Management of inhalation intoxications

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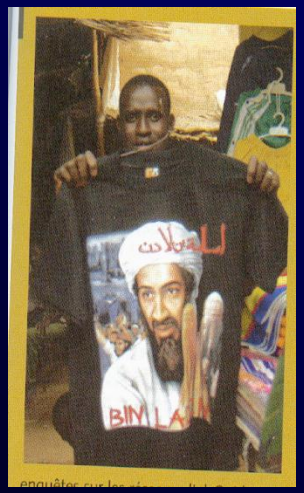
Circumstances of poisoning with gaseous toxicants

The chemical risk is consistently present in our society

Workplace

Environnement

Military



Terrorism

Seveso	Dioxine	10 July 1976
Bophal	Isocyanate of methyl	3 December 1984
Tokyo metro	Saran gas	20 March 1995
AZF in Toulouse	Ammonium nitrate	21 September 2001
World Trade Centre	Fumes and smokes	11 September 2001

Air Pollution: a serious worldwide issue

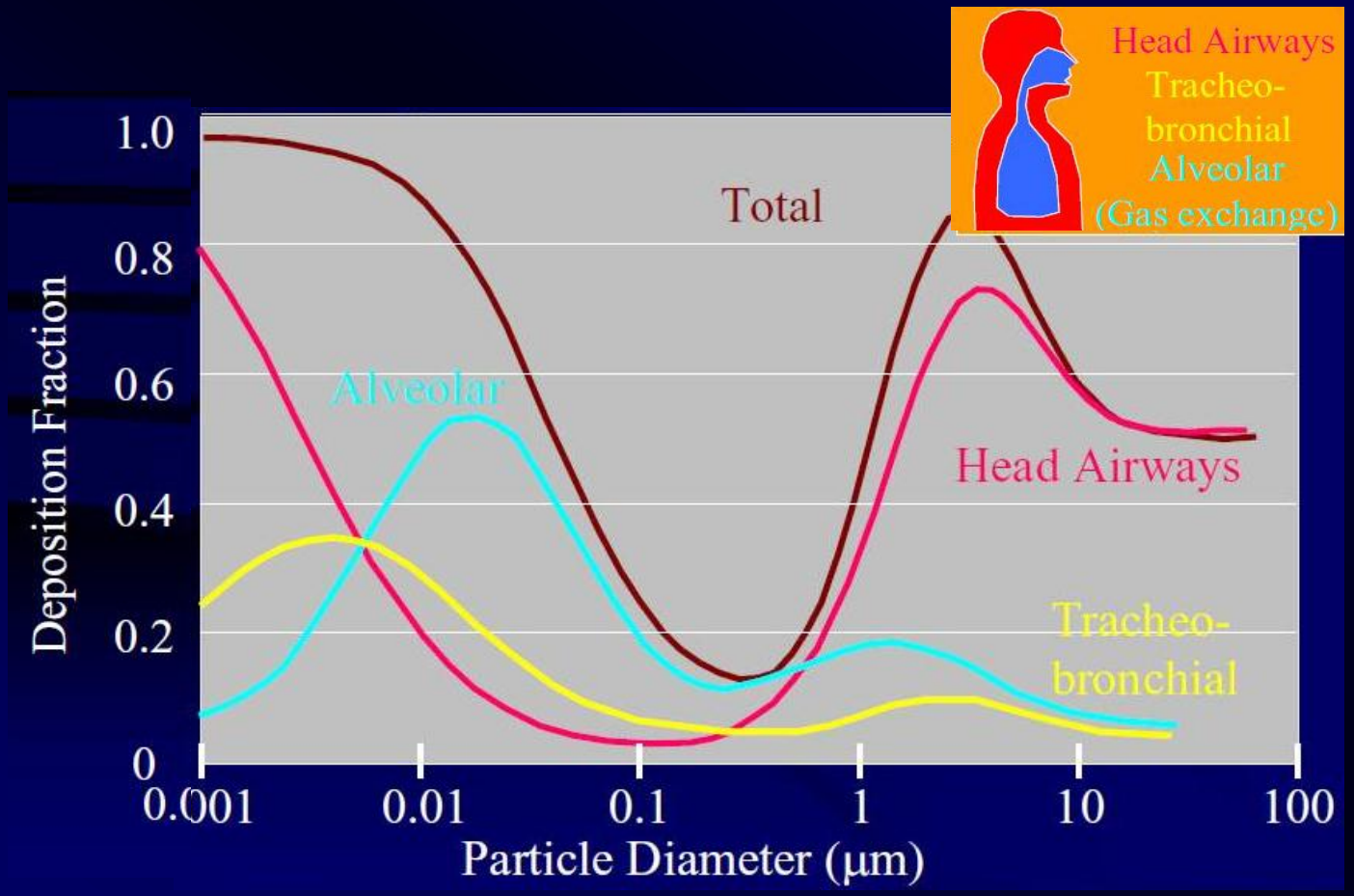
Shanghai, China

Five Major Pollutants:

1) Carbon Monoxide
2) Sulfur Dioxide
3) Nitrogen Dioxide
4) Particulate Matter
5) Ground Level Ozone

Behavior of airborne particles

The air we breathe always contains solid particles or droplets (from natural sources or man-made sources) and is therefore an aerosol

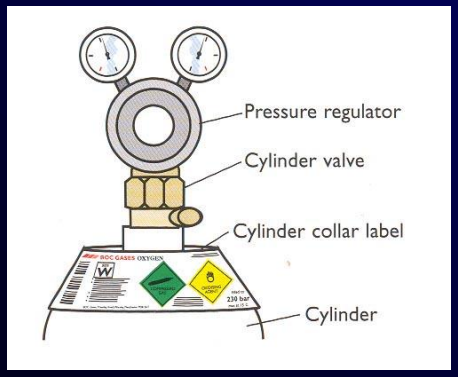


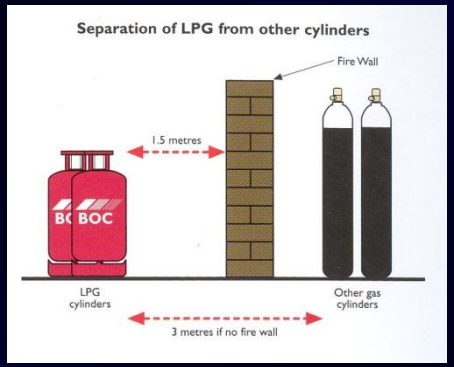
Industrial toxicants at the workplace that produce respiratory diseases

Toxicant	Site of Action	Acute Effect	Chronic Effect
Ammonia	Upper Airways	Irritation, edema	Bronchitis
Arsenic	Upper Airways	Bronchitis, irritation, pharyngitis	Cancer, bronchitis, laryngitis
Asbestos	Lung parenchyma	--	Fibrosis, cancer
Chlorine	Upper airways	Cough, irritation, asphyxiant (by muscle cramps in larynx)	--
Isocyanates	Lower airways, alveoli	Bronchitis, pulmonary edema, asthma	--
Nickel Carbony	Alveoli	Edema (delayed symptoms)	--
Ozone	Bronchi, alveoli	Irritation, edema, hemorrhage	Emphysema, bronchitis
Phosgene	Alveoli	Edema	Bronchitis, fibrosis, pneumonia
Toluene	Upper airways	Bronchitis, edema, bronchospasm	--
Xylene	Lower airways	Edema, hemorrhage	--

Prevention and control measures (detection)

