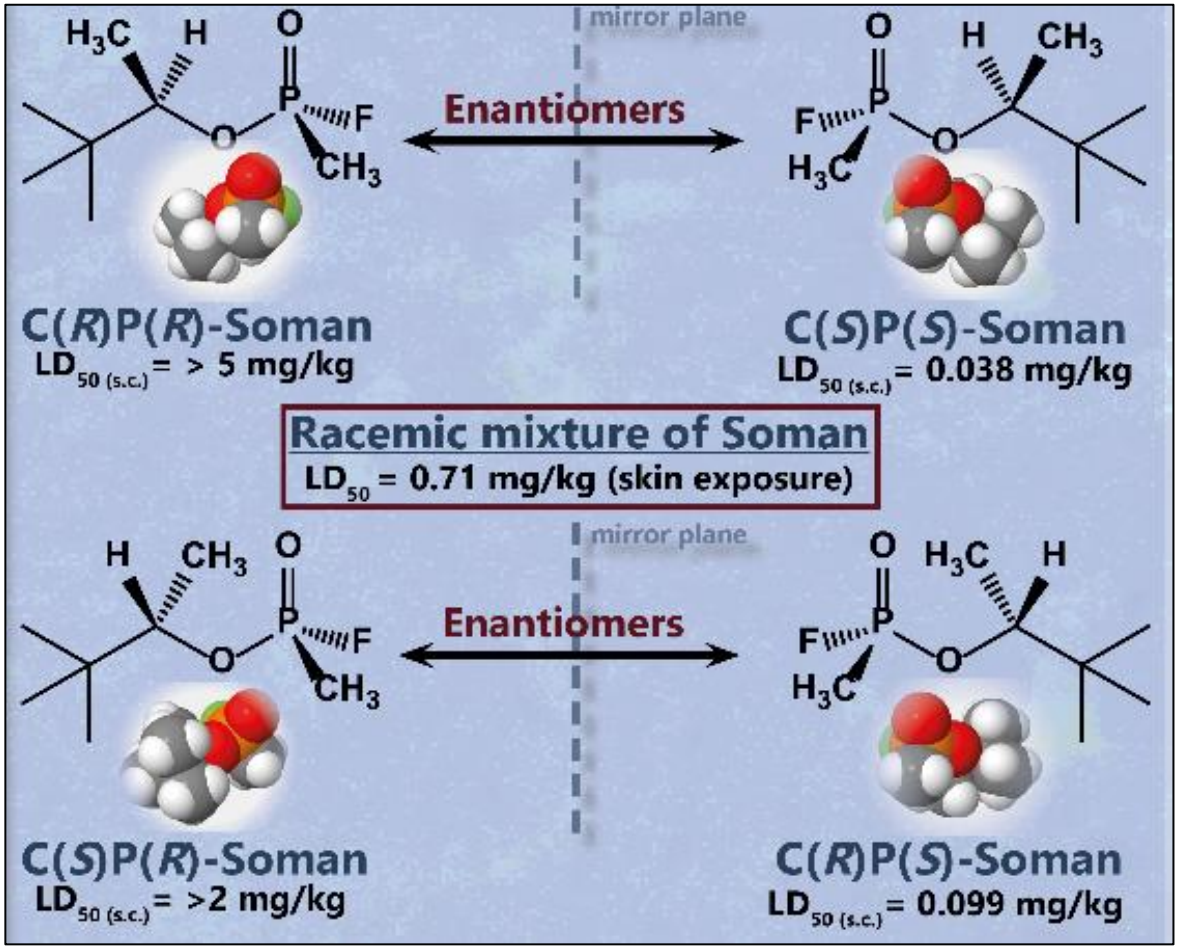
Acetylcholinesterase Inhibition: Nerve Agent Size, Shape and Orientation



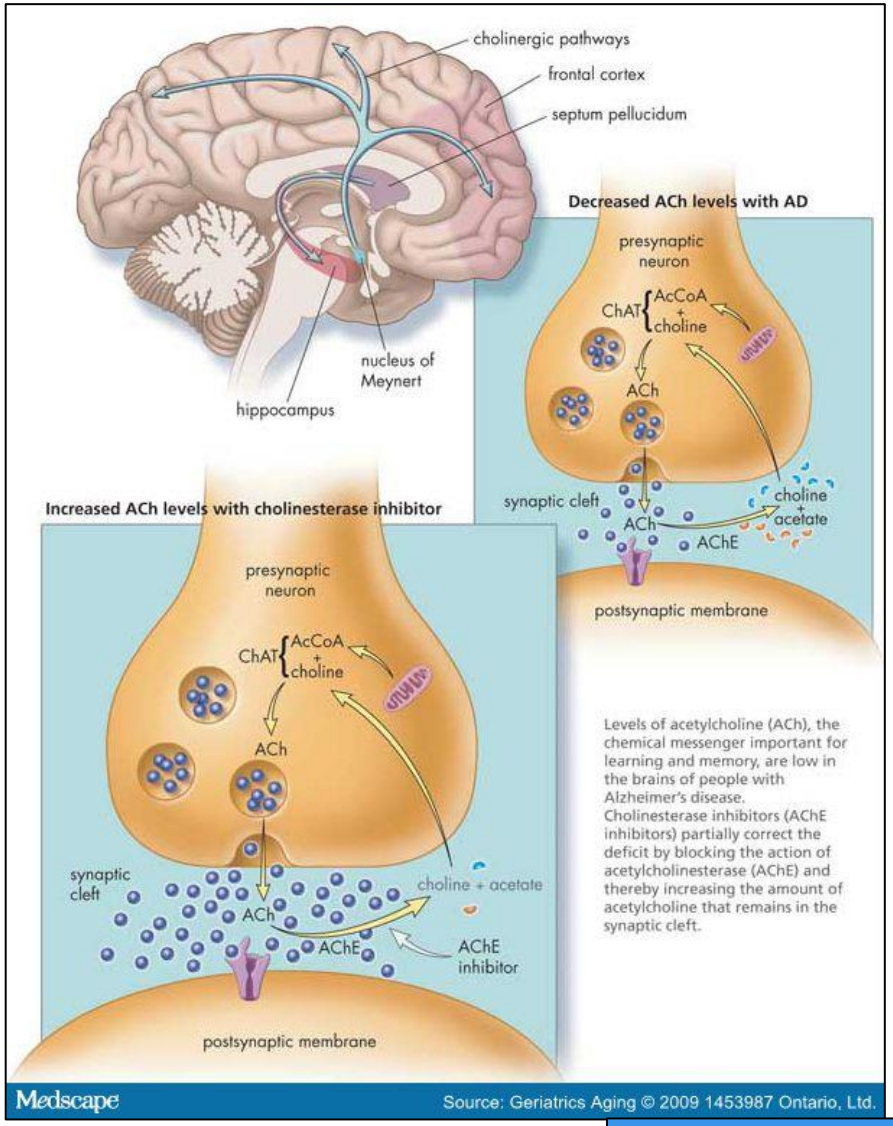
Acetylcholinesterase Inhibition: Nerve Agent Size, Shape and Orientation



Acetylcholinesterase Inhibition: Nerve Agent Size, Shape and Orientation



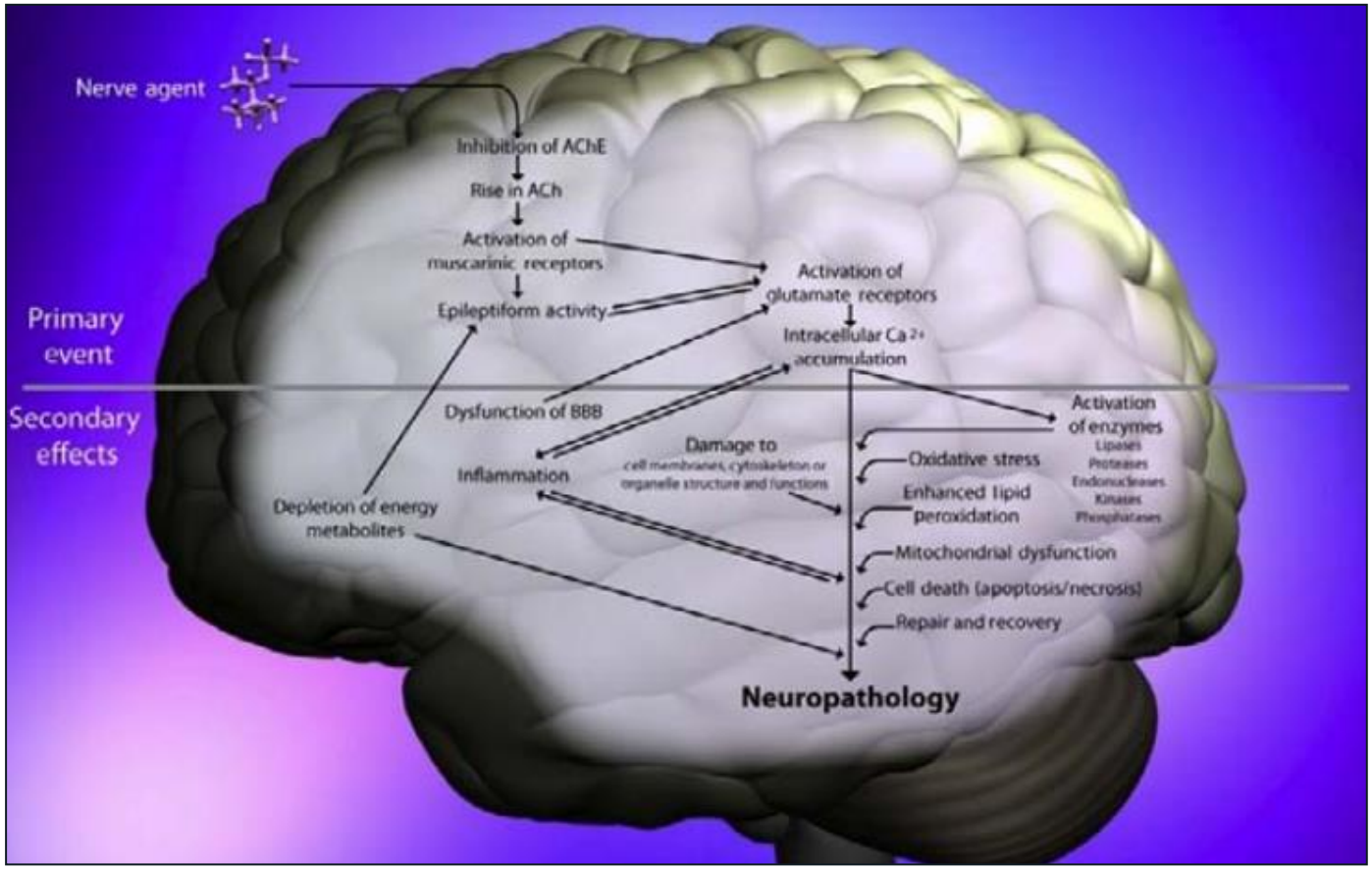
Acetylcholinesterase is also Found in the Brain...