- Wear appropriate Personal Protective Equipment (PPE)
- Ensure adequate ventilation
- Ensure suitable physical environment for dispensing (liquid nitrogen)
- Consider fixed point gas detection monitors / alarms
- Ensure emergency procedures
- Ensure the correct storage: regulators, segregation between flammable/non-flammable gases, full/empty cylinders
- Ensure the correct manual handling of cylinders and vessels





Mechanisms of gas toxicity

Irritant agents

- Primary irritants : local toxicity; effects depending on aqueous solubility
  - + Highly soluble gases: affect mostly eyes and oro/nasopharynx
    Ex. NH_3, chlorine, HCl, HNO_3, H_2SO_4, SO_2
  - + Low solubility gases: affect mostly deep pulmonary structures (alveoli)
    Ex. NO_2, O_3, phosgene
- Secondary irritants: local + general toxicity
  Ex. Hydrogen sulfide (H_2S), H_3P, CS_2

Asphyxiant agents

- Simple effects : reduction of FiO_2
  Ex. inert gas like CO_2, H_2, N_2, alcanes (methane…)
- Chemical effects : reduction of transport, extraction and use of O_2
  Ex. CO, HCN, ClCN, acetonitrile

Agents with other systemic activity than asphyxia

Ex. Arsine (AsH_3)

Determinants of gas toxicity

Toxicity of a gas is determined by

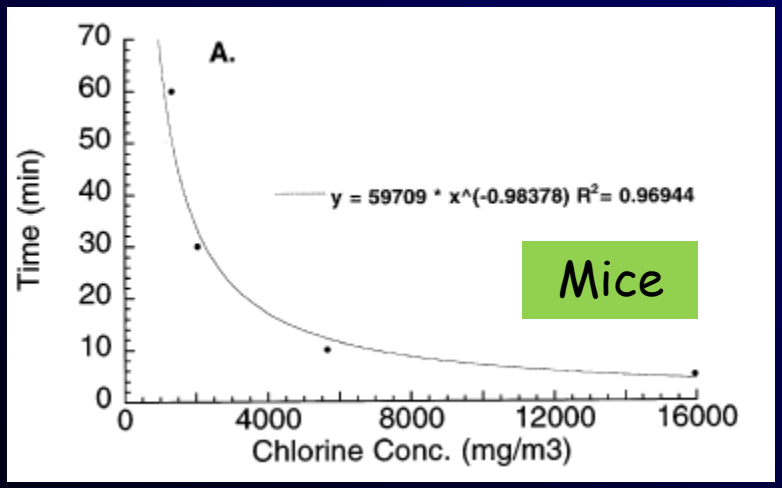
- Dose (concentration x time)
- Inherent toxicity
- Water solubility
- Warming properties

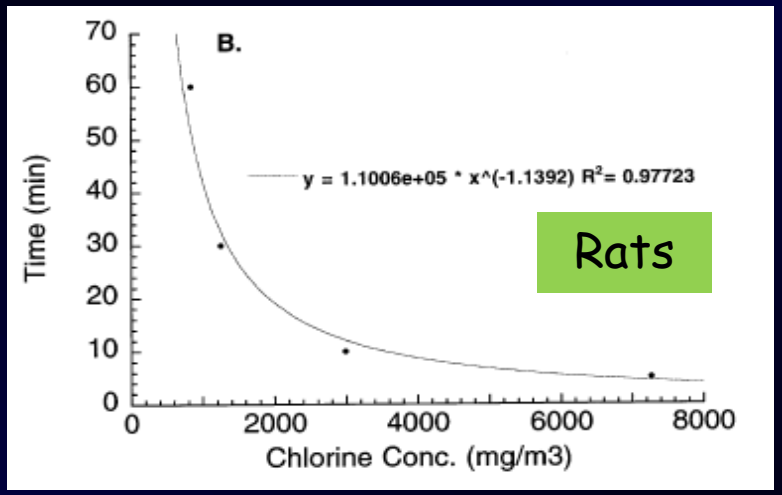
Haber's rule: The relationship between the concentration of a poisonous gas and how long the gas must be breathed to produce death or toxic effect

$$C \times t = k \quad \text{or} \quad \int C dt = k$$

The relationship between *C* and t is linear on a log-log scale

Lethality in rodents following brief exposures to chlorine





Principles of inhalation poisoning management

TRIAGE ++++

exposition ≠ intoxication

- Identification of life-threatening presentations
- Determination of the circumstances of exposure
- Physical examination + Biological tests/imaging
- Therapeutic indications
  - 1- Supportive care
  - 2- Decontamination
  - 3- Elimination enhancement techniques
  - 4- Antidotes
- Toxicological analysis

Clinical syndromes and readily available biomarkers are more useful than analytical results for emergent decisions

Smoke inhalation

Fire may expose to 3 dangers:

- Thermal risk (flames, heated gases)
- Traumatic risk (blast, defenestration)
- Chemical risk

Smoke inhalation associates:

- Neurological and cardiac anoxic systemic injuries
- Ocular and respiratory irritant injuries

~ 80% of deaths are related to toxic smoke inhalation:

- Early death (*per* exposition) 80%
- Late death (*post*-exposition) 20%

Smoke composition

Polyintoxication: combustion or pyrolosis products in fire smokes

Compounds responsible of direct cellular anoxic toxicity :

- Carbon dioxide (CO_2)
- Carbon monoxide (CO)
- Hydrogen cyanide (HCN)
- Anhydro- derivates : sulfur dioxide, hydrogen sulfide
- Nitric oxide (NO)

Compounds responsible of mucous membrane irritant toxicity :

- Soot (particulates of polycyclic nitric and carbon compounds)
- Aldehydes : acrolein, formaldehyde, butyraldehyde, acetaldehyde, …
- Nitrous derivates : nitric oxide and ammonia, isocyanides and amines
- Mineral acids : hydrochloric, hydrofluoric, hydrobromic acids, …
- Carbon halogenated oxides : phosgene, chlorine
- Water vapors

Composition varies with environment

CN: residential fires, including pipe and furniture, organic materials, plastics (polyurethane), and melanine resines