OPCW

AChE inhibitors are used in the treatment of Alzheimer's Disease!
(but not Scheduled "nerve agents")

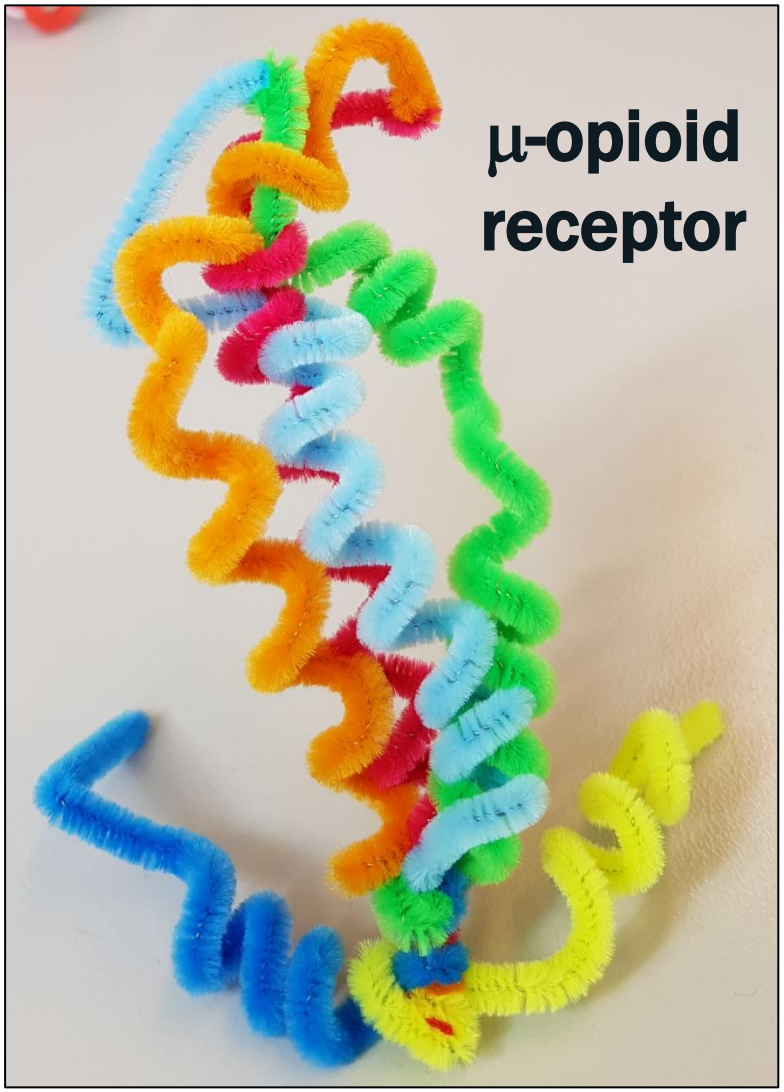
Acetylcholinesterase is also Found in the Brain…



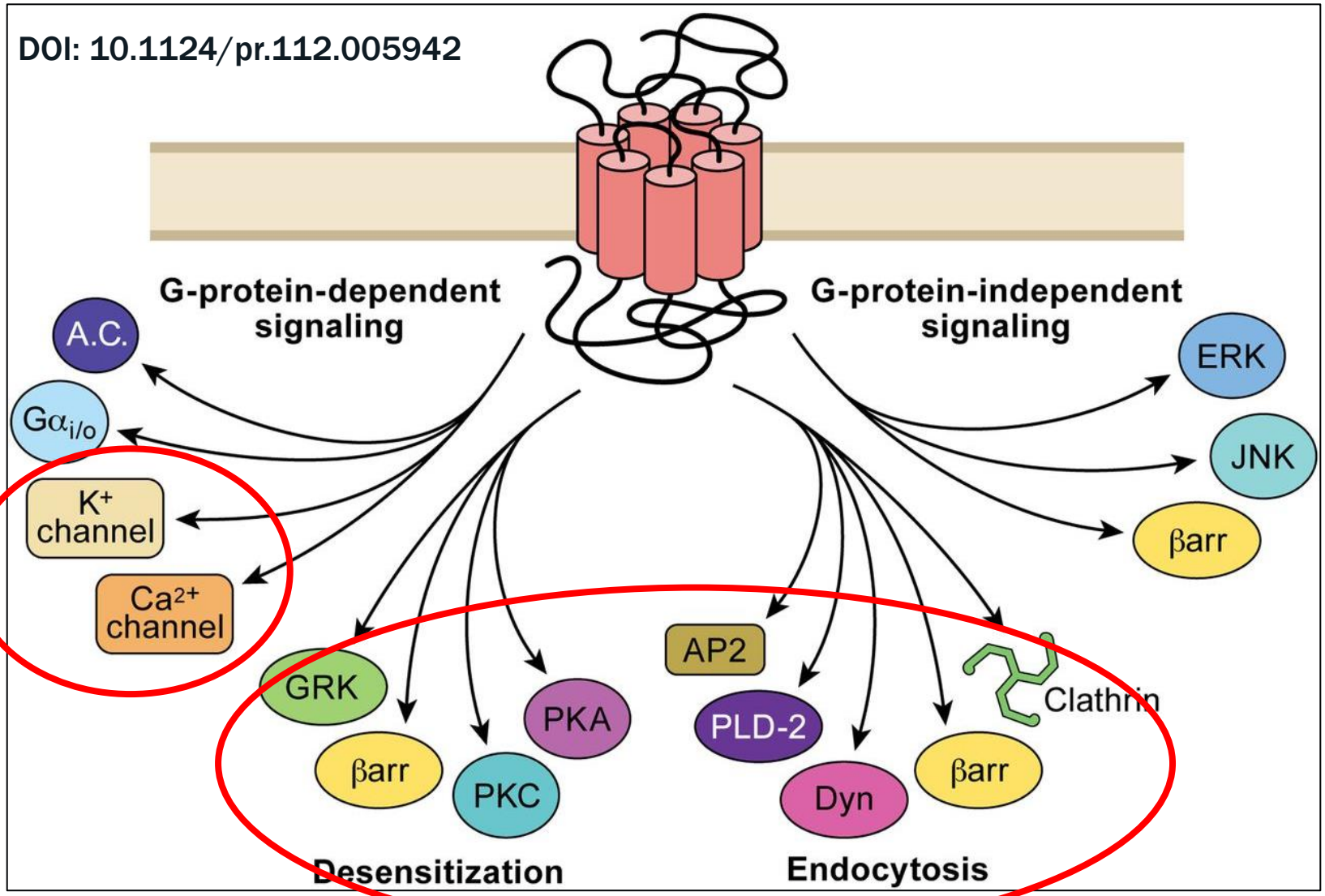
Interference with life processes in the brain