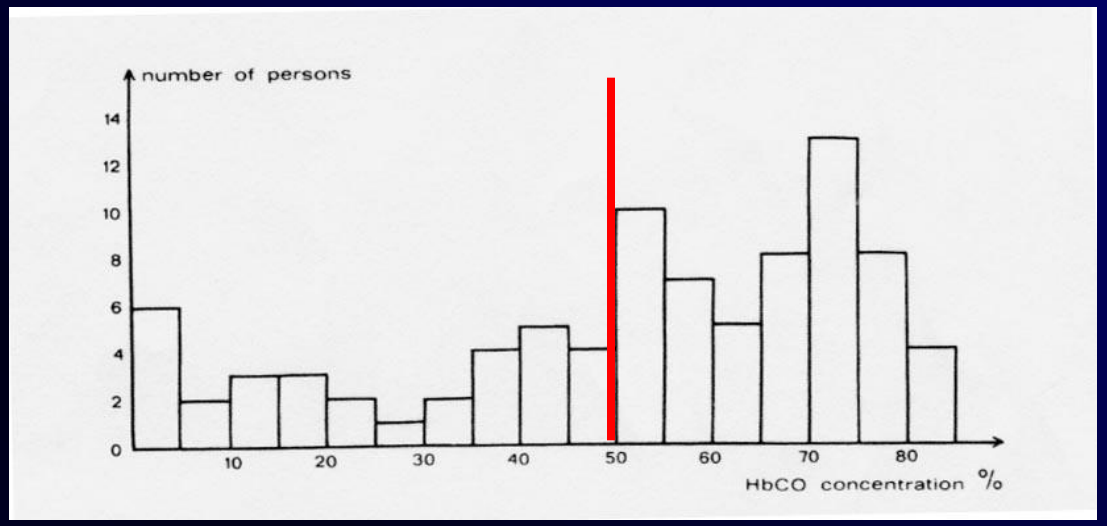
Smoke inhalation ≠ CO poisoning

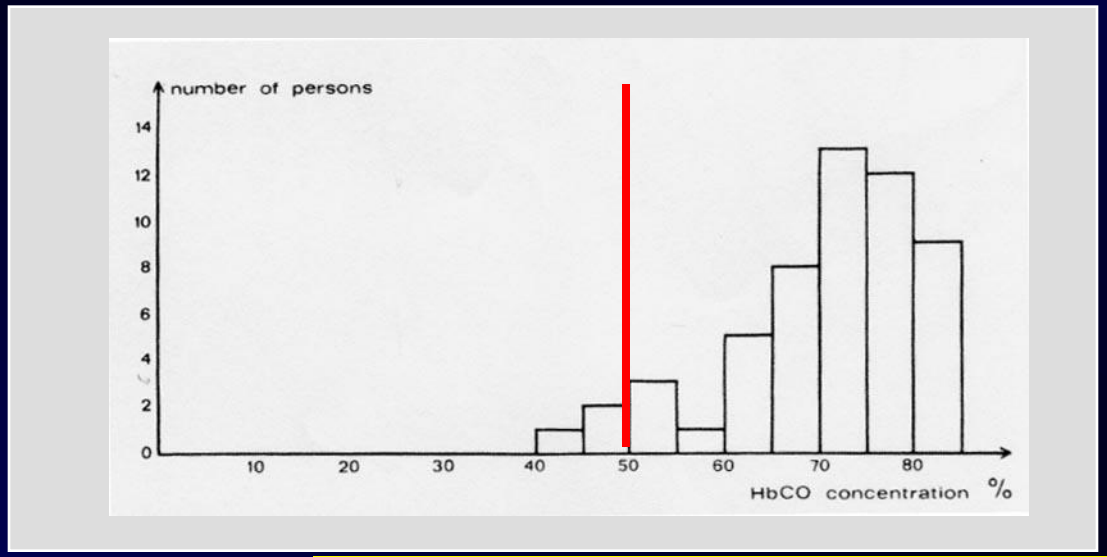
Post-mortem HbCO in 57 fire victims

Exposition duration: 30 min

Post-mortem HbCO in 54 cases of fatal CO poisoning

Exposition duration: 8 à 12 h

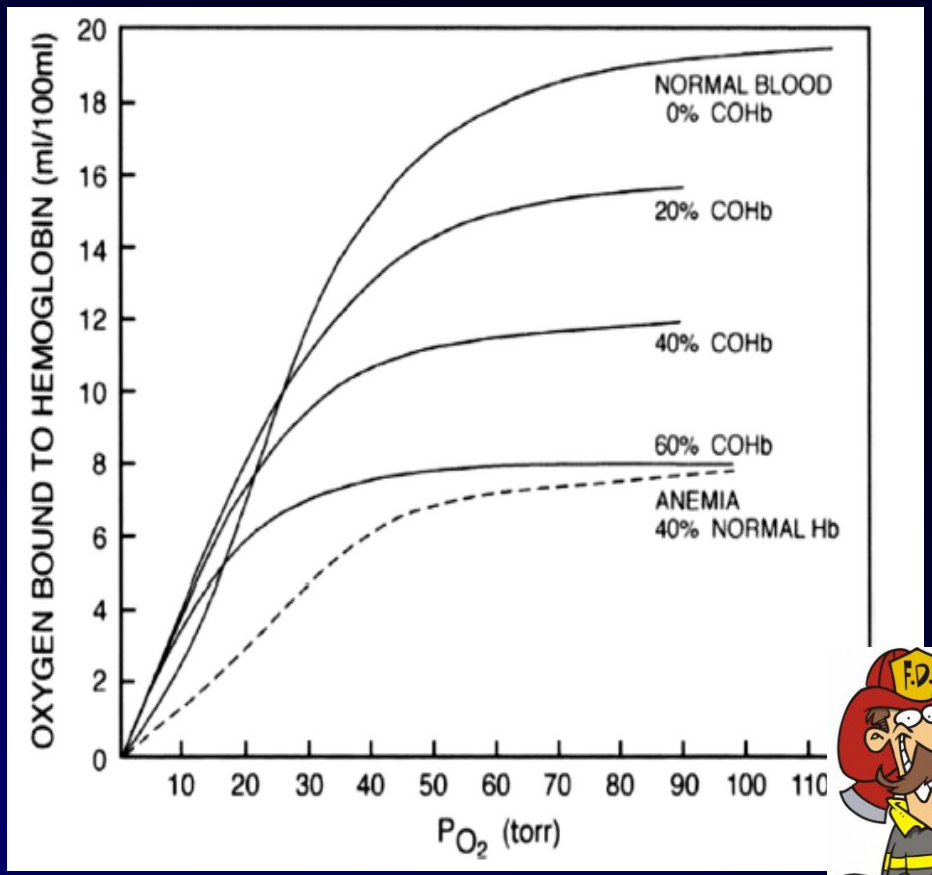




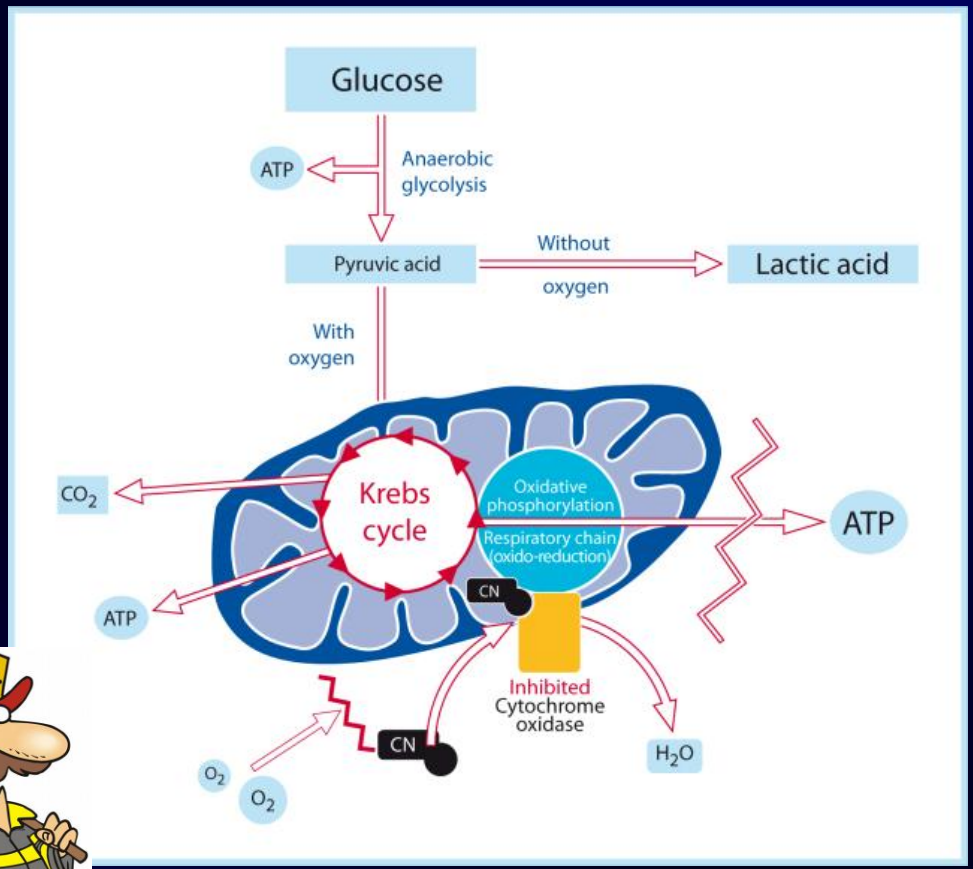
Teige et al. Z Rechtsmedizin 1977

Pathways of CO and CN toxicity

CO-Hb binding causes leftward shift in the O_2-Hb dissociation curve



Attachment to the ferric form of enzymes (Cytochrome oxidase)