nerve agent exposure can lead to long-term post-exposure neurological conditions

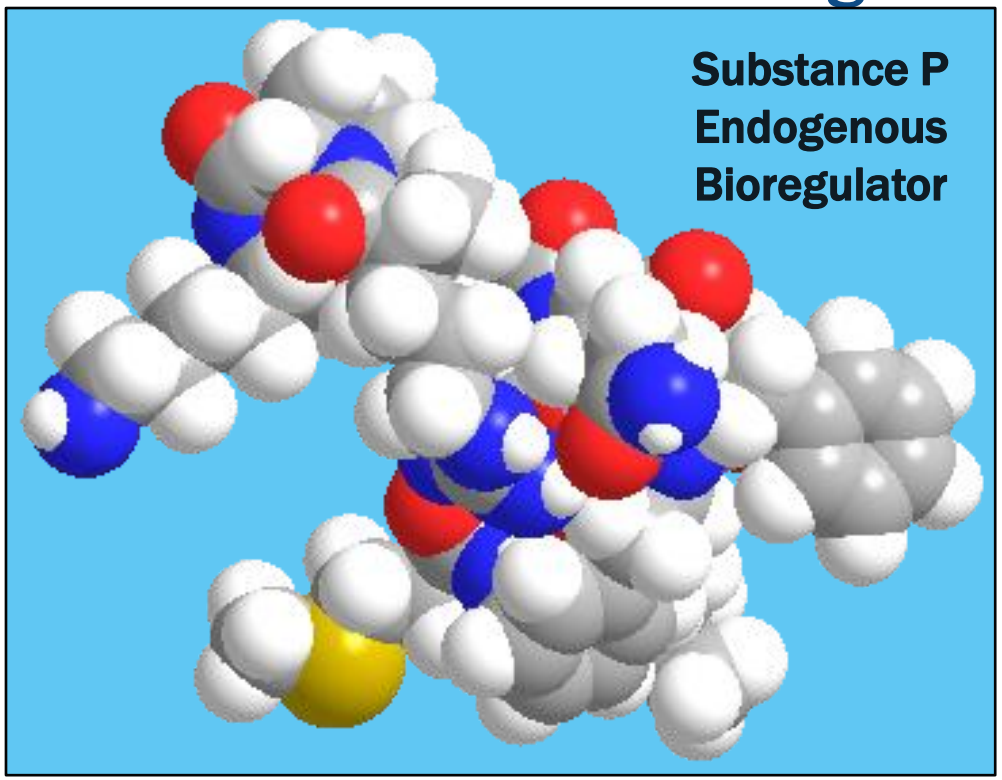
Modulating Pain Response

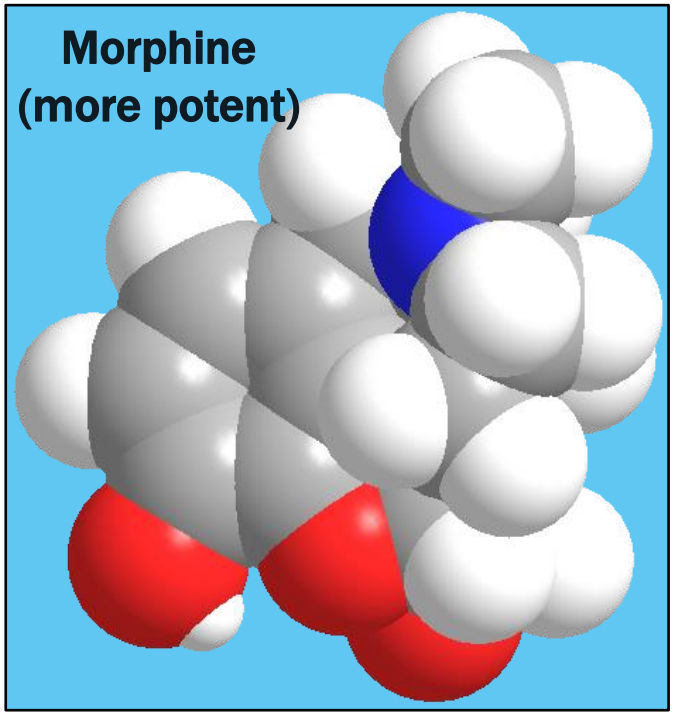


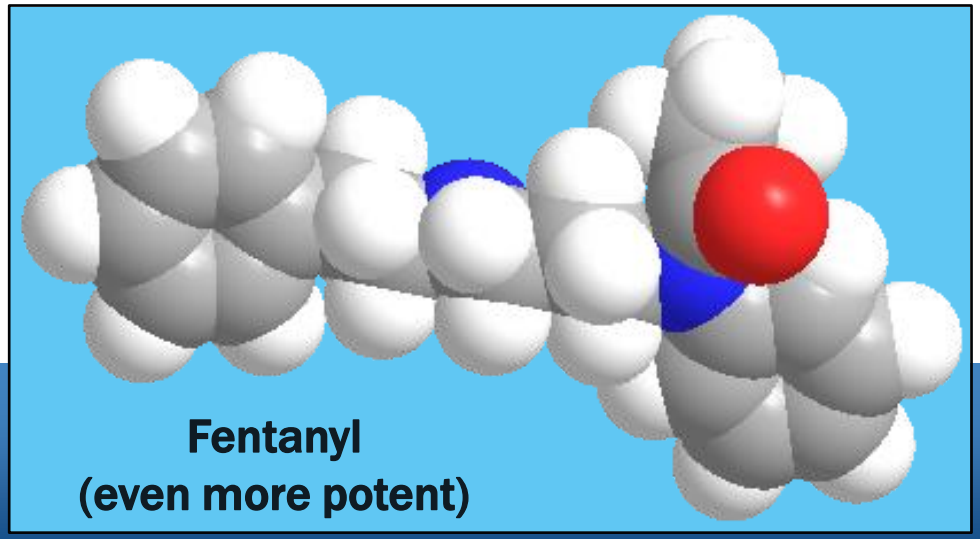
Modulating Pain Response



Modulating Pain Response







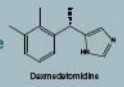
Central Nervous System (CNS)-Acting Chemicals

by Sofia Sola Sancho, Maria Hemme and Ayah wafi
Office of the Science Policy Advisor

Toxic chemicals that target the central nervous system (CNS). These chemicals can act as anaesthetics, sedatives, and analgesics. Specific CNS-acting chemicals discussed in the context of the Chemical Weapons Convention have included α2-adrenergic receptor agonists, inhaled anaesthetics, fentanils and the Schedule 2A.03* chemical BZ.

α2-adrenergic receptor agonist examples

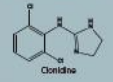
Dexmedetomidine



Mechanism of action:

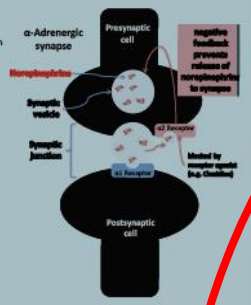
- Presynaptic activation of the α2-adrenoceptor, inhibiting norepinephrine release, preventing entry of the neurotransmitter into the synaptic junction (negative feedback).
- Postsynaptic activation of the α1-adrenoceptor
- inhibiting sympathetic activity. This results in decreased blood pressure and heart rate.
- Produces analgesic, sedative, and anxiolytic effects.
- Occupational exposure band (OEB) 5: control exposure to < 1 µg/m³.

Clonidine



Mechanism of action:

- Reduces release of noradrenaline at both central and peripheral sympathetic nerve terminals.
- Produces dose-related sedation, analgesia and anxiolysis.
- A reduction in the effective dose of other anaesthetic agents and opioids is also observed.
- LC_{50} (rat inh): 19.7 mg/m³/4 Hours
- LD_{50} (rat i.v.): 29 mg/kg

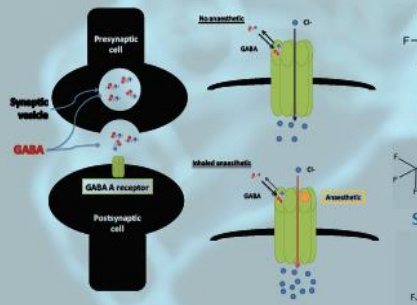


Mechanism of action of Dexmetomidine and Clonidine.

Inhaled anaesthetic examples

Mechanism of action:

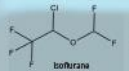
- Enhances γ-aminobutyric acid (GABA) binding to its chloride ion-channel receptor.
- The increase in intra-cellular chloride levels produces an inhibitory effect (anaesthesia).



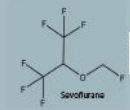
Mechanism of action of inhaled anaesthetics.

Halothane

Isoflurane



Sevoflurane



Toxicity Data	Oral LD_{50} (Human) (µL/kg)	Oral LD_{50} (rat)	Inhalation LC_{50} (rat) (ppm)	Oral LD_{50} (mouse) (µL/kg)	Inhalation LC_{50} (mouse) (ppm (3 hrs))
Halothane	-	5000 mg/kg	25000 (1h)	-	-
Isoflurane	1071	4770 µL/kg	16300 (3h)	5000	16000
Sevoflurane	-	10000 µL/kg	20000 (3h)	18200	28000

LD_{50}: the lowest dosage of a substance observed to cause a fatality within a specific subject population under a specific set of exposure conditions. LD_{50}: the median value of all the observed dosages of a substance resulting in a fatality within a specific subject population under a specific set of exposure conditions. LC_{50}: the median value of all the observed concentrations (based on an exposure time) of a substance resulting in a fatality within a specific subject population under specific set of exposure conditions. Lethal dose and lethal concentration values are statistics derived from specific populations and exposure conditions (typically controlled animal studies), they may not be representative of alternate populations and/or exposure conditions.

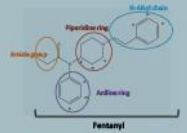
Fentanils

- Fentanils are a highly potent family of opioid narcotic analgesic drugs.
- The family includes fentanyl, a narcotic linked to an increased risk of overdose amongst opioid addicts.
- As of May 2018, there were 20 fentanil derivatives scheduled under the Single Convention on Narcotic Drugs

Properties

- Fentanyl and its analogues are solids that require aerosolisation for weaponisation purposes.
- Routes of exposure for fentanils include inhalation (aerosolized form), oral exposure or ingestion. Transdermal absorption is possible (for example, the use of transdermal patches), however as the process is slow, such that brief incidental exposures may not cause significant opioid toxicity.

- Fentanyl and its analogues have higher potency than morphine and heroin.
- Poor drug dosage, poly-drug use and addiction are all contributors to the high rates of overdose, respiratory depres-



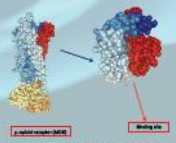
Fentanyl

Structure and substitution positions for fentanyl and derivatives.

Fentanyl derivative	Amide group	Piperidine ring	N-Alkyl chain	Aniline ring
Sufentanil				
Carfentanil				
Ocfentanil				
Remifentanyl				
3-Fluorofentanyl				
Phenylfentanyl				
α'-methyl Butyrylfentanyl				
Cyclopentenylfentanyl				
Cyclopropylfentanyl				
para-chloro Valerylfentanyl				
Valerylfentanyl				
Acetylfentanyl				
Furanylfentanyl				
4F-IBF				
Tetrahydrofuranylfentanyl (THF-F)				
Methoxyacetylfentanyl				
ortho-methyl Cyclopropylfentanyl				
Acrylfentanyl				
2'-fluoro ortho-Fluorofentanyl				

Mechanism of action:

- In the CNS, fentanils bind to opioid receptors, specifically μ-receptors. These receptors are found predominantly in the brain and spinal cord
- They act to depress CNS function.
- Bioavailbility from inhalation exposure can range from 12-100%.



Crystal structure of the μ-opioid receptor bound to a morphinan antagonist (Protein Data Bank Structure 4DKL)

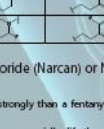
Effects:

- Loss of pain sensation
- Miosis
- Decreased intestinal paristalsis (constipation)
- Nausea and vomiting
- Dose-dependent respiratory depression (which can lead to death)
- Diminished mental alertness resulting in a feeling of drowsiness, euphoria, sleepiness, or unconsciousness

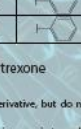
Antidotes: Naloxone hydrochloride (Narcan) or Naltrexone

- Opioid receptor antagonists.
- Bind to the opioid receptors more strongly than a fentanyl derivative, but do not activate the receptor.
- Quickly reverse signs and symptoms, especially life-threatening respiratory depression.
- Short half-life, symptoms may return in an apparently stabilized patient and antidotes might need to be readministered.
- 0.4 mg is the standard starting dose but for some fentanyl derivatives dose up to 2 mg have been required.

Narcan



Naltrexone



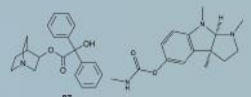
Time Weighted Average – Occupational Exposure Limits (OEL-TWA)	
Alfentanil	1 µg/m³
Fentanyl	0.1 µg/m³
Sufentanil	0.01 µg/m³

BZ (3-quinuclidinyl benzilate)

BZ is a glycolate anticholinergic compound and is a only "CNS-acting chemical" found in the Annex of Chemicals of the Chemical Weapons Convention (Schedule 2A.03*).

Properties

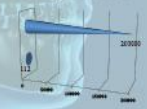
- Odourless crystalline powder with bitter taste.
- Persistent in soil and water and on most surfaces.
- Half-life in moist air ~ 3-4 weeks.



Antidote: Physostigmine

- Temporarily raises acetylcholine concentrations by binding reversibly to anticholinesterase.

Safety Ratio of BZ



The large difference between the median lethal concentration (LC_{50}) and the median incapacitating concentration (IC_{50}) allows for the onset of CNS-acting symptoms to appear at a dosage much lower than a lethal dose.

Dose in [mg.min/m³]

Mechanism of action:

- Acts as a competitive inhibitor of the neurotransmitter acetylcholine (ACh) in postsynaptic ACh receptors.
- As the concentration of BZ at these sites increases, the proportion of receptors available for binding to acetylcholine decreases, resulting in an understimulation of nerve signal transduction.
- When administered by inhalation (in aerosolised form), absorption to the bloodstream is more pronounced than with oral administration.

Mechanism of action of BZ.

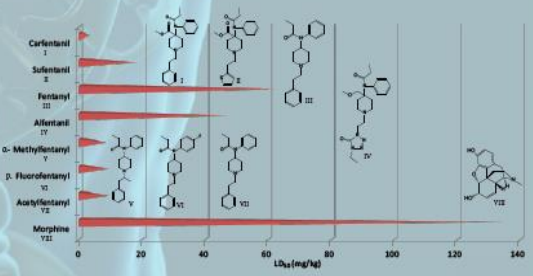
CNS effects:

- Stupor, ataxia, confusion, and confabulation. Induces concrete and panoramic illusions and hallucinations.

Peripheral effects:

- Mydriasis, blurred vision, dry mouth and skin, initially rapid heart rate; later, normal or slow heart rate.

Toxicity



Riot Control Agents

OPCW

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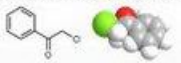
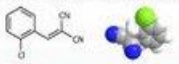


2-Chloroacetophenone (CN)

Synonyms:
Mace, CAP, Khlorketon (10% CN, 45% benzene, 40% carbon tetrachloride), CNC (30% CN, 70% chloroform), and CNS (23% CN, 38.4% chloropicrin, 38.4% chloroform).

Physical states:
White solid with odour of apple blossom
Melting Point 54-56 °C; Boiling Point 245 °C



2-Chlorobenzylidenemalononitrile (CS)

Synonyms:
2-Chlorobenzalmalononitrile, o-chlorobenzylidene malononitrile, K62 CS (pure), CS1 (95% CS, 5% silica aerogel), CS2 (CS and silica aerogel), CSX (1 g CS, 99 g tri-n-octyl phosphite). CS dissolved in methyl ethyl ketone is used in spray devices.

Physical states:
White solid with pungent peppery odour
Melting Point 93-95 °C;
Boiling Point 310-315 °C dec

Dibenzo[b,f][1,4]oxazepine (CR)

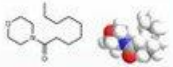
Synonym:
CR

Physical states:
Yellow stable powder
Melting Point 72 °C; Boiling Point 335 °C

2'-Chloroacetophenone

Synonyms:
o-chloroacetophenone

Physical states:
Colourless liquid
Boiling Point 229 °C



4-Nonanoylmorpholine

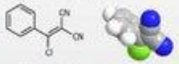
Synonyms:
MPA, MPK, pelargonic acid morpholide

Physical states:
Liquid
Boiling Point 310 °C

3'-Chloroacetophenone

Synonyms:
m-chloroacetophenone

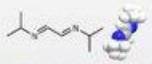
Physical states:
Colourless liquid
Boiling Point 228°C



α-Chlorobenzylidenemalononitrile

Synonym:
none

Physical states:
White solid
Melting Point 68-70 °C;
Boiling Point 126 °C/0.1 mmHg



N,N'-Bis(isopropylethylene)diimine

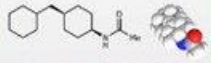
Synonym:
Diimine

Physical states:
Volatile tan-coloured solid
Melting Point 48-50 °C

N,N'-Bis(tert-butylethylene)diimine

Synonyms:
none

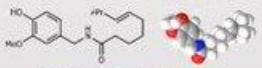
Physical states:
White solid
Melting Point 39-43 °C



Cis-4-Acetylaminocyclohexylmethane

Synonyms:
none

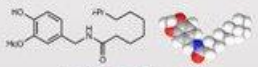
Physical states:
White solid
Melting Point 112 °C



8-Methyl-N-vanillyl-trans-6-nonenamide

Synonyms:
C, capsoicin, Moltin, Zacin

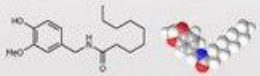
Physical states:
White solid
Melting Point 62-65 °C; Boiling Point 210-220 °C at 0.01 mmHg



8-Methyl-N-vanillylnonanamide

Synonyms:
Dihydrocapsaicin, DHC

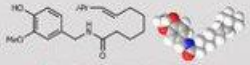
Physical states:
White solid
Physical data unavailable



N-Vanillylnonanamide

Synonyms:
N-(4-hydroxy-3-methoxy-benzyl)nonanamide, nonivamide, pseudo-capsaicin, pelargonic acid vanillylamide, PAVA

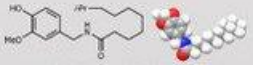
Physical states:
White solid with stinging odour
Melting Point 57 °C



N-Vanillyl-9-methyldec-7-(E)-enamide

Synonym:
homocapsaicin

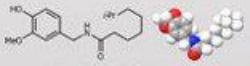
Physical states:
Lipophilic colourless odourless crystalline or waxy solid



N-Vanillyl-9-methyldecanamide

Synonym:
homodihydrocapsaicin

Physical states:
Lipophilic colourless odourless crystalline or waxy solid



N-Vanillyl-7-methyloctanamide

Synonym:
nordihydrocapsaicin

Physical states:
Lipophilic colourless odourless crystalline or waxy solid

Oleoresin capsicum (OC)

This is a mixture containing ≥ 8% capsaicins: capsaicin, dihydrocapsaicin, and nordihydrocapsaicin dissolved in an organic solvent.

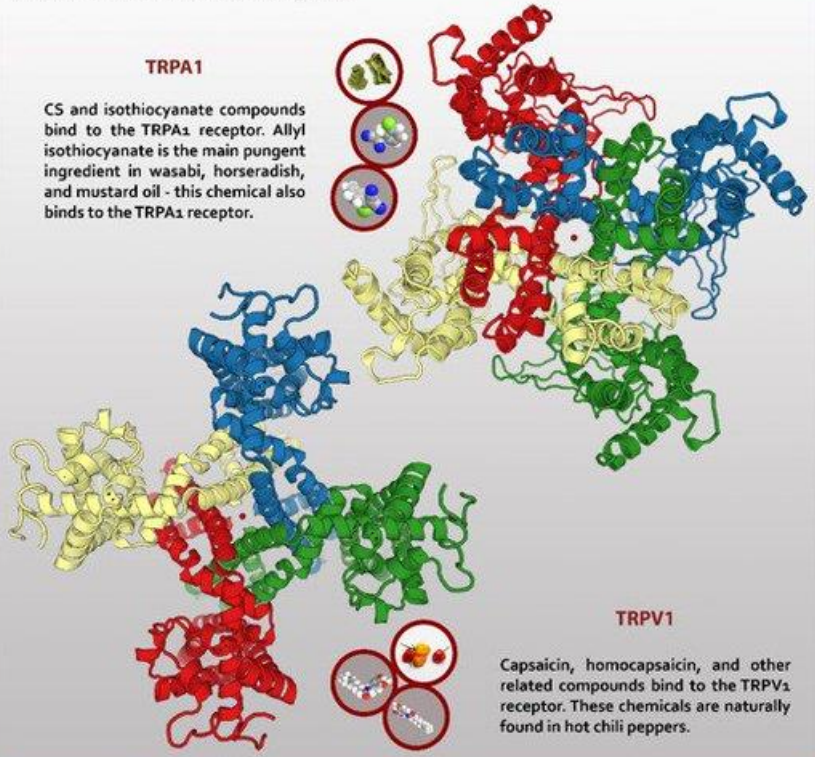
What are TRP Receptors?

TRP receptors are a family of ion channel receptors mainly located on cell membranes of multicellular organisms. TRP receptors are classified into seven subfamilies: TRPC (canonical or classical), TRPV (vanilloid), TRPM (melastatin), TRPA (ANKTM1 homologues), TRPP (polycystin), TRPML (mucolipin), and TRPN (NOMP-C homologues).

TRP receptor functions are diverse; the receptors serve as versatile sensors that allow individual cells and entire organisms to detect changes in their environment. This includes experiencing changes in temperature, touch, taste and other stimuli (including pain).

TRPA1

CS and isothiocyanate compounds bind to the TRPA1 receptor. Allyl isothiocyanate is the main pungent ingredient in wasabi, horseradish, and mustard oil - this chemical also binds to the TRPA1 receptor.



TRPV1

Capsaicin, homocapsaicin, and other related compounds bind to the TRPV1 receptor. These chemicals are naturally found in hot chili peppers.

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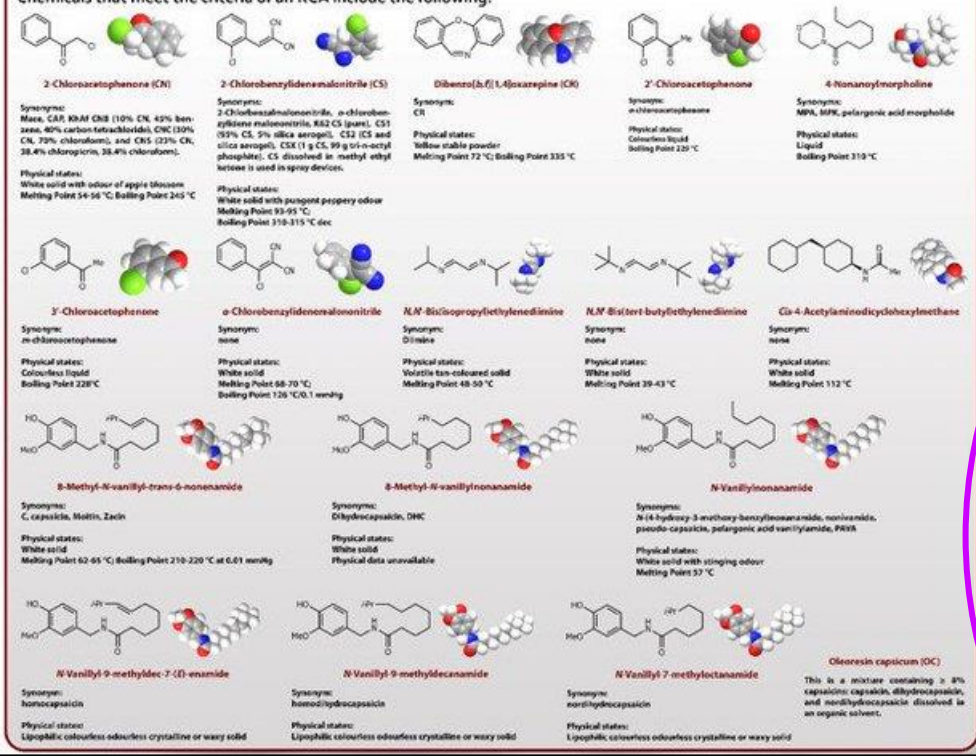