Positive diagnosis

Smoke inhalation

The two fundamental signs are :

1)- Soot in the airways (nostrils, mouth, throats)

2)- Neurological impairment (Headaches, dizziness, confusion, seizures, changes in mental status, coma)

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Carbon monoxide intoxication	83	63	43	92
Cyanide intoxication	98	56	28	99

Vital signs in pure CO poisoning

Symptoms	*CO (mmol/l)*	*SBP (mmHg)*	*HR (/min)*	RR (/min)	Lactates (mmol/1)
Severe (n= 54)	2.87 ± 2.15	124 ± 19	88 ± 15	19 ± 4	3.2 ± 1.7
Moderate (n= 12)	0.84 ± 0.82	126 ± 18	85 ± 20	19 ± 3	2.3 ± 1.2
Mild (n= 65)	0.43 ± 0.56	125 ± 18	82 ± 13	19 ± 5	1.9 ± 0.9
Asymptomatic (n=15)	0.38 ± 0.45	128 ± 19	80 ± 6	17 ± 4	1.9 ± 0.7
p value		0.9	0.07	0.6	< 0.0001

Benaissa ML. *Intensive Care Med* 2003

Diagnosis of cyanide poisoning

1- Cardiovascular impairment

Hypotension, collapse, shock, or cardiac arrest
Transient reversible cardiomyopathy

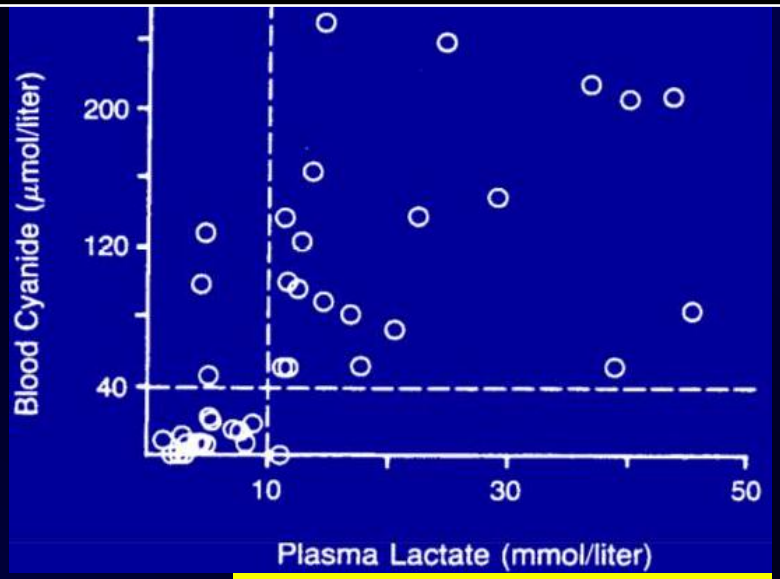
2- Abnormal respiratory pattern

Polypnea, wide ventilation, hypopnea or apnea

Se: 87 % - Spe: 94 % - PPV: 95 %

3- Metabolic impairment

Lactate concentration > 10 mmol/l in the presence of smoke inhalation without severe burns is strongly suggestive of CN (≥ 40 µmol/l) intoxication.

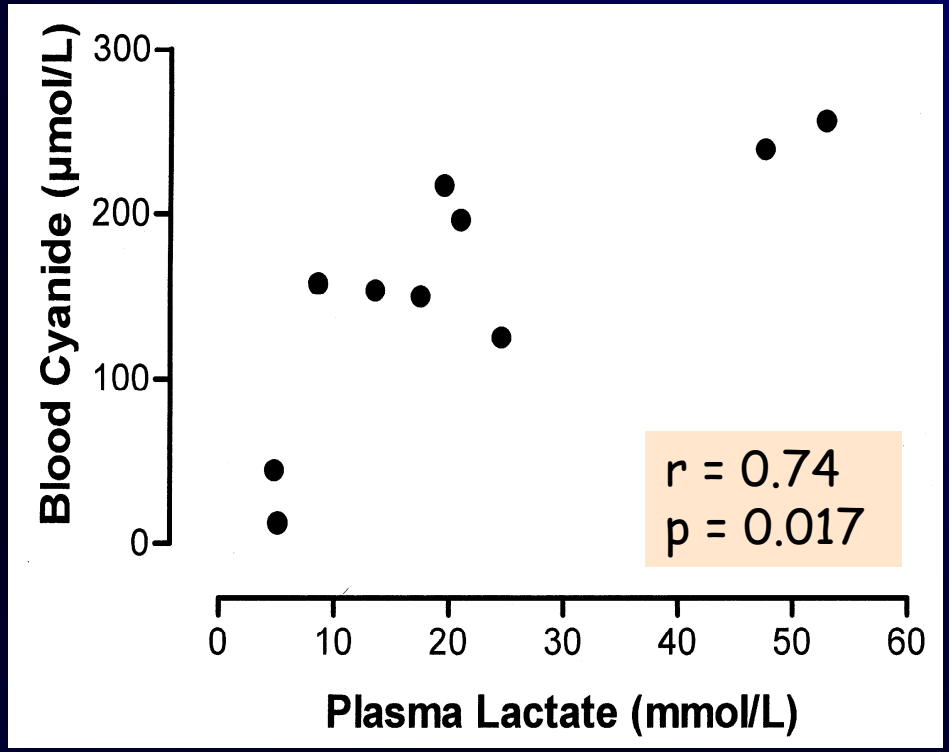


Baud FJ. *NEJM* 1991

Correlation between blood cyanide & lactate concentrations

Factors contributing to lactic acidosis

- Cardiovascular failure
- Apnea
- Seizures
- Acute liver failure
- Catecholamine rush
- Mitochondrial dysfunction



Baud FJ. *Crit Care Med* 2002

Occurrence of signs and symptoms in cases of CO and CN poisonings

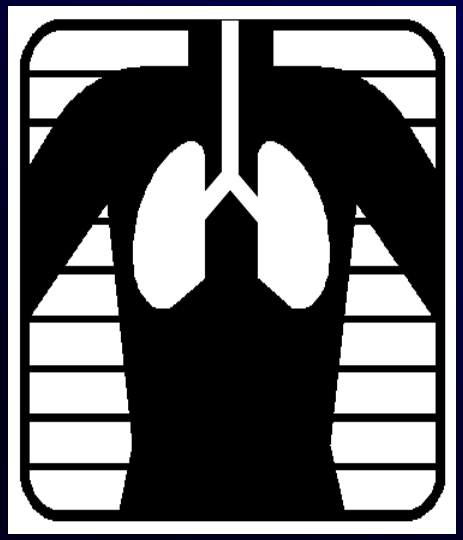
Signs and symptoms	CO (%)	CN (%)
Headache	64	6
Dizziness	56	6
Gastro-intestinal	43	33
Altered mental status	15	13
Loss of consciousness	31	NR
Coma	25	70
Dilated pupils	6	77
Seizures	3	34
Abnormal respiratory pattern	23	95
Pulmonary oedema	6	6
Hypotension/shock	7	61
Plasma lactate (mM) + coma	2.8	13.4

Irritant chemical injury

Toxic irritant gas syndrome

Responsible toxicants : multiple and not individualized

- C ➔ aldehydes
- N ➔ nitric oxide, amines
- S ➔ Sulfur oxide
- Cl ➔ Cl_2, HCl, $COCl_2$, ...