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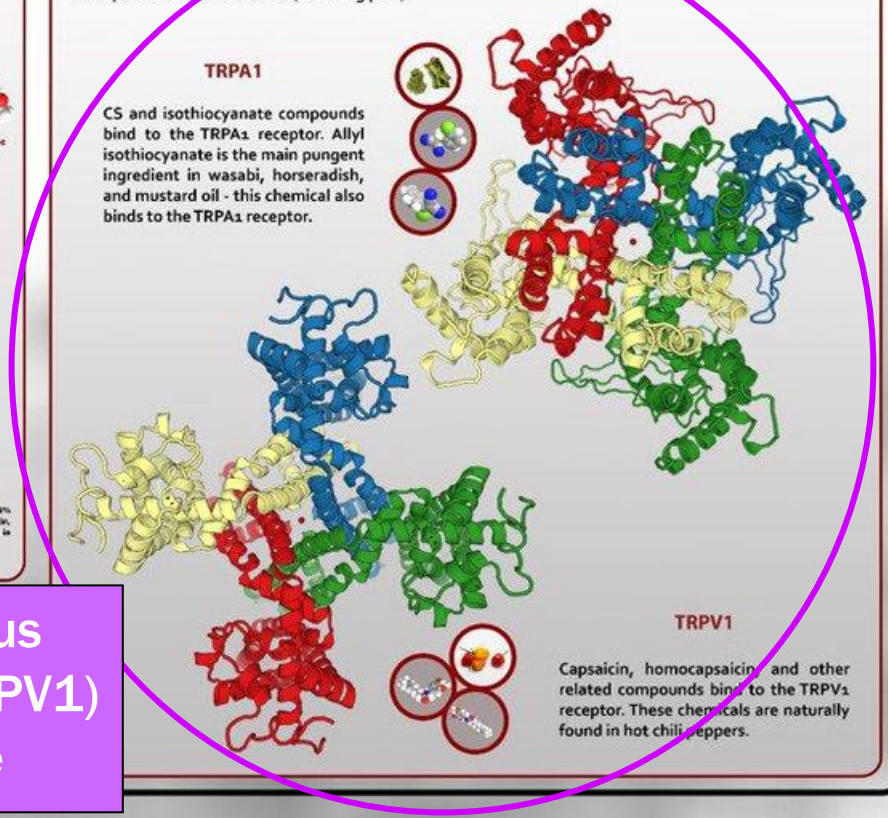

The 17 RCA's activate peripheral nervous system ion channel receptors (TRPA1, TRPV1) – these initiate an irritation response

Proteins as Toxic Chemicals…

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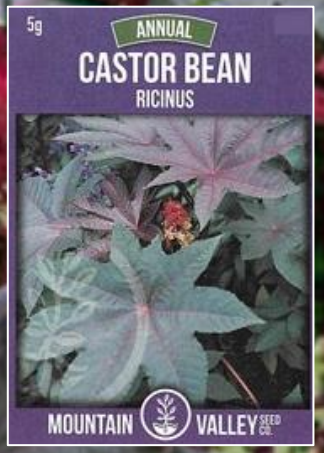
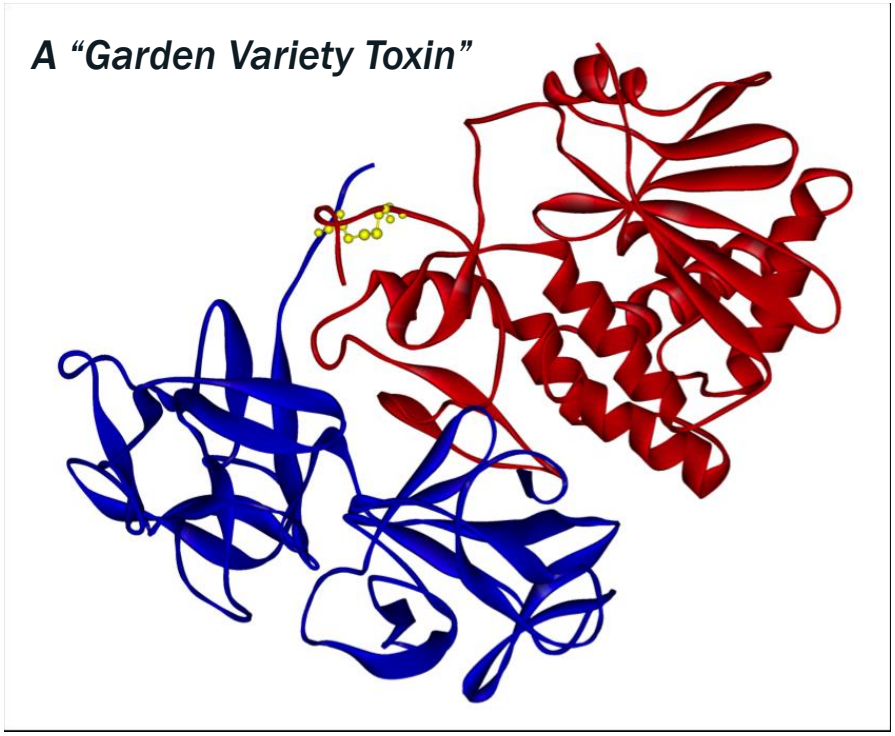
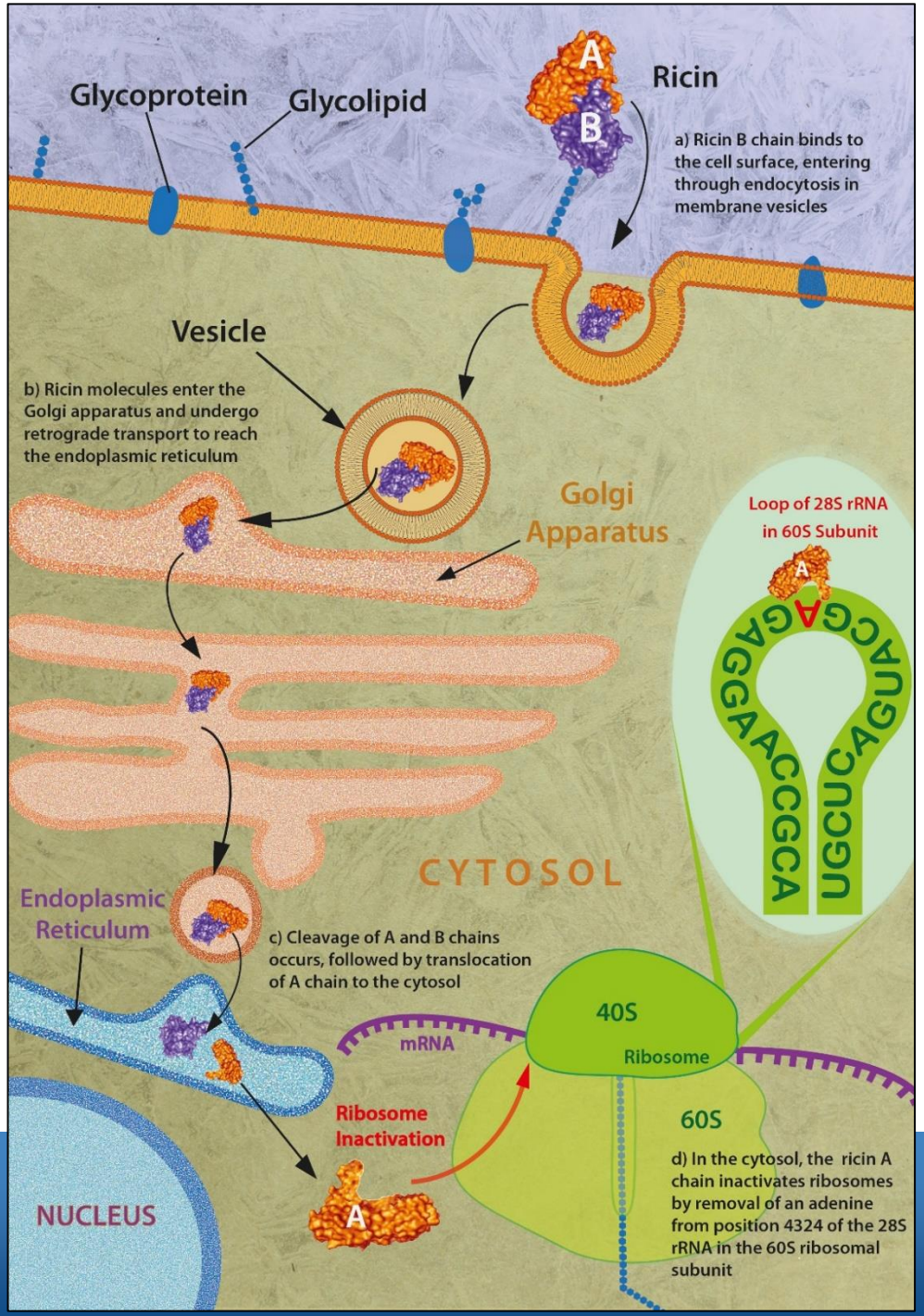