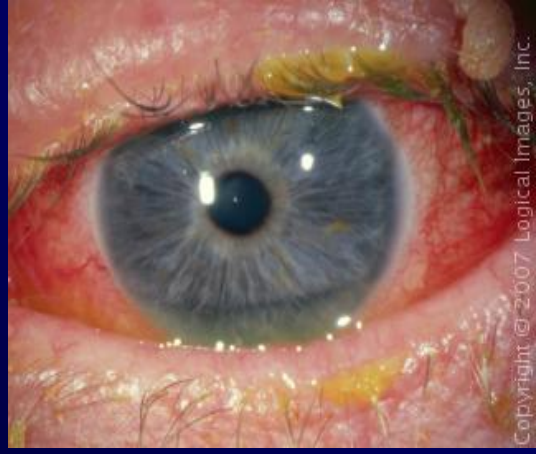
Irritation-related symptoms:

- Ocular
- Respiratory

They participate in the incapacitating action.

Their effects could be delayed (till > 48 hours).

1- Ocular symptoms



- Red eyes
- Cornea burns

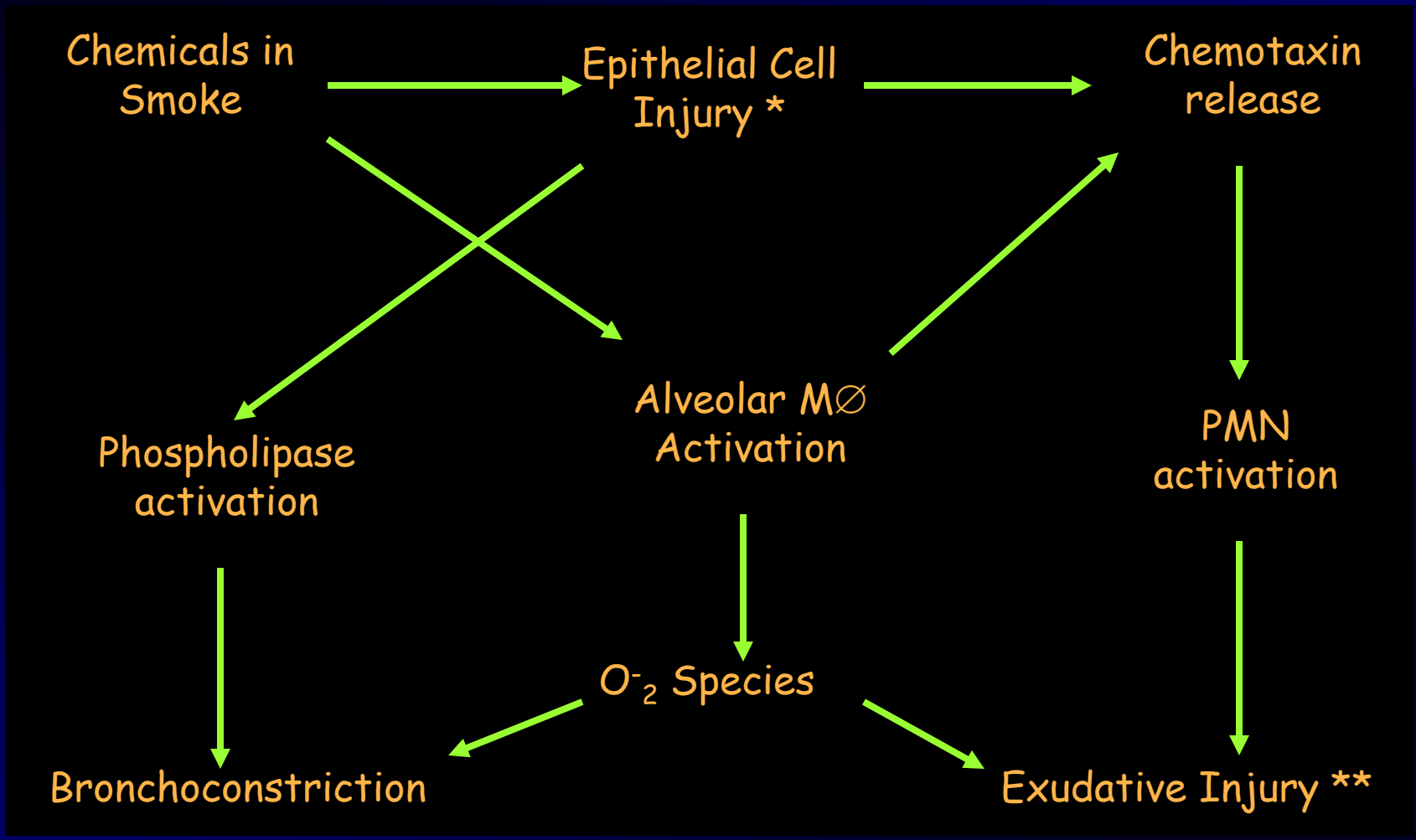
Persistent conjunctivitis on hospital admission is predictive of an associated respiratory injury.

2- Respiratory symptoms

- Dysphonia + inspiratory dyspnea = obstructive laryngitis
- Expiratory dyspnea + wheezing = bronchospasm
- Rapid breathing + crackles = chemical bronchopneumonia

Dysphonia and rhonchi are associated with a longer hospital stay.

Pathophysiology of tracheobronchial injury



* Loss of ciliary action, mucosal edema, diminished surfactant activity, atelectasis
** Resulting in necrotizing bronchiolitis, alveolar pulmonary edema, hyaline membrane formation, and intra-alveolar hemorrhage

Patient management

Assessments

On the scene

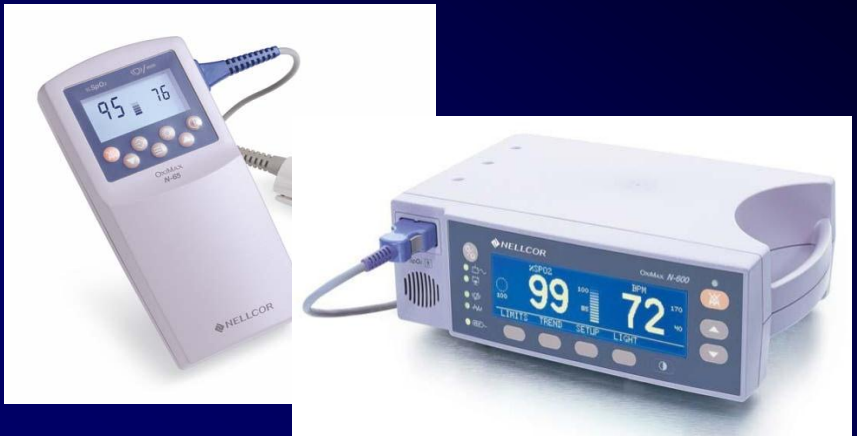
1- Pulse oximetry may not distinguish between O_2-Hb and CO-Hb, resulting in inaccurate SpO_2.

2- Pulse CO oximetry or atmospheric CO measurement.

3- Blood sampling for CO-Hb or CO measurement (if possible immediately after O_2 administration).

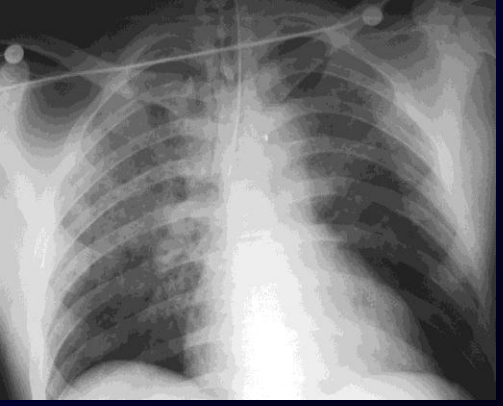
4- Blood sampling for further CN concentration determination.

5- Arterial blood gases.



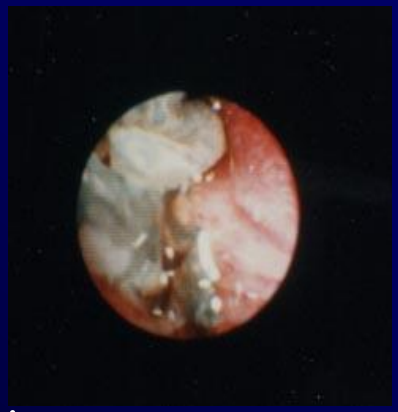
Useful in smoke inhalation mass casualty incidents without dermal burns

Goh SH. Eur J Emerg Med 2006



Assessments (2)

After hospital admission



1- Chest X-Ray: low specificity and predictive value; initially normal despite symptoms; to be repeated to look for delayed lung injury.

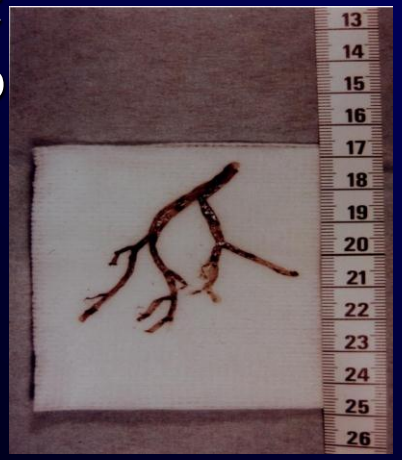
2- Sputum microbiology: high incidence of aspiration (38%)

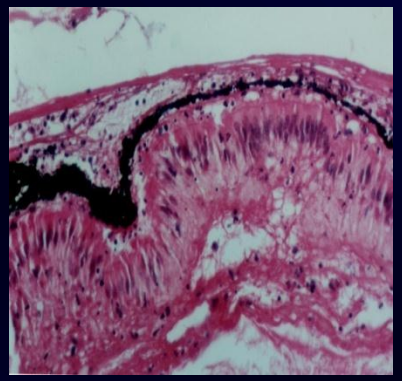
3- Bronchoscopy:

In burnt patient: predict severity, ARDS, mortality

In non-burnt patients: no correlation with PaO_2/FiO_2 ratio, infection, X-ray features, ICU stay duration.

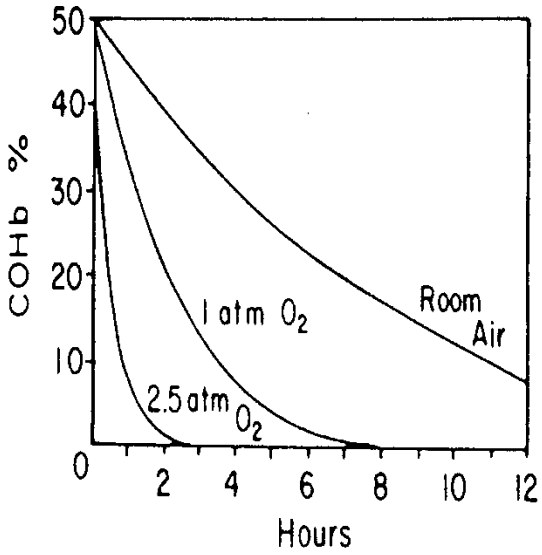
No evaluation of its therapeutic interest (toilet).





Treatment of CO poisoning

- Normobaric oxygen
- Hyperbaric oxygen (60-90 min à 2.5 ATA, compression chamber)
  - Consciousness loss
  - Coma
  - Neurological deficiency
  - Coronary insufficiency
  - Children
  - Pregnant women



Winter PM. *JAMA 1976*

- Some studies demonstrated a reduction in CNS symptoms and quicker recovery if CO poisoning

- Indications and availability vary depending on the institution and region

Metaanalysis of usefulness of hyeprbaric O_2 in CO poisoning

Analysis 1.1. Comparison 1 Hyperbaric Oxygen (HBO) vs. Normobaric Oxygen (NBO), Outcome 1 Presence of symptoms or signs at time of primary analysis (4-6 weeks).

Review: Hyperbaric oxygen for carbon monoxide poisoning

Comparison: 1 Hyperbaric Oxygen (HBO) vs. Normobaric Oxygen (NBO)

Outcome: 1 Presence of symptoms or signs at time of primary analysis (4-6 weeks)

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Presence of signs or symptoms					
Raphael 1989	51/159	50/148		23.7 %	0.93 [0.57, 1.49]
Thom 1995	0/30	7/30		1.5 %	0.05 [0.00, 0.95]
Mathieu 1996	69/299	73/276		27.8 %	0.83 [0.57, 1.22]
Scheinkestel 1999	30/48	25/40		12.1 %	1.00 [0.42, 2.38]
Weaver 2002	19/76	35/76		16.4 %	0.39 [0.20, 0.78]
Annane 2010	33/93	29/86		18.5 %	1.08 [0.58, 2.00]
Total (95% CI)	**705**	**656**		**100.0 %**	**0.78 [0.54, 1.12]**

Total events: 202 (Treatment), 219 (Control)

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 9.22$, df = 5 (P = 0.10); $I^2 = 46\%$

Test for overall effect: Z = 1.37 (P = 0.17)

0.1 0.2 0.5 1 2 5 10

Favours HBOT Favours Control

Buckley NA. *Cochrane Database Syst Rev* 2011

When to suspect cyanide poisoning ?