Molecular Machinery…

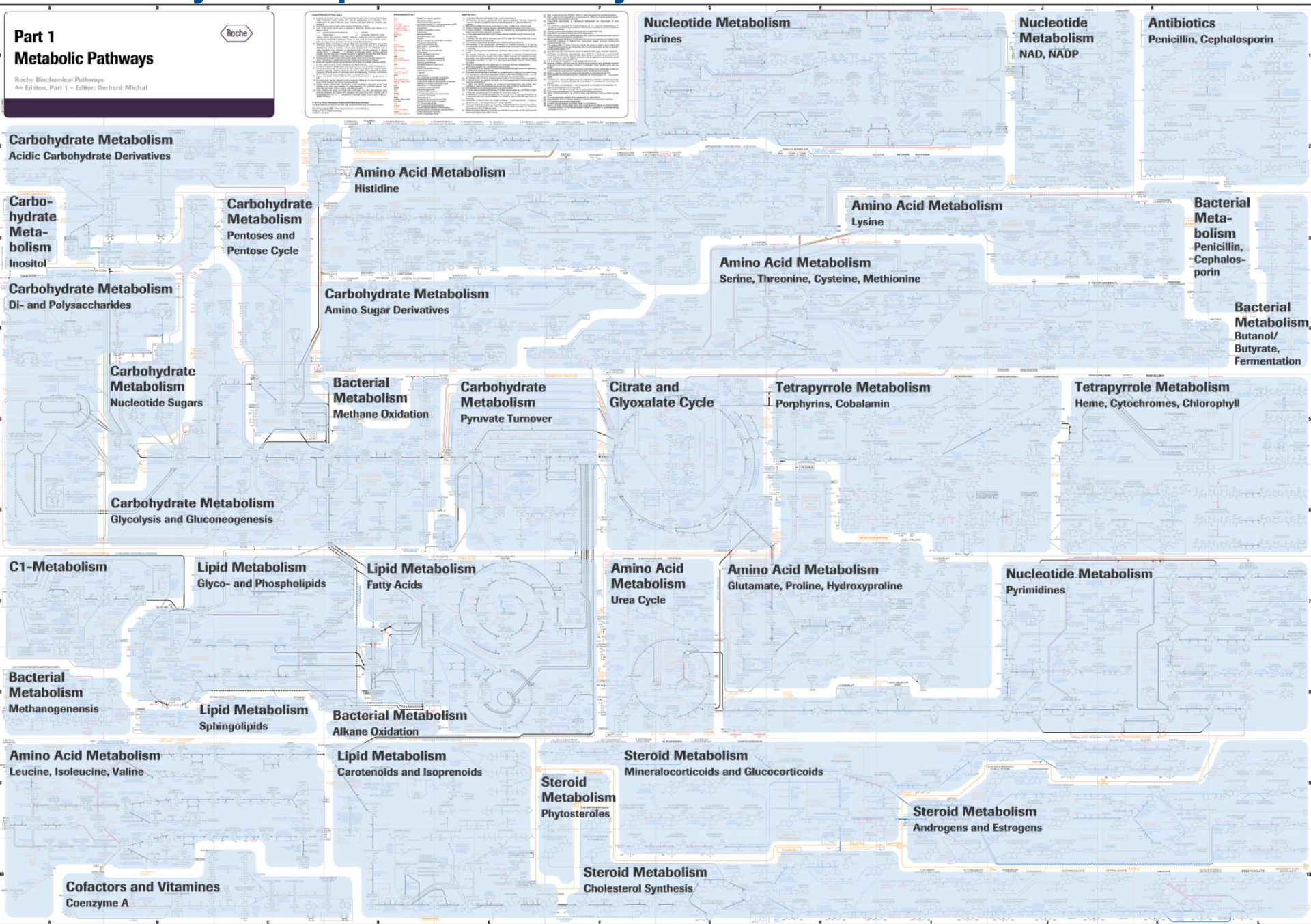


Shuts down protein synthesis. Impacts on life processes throughout the cell.

Ricin B chain can be removed from the A chain and used to deliver other “chemicals” into a cell



Why its Important to Fully Understand Life Processes



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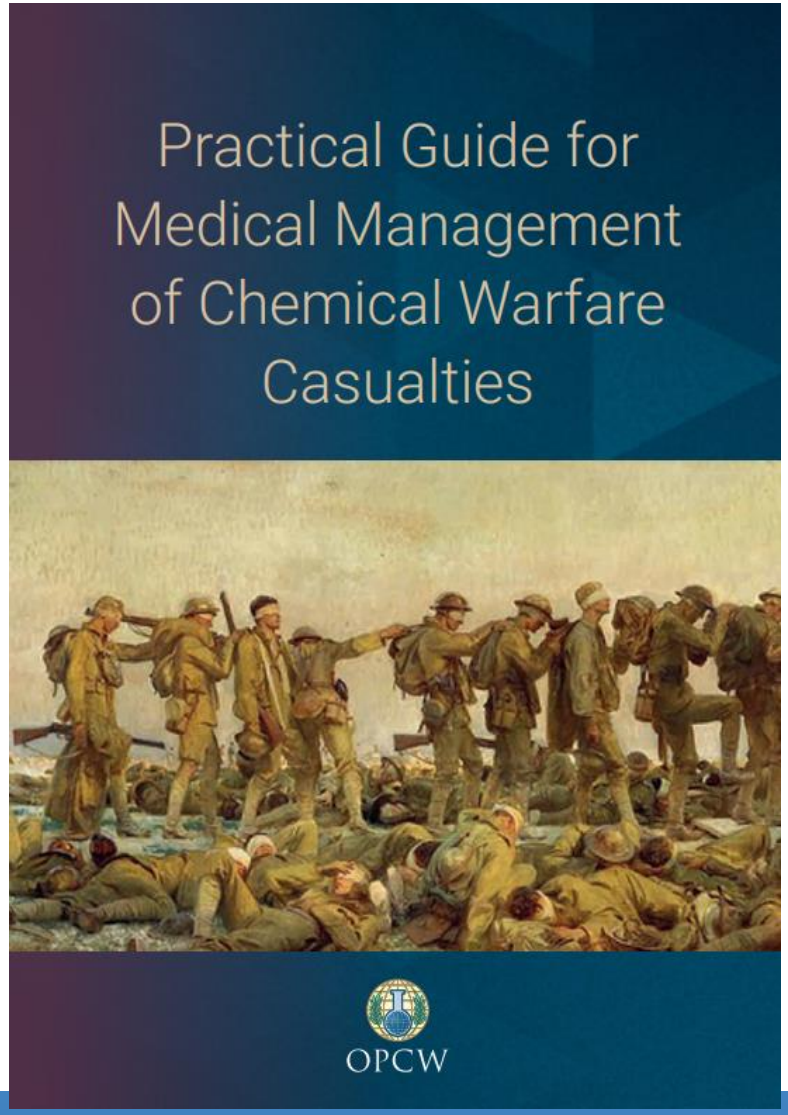
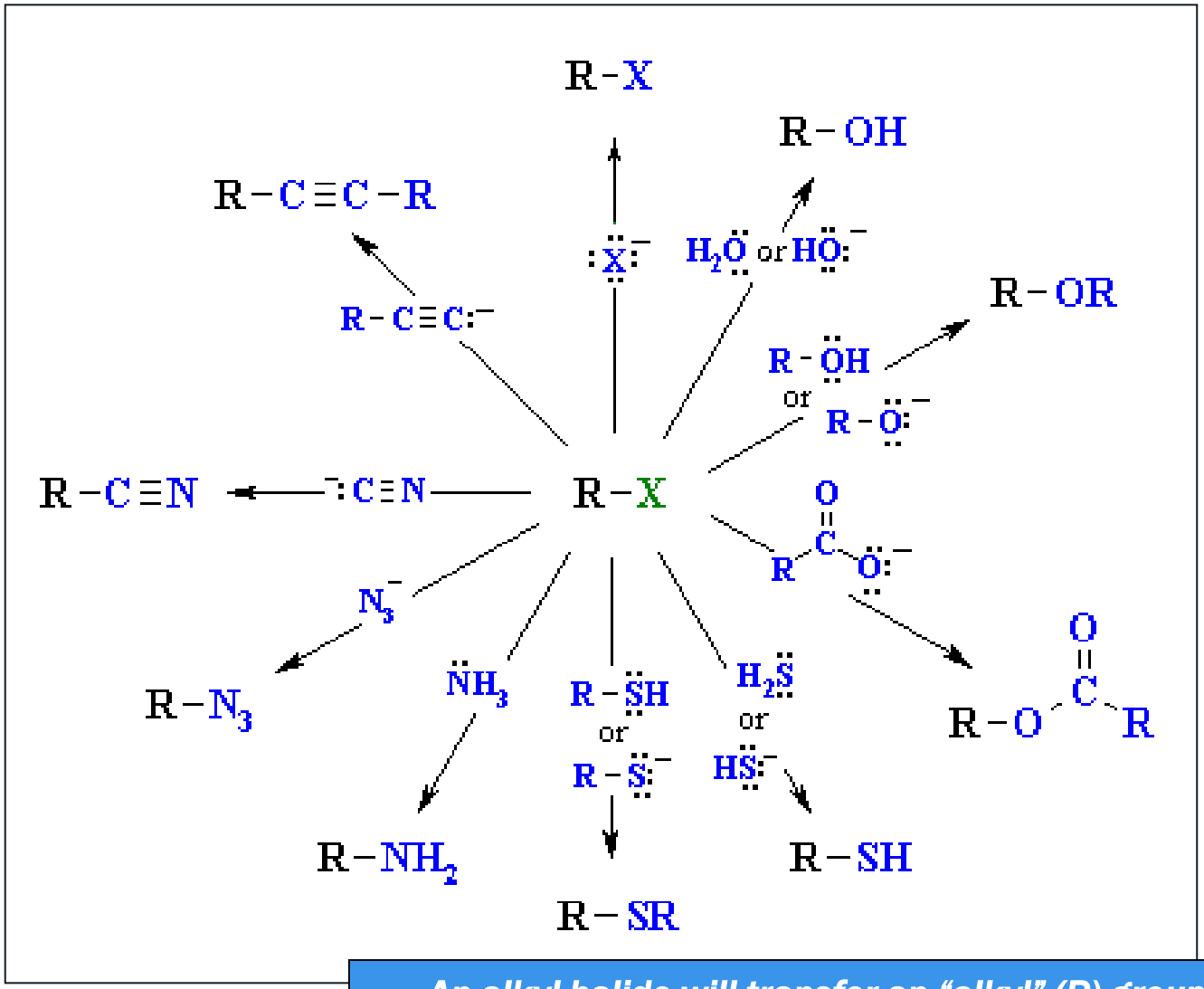


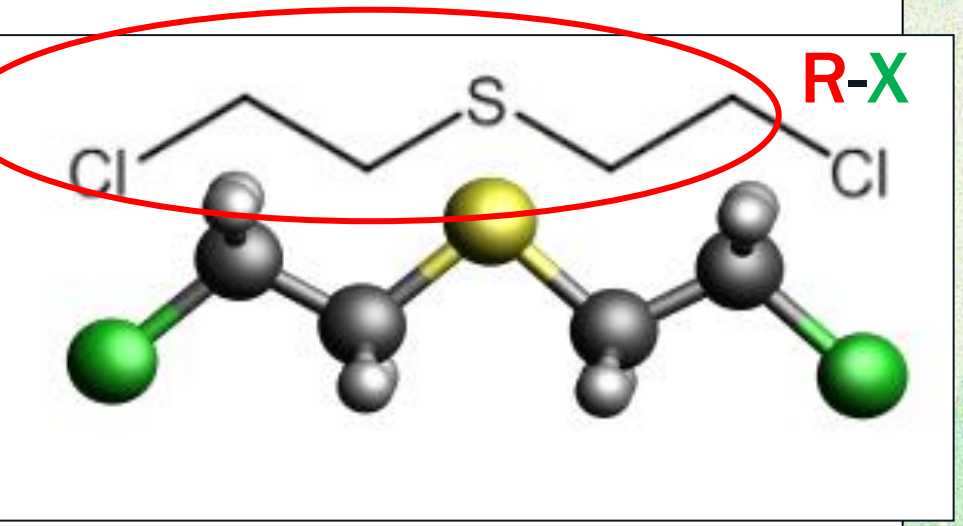
A more specific effect on a unique life process allows more targeted/effective medical countermeasures to be developed

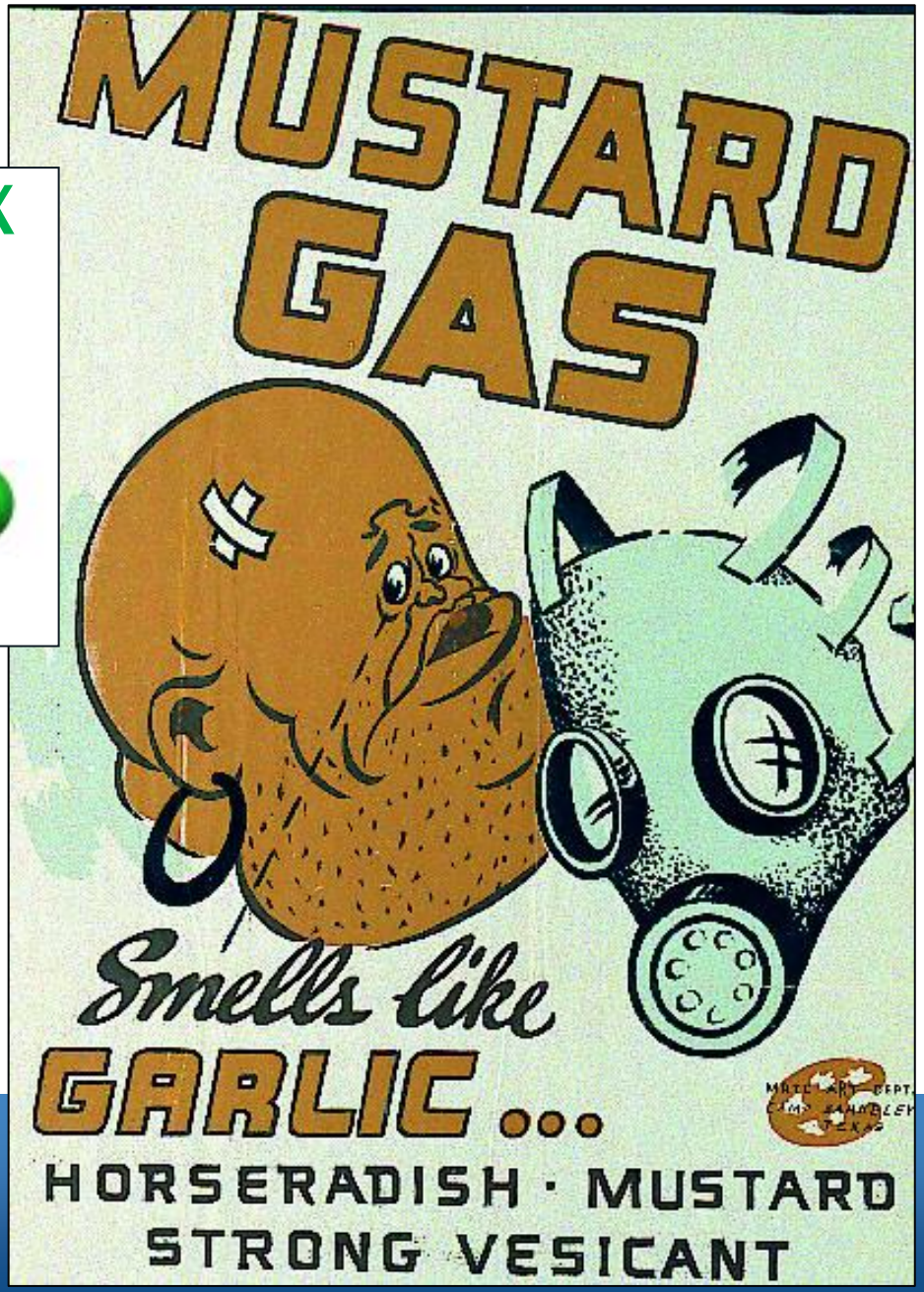
Chemical Action Does Not Always Need to be So Complicated..



An alkyl halide will transfer an "alkyl" (R) group to another molecule through reaction with a "nucleophilic" functional group

Chemical Action Does Not Always need to be So Complicated..

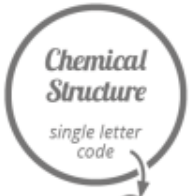


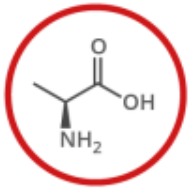


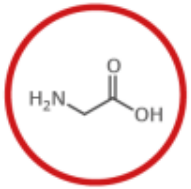
A GUIDE TO THE TWENTY COMMON AMINO ACIDS

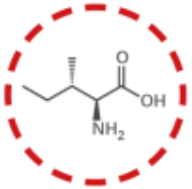
AMINO ACIDS ARE THE BUILDING BLOCKS OF PROTEINS IN LIVING ORGANISMS. THERE ARE OVER 500 AMINO ACIDS FOUND IN NATURE - HOWEVER, THE HUMAN GENETIC CODE ONLY DIRECTLY ENCODES 20. 'ESSENTIAL' AMINO ACIDS MUST BE OBTAINED FROM THE DIET, WHILST NON-ESSENTIAL AMINO ACIDS CAN BE SYNTHESISED IN THE BODY.

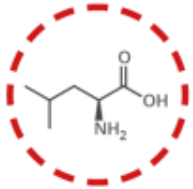
Chart Key: ALIPHATIC · AROMATIC · ACIDIC · BASIC · HYDROXYLIC · SULFUR-CONTAINING · AMIDIC · NON-ESSENTIAL · ESSENTIAL

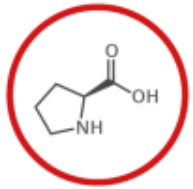


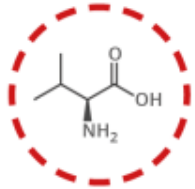

ALANINE A
Ala
GCT, GCC, GCA, GCG

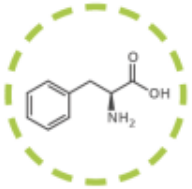

GLYCINE G
Gly
GGT, GGC, GGA, GGG

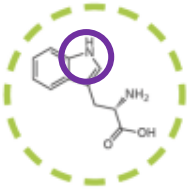

ISOLEUCINE I
Ile
ATT, ATC, ATA

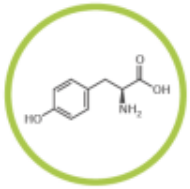

LEUCINE L
Leu
CTT, CTC, CTA, CTG, TTA, TTG

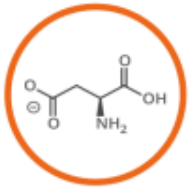

PROLINE P
Pro
CCT, CCC, CCA, CCG

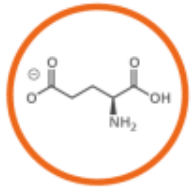

VALINE V
Val
GTT, GTC, GTA, GTG

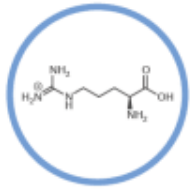

PHENYLALANINE F
Phe
TTT, TTC

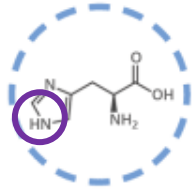

TRYPTOPHAN W
Trp
TGG

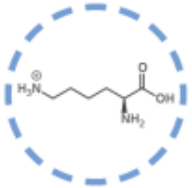

TYROSINE Y
Tyr
TAT, TAC

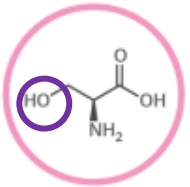

ASPARTIC ACID D
Asp
GAT, GAC

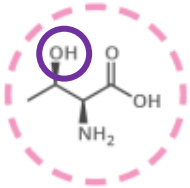

GLUTAMIC ACID E
Glu
GAA, GAG

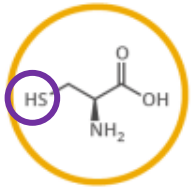

ARGININE R
Arg
CGT, CGC, CGA, CGG, AGA, AGG

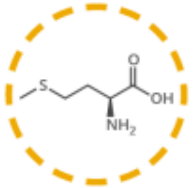

HISTIDINE H
His
CAT, CAC

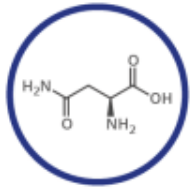

LYSINE K
Lys
AAA, AAG

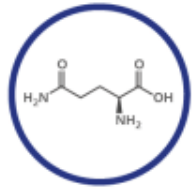

SERINE S
Ser
TCT, TCC, TCA, TCG, AGT, AGC


THREONINE T
Thr
ACT, ACC, ACA, ACG


CYSTEINE C
Cys
TGT, TGC


METHIONINE M
Met
ATG


ASPARAGINE N
Asn
AAT, AAC

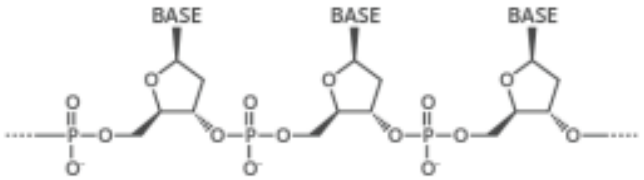

GLUTAMINE Q
Gln
CAA, CAG

Note: This chart only shows those amino acids for which the human genetic code directly codes for. Selenocysteine is often referred to as the 21st amino acid, but is encoded in a special manner. In some cases, distinguishing between asparagine/aspartic acid and glutamine/glutamic acid is difficult. In these cases, the codes asx (B) and glx (Z) are respectively used.

○ nucleophilic groups

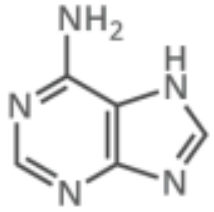
THE CHEMICAL STRUCTURE OF DNA

THE SUGAR PHOSPHATE 'BACKBONE'

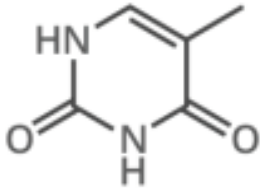


DNA is a polymer made up of units called nucleotides. The nucleotides are made of three different components: a sugar group, a phosphate group, and a base. There are four different bases: adenine, thymine, guanine and cytosine.