Neurological

Dizziness
Restlessness
Anxiety
↓
Confusion
↓
Coma
Seizures

↓

CO and CN

Respiratory

Hyperpnea
↓
Central
apnea
±
Pulmonary
edema

Abnormal respiratory pattern

↻ CN

or

Cardiovascular

Hypertension
↓
Shock
↓
Cardiac
arrest

Abnormal arterial pressure

↻ CN

or

Metabolic

↗Blood glucose
↗Lactate
Metabolic acidosis
Rhabdomyolysis
Renal failure

Lactates
> 10 mmol/l

↻ CN

Hydroxocobalamin (Cyanokit®)

- Currently used in Europe and more recently in the USA
- 50 g bind 1 g of CN
- Dose: 5 g, to be repeated according to severity
- Ability to cross through the BBB
- Side effects: reddish discoloration of skin and urine, allergic reactions

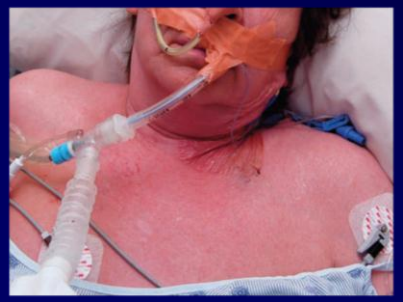
First-line antidote

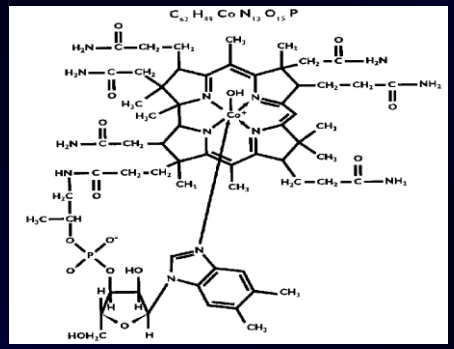
Other CN antidotes

Sodium thiosulfate:
efficient - safe
delayed action

MetHb forming agents:
potent
impairment of O_2 delivery

Cobalt EDTA:
very potent
immediate action
effective if late
numerous side effects





Pre-hospital algorithm

EuSEM guidelines 2012

Smoke inhalation incident

Evaluate:
- Fire in an enclosed space
- Duration of exposure
- Nimber of victims

Administer O_2 100%

Severe poisoning GCS ≤ 9	Intermediate poisoning GCS 10-13 and/or abnormal ABC	No neurological and/or hemodynamic symptoms GCS ≥14
Collect blood samples, if possible		
Hydroxocobalamin 5g (70 mg/kg)*	Hydroxocobalamin 5g (70 mg/kg)**	Monitoring

Transfer to hospital

Inhalation injury therapy and airway Management

- Humidified Oxygen
- Bronchodilators (IV or nebulized)
- Mucolytics and/or expectorants
- Intubation, mechanical ventilation, PEEP, HFO
- Pulmonary edema: role of fluid therapy
- Antibiotics: gram+ versus gram- coverage
- Corticosteroids controversial
- Investigational adjuncts:
  - Aerosolized Heparin: endobronchial fibrin-mucus casts
  - Exosurf: surfactant inactivation
  - Exogenous antiprotease: antiprotease consumption
  - PAF antagonists: ROI generation, membrane lipid peroxidation
  - Whole body hypothermia
  - ECMO

Enkhbaatar P. Crit Car Med 2007

Other toxic gases ?

In a prospective study (54 fire victims versus 116 controls), 15 volatile organic compounds were associated with death in fire victims

- ethyl acetate
- acrylonitrile
- propionitrile
- tetrahydrofuran
- toluene
- benzene
- o-xylene
- p-xylene
- ethylbenzene
- nitromethane
- trichlorofluoromethane
- indene
- trichloroethylene
- 2 pentanone
- acetaldehyde

Three (benzene, nitromethane, ethyl acetate) are remarkable in regard to their detection in blood with an elevated incidence and correlation with CO.

Houeto P. Unpublished data

Complications and sequellae

Early complications :

- Barotrauma injuries
- Hospital-acquired pulmonary infections

Late complications :

- Tracheal or bronchial stenosis
- Non-specific bronchial reactivity (Brooks syndrome)
- Bronchiolitis obliterans
- Bronchiectasis
- Chronic bronchitis
- Pulmonary fibrosis

Neurological sequellae :

- Smoke inhalation is a cause of post-interval syndrome
- Persistent hoarseness of the voice (surgical treatment)

Hydrogen sulfide (H_2S)

- Colorless, highly flammable and explosive gas, characteristic rotten-egg odor (sense of smell for H_2S fatigues in seconds)

- Naturally produced from putrefaction of organic substances, off-gassing of volcanos, and by certain industrial processes (oil)

- Irritant toxicity on mucous membranes and distal airway injury (exfoliation)

- Asphyxiant toxicity from interaction with metalloproteins including cytochrome oxidase + inhibition of succinic dehydrogenase by reducing disulfide bridges

➔ Knockdown effect
➔ Pulmonary effects
➔ Cardiovascular effects
➔ Neurological effects
➔ Lactic acidosis

Sargassum seaweed on Caribbean islands: an international public health concern

Between January and August 2018, 3341 cases in Guadeloupe and 8061 cases in Martinique

Subchronic exposure causes conjunctiva and upper airway irritation, headaches, vestibular syndrome, memory loss, and modification of learning abilities.

Résière D. *Lancet* 2019

Management of H_2S poisoning

-Supportive care

- Removal from exposure
- Oxygen (avoid mouth-to-mouth)
- Irrigation of exposed skin and eyes with normal saline
- Ventilatory support, anticonvulsants, antibiotics, …

- **Specific treatments** if persistent acidosis, coma, severe arrhythmia

- MethHb induction: CN antidote kit [amyl nitrate (gauze pad) + sodium nitrite (IV)]
- Hyperbaric oxygen
- Hydroxocobalamine ??

Scenarios of an attack with Chemical Warfare Agents

World War

Saddam Hussein bombing the Kurds

Syria Civil War

Tokyo tube attack by Aum Shinrikyo sect

Life-threatening effects of Organophosphorus Compounds

Mechanisms of toxicity:

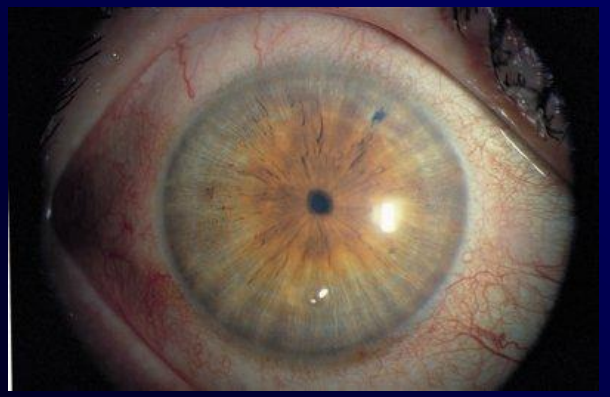
- Inhibition of AChE
- Accumulation of ACh
- Disturbance of cholinergic functions

Lethal effects:

- Bronchoconstriction/Bronchorrhoea (M)
- Central respiratory arrest (M, N)
- Peripheral respiratory muscle paralysis (N)
- Inhalation and ARDS (solvent)