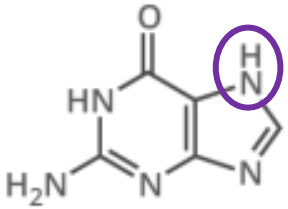
A ADENINE



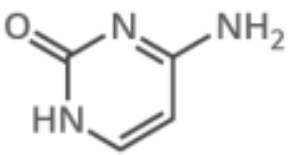
T THYMINE



G GUANINE

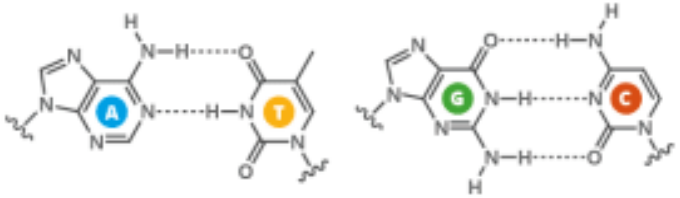


C CYTOSINE



WHAT HOLDS DNA STRANDS TOGETHER?

DNA strands are held together by hydrogen bonds between bases on adjacent strands. Adenine (A) always pairs with thymine (T), while guanine (G) always pairs with cytosine (C). Adenine pairs with uracil (U) in RNA.



FROM DNA TO PROTEINS

The bases on a single strand of DNA act as a code. The letters form three letter codons, which code for amino acids - the building blocks of proteins.

An enzyme, RNA polymerase, transcribes DNA into mRNA (messenger ribonucleic acid). It splits apart the two strands that form the double helix, then reads a strand and copies the sequence of nucleotides. The only difference between the RNA and the original DNA is that in the place of thymine (T), another base with a similar structure is used: uracil (U).

In multicellular organisms, the mRNA carries genetic code out of the cell nucleus, to the cytoplasm. Here, protein synthesis takes place. 'Translation' is the process of turning the mRNA's 'code' into proteins. Molecules called ribosomes carry out this process, building up proteins from the amino acids coded for.

THE CHEMICAL STRUCTURE OF DNA

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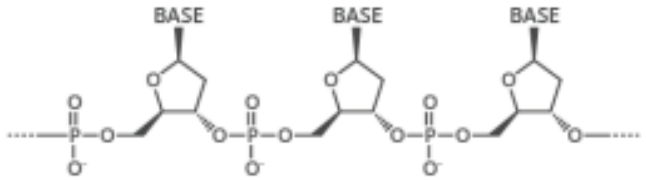

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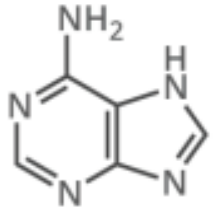
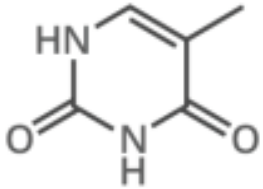


T THYMINE



G GUANINE

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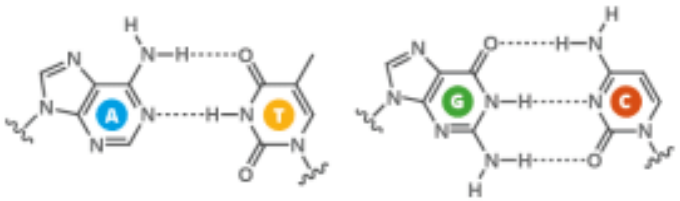

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DNA → (TRANSCRIPTION) RNA → (TRANSLATION) PROTEIN

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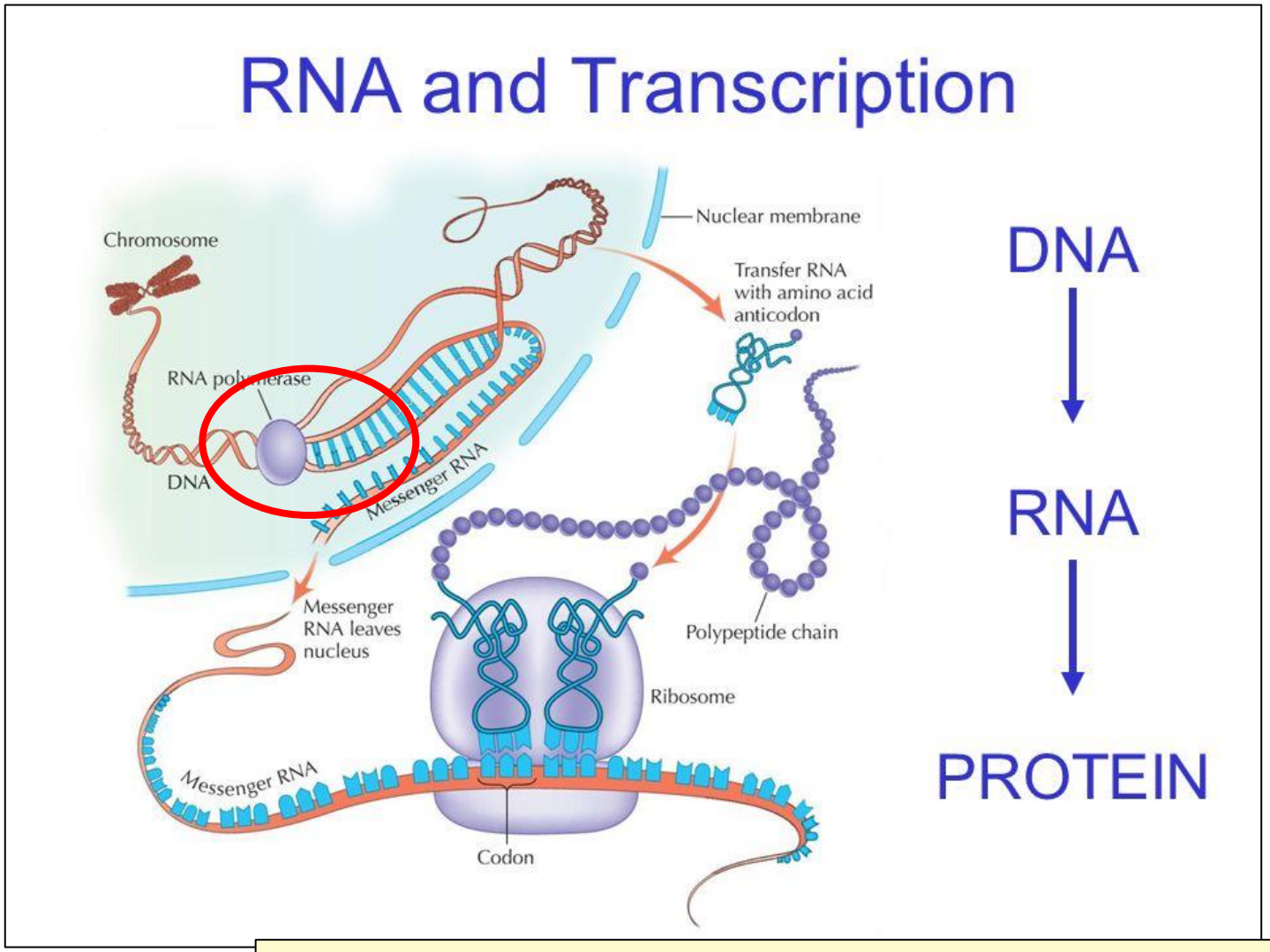
Thymine
G
C
Cytosine
Cytosine

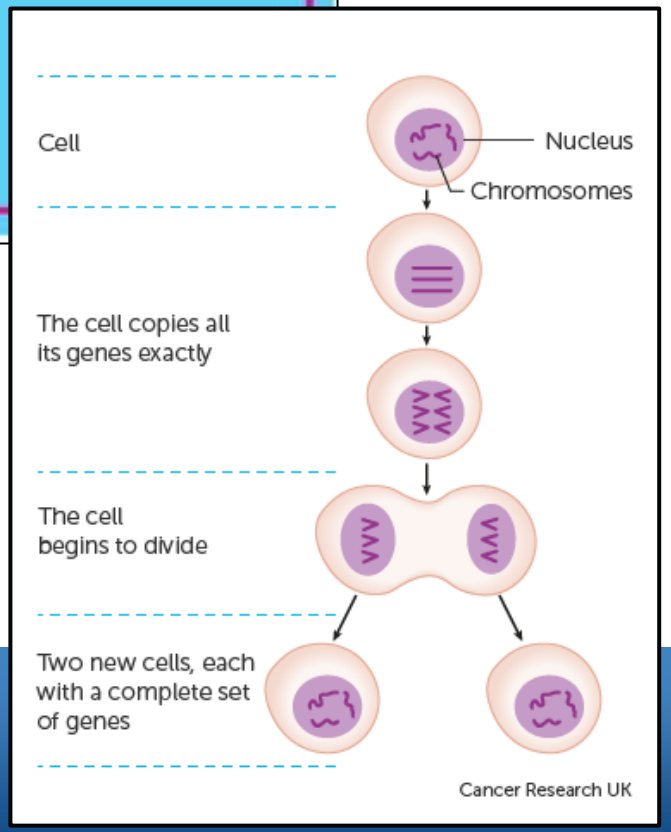
DNA: The "Instructions"



If the DNA strands cannot separate, there are "reading errors"

- **can generate impact on downstream life processes**
- **can lead to cell death and/or long-term health effects of exposure**

DNA: The “Instructions”



What Did We Learn Today?

- **The scientific basis of the Chemical Weapons Convention is "biology"**
- **The scientific basis of "biology" is "chemistry"**
  - *functional groups of connected atoms (molecular structures) matter!*
- **Biological systems are made up of interacting components and chemical signals are an integral part of these processes**
  - Different classes of chemicals impact life processes through different mechanisms – understanding these mechanisms provides a basis for effective medical response
- **Models and analogies of how it all works are useful for understanding**
  - *However, the molecules of life are not rigid plastic parts!*
- **Science is fun!**

What Did We Learn Today?

The purpose of the Chemical Weapons Convention is NOT to define scientific disciplines!

The purpose is to ban chemical weapons

The Convention draws upon a sound (and trans-disciplinary) scientific basis to set out its definitions

OPCW

منظمة حظر الأسلحة الكيميائية

禁止化学武器组织

Organisation for the Prohibition of Chemical Weapons

Organisation pour l'Interdiction des Armes Chimiques

Организация по запрещению химического оружия

Organización para la Prohibición de las Armas Químicas