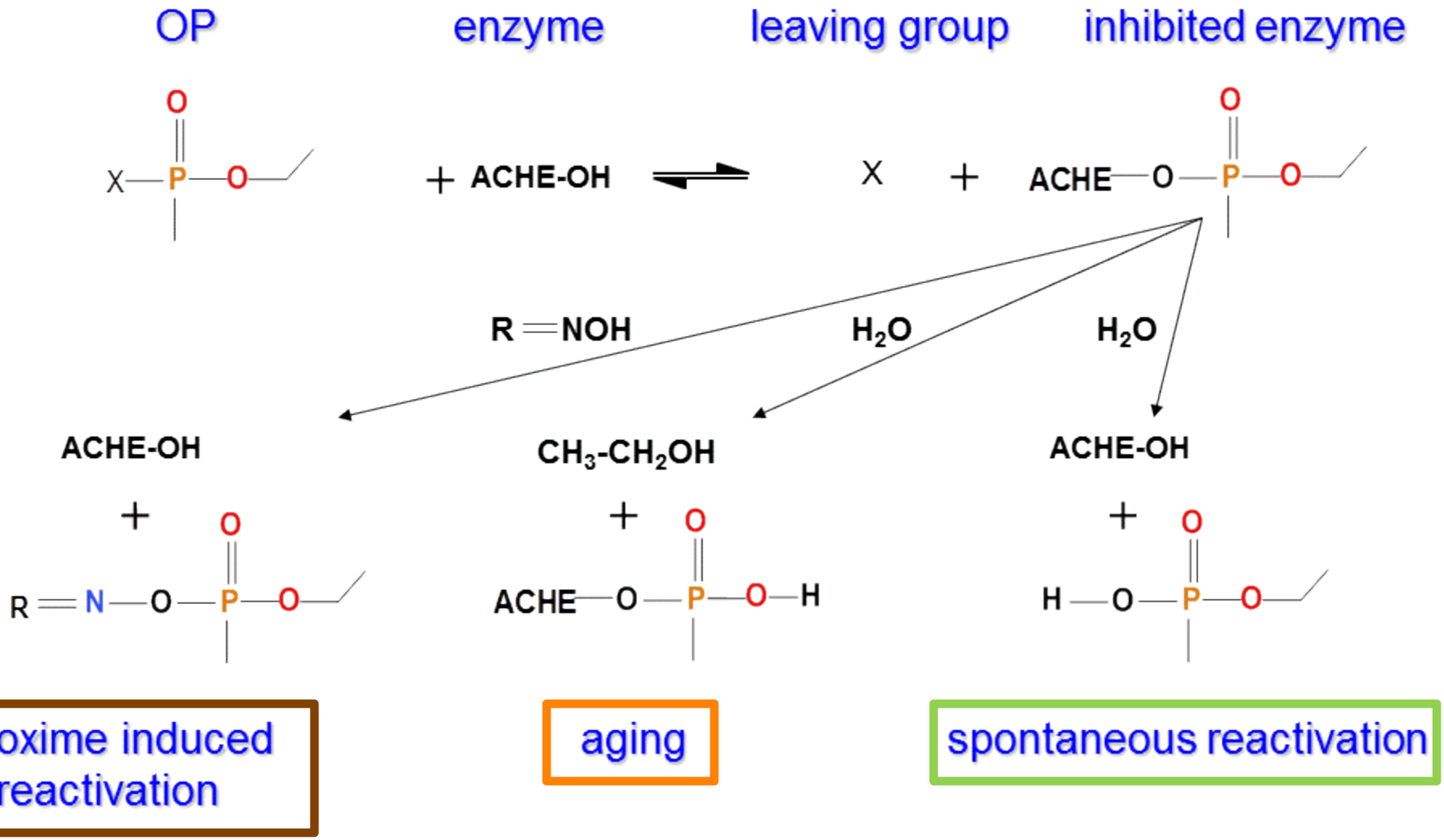
Diagnosis

Clinical Diagnosis: Signs and symptoms, circumstances
Confirmation with simple and easy to use laboratory methods



www.tumblr.com

Reactions occurring at AchE with an OP and an oxime



Therapeutic approach in Nerve Agent-poisoning

Self protection: Utmost important due to serious threat of percutaneous and inhalational poisoning

Treatment of muscarinic syndrome by atropine

Treatment and/or prevention of seizures by benzodiazepines

Prompt reactivation of inhibited AChE
- Even in the absence of severe signs by effective oximes
- Prolonged oxime treatment is expected to be mandatory in most patients

+ Supportive therapy: mechanical ventilation, sedation, cardiovascular stabilisation

Conclusions

- Gas may be responsible for acute life-threatening systemic and irritant respiratory toxicity as well as chronic disease resulting in respiratory and neurological functional disabilities.

- Smoke inhalation must be viewed as a polyintoxication. Cyanide plays an important role. While not uniformly present, it may often contribute to toxicity and lethality. Volatile organic compounds should also be considered. Hydroxocobalamin is recommended as first-line antidote due to its safety and assessed efficiency, in association with oxygen and supportive treatment, administered as rapidly as possible.

- Many various gas could be involved at the workplace. Reduction in FiO_2 is one major mechanism of toxicity. Management is mainly supportive. Prevention and detection are mandatory.

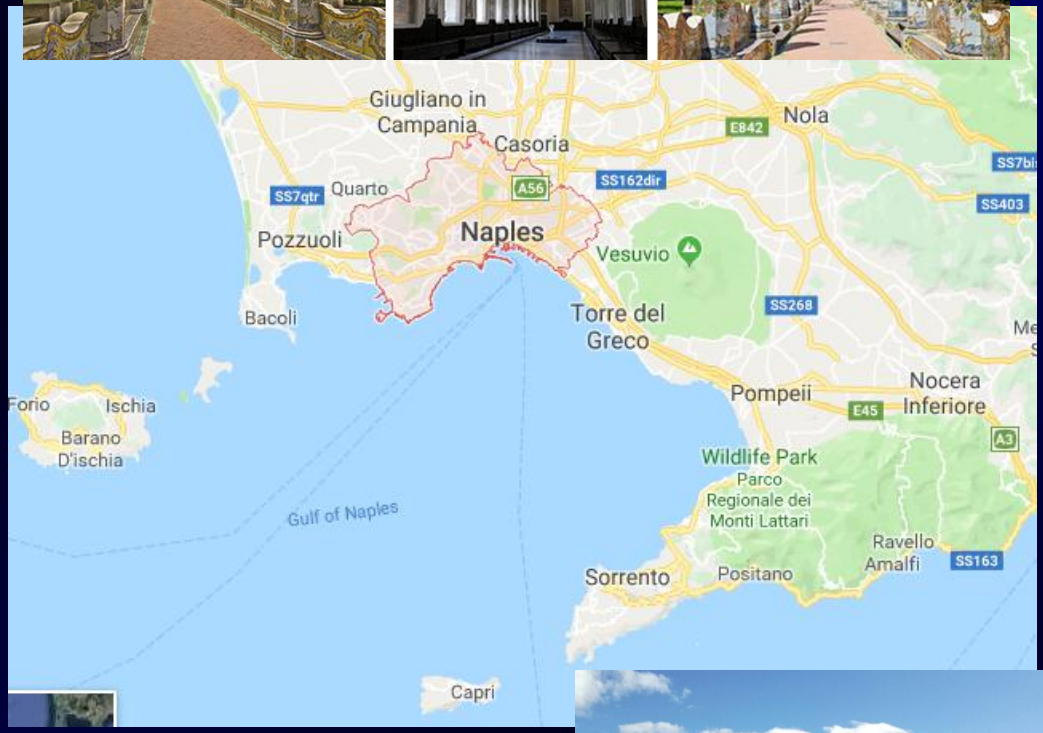
EAPCCT CONGRESS 2019

39th Congress of the European Association of Poison Centres and Clinical Toxicologists

21-24 May
Naples

European Association of Poison Centres and Clinical Toxicologists

21-24 May 2019: 39th EAPCCT Congress, Naples, Italy



Venue: Terminal Napoli SpA, Centro Congressi Stazione Marittima

QUESTIONS ?