



The impact of route of exposure on toxicological hazard assessment: How do you take your mustard?

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Routes of exposure to toxic chemicals

- Oral
- Dermal
- Inhalation
- Other routes

Organs through which chemicals enter the body can also be sites of action

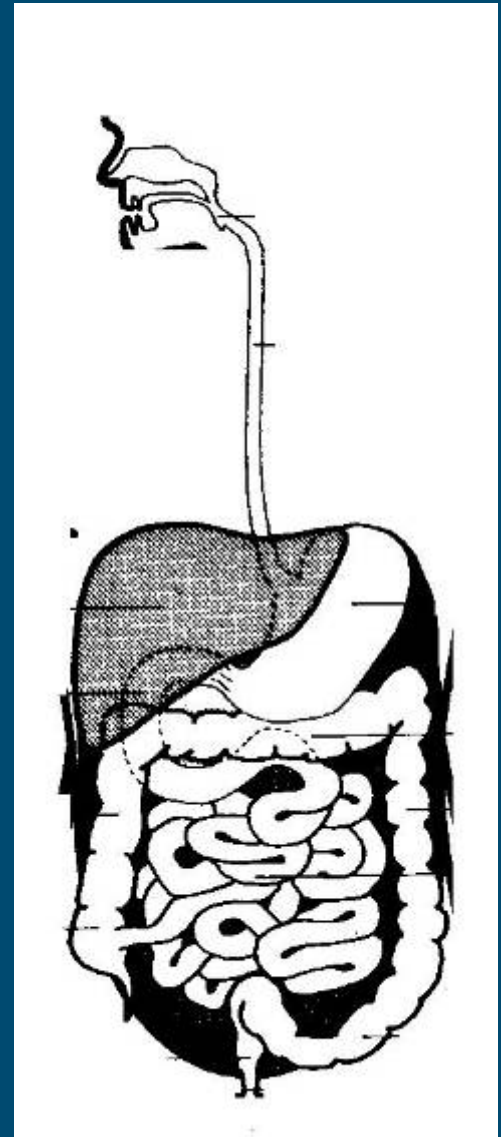
- Aim
 - To identify and quantify the hazard represented by all these routes combined.
 - Recommend a dose which will not cause harm in the short or long term.

Oral

- Dose in $\text{mg}\cdot\text{kg}^{-1}$
- Intake in contaminated food
- Intake from contact with fingers, clothing etc.
- One of the most common route for toxicological screening

Oral

- Conditions in the alimentary canal
 - Mouth
 - Stomach
 - Small intestine
 - Large intestine



Sulphur Mustard

Oral toxicity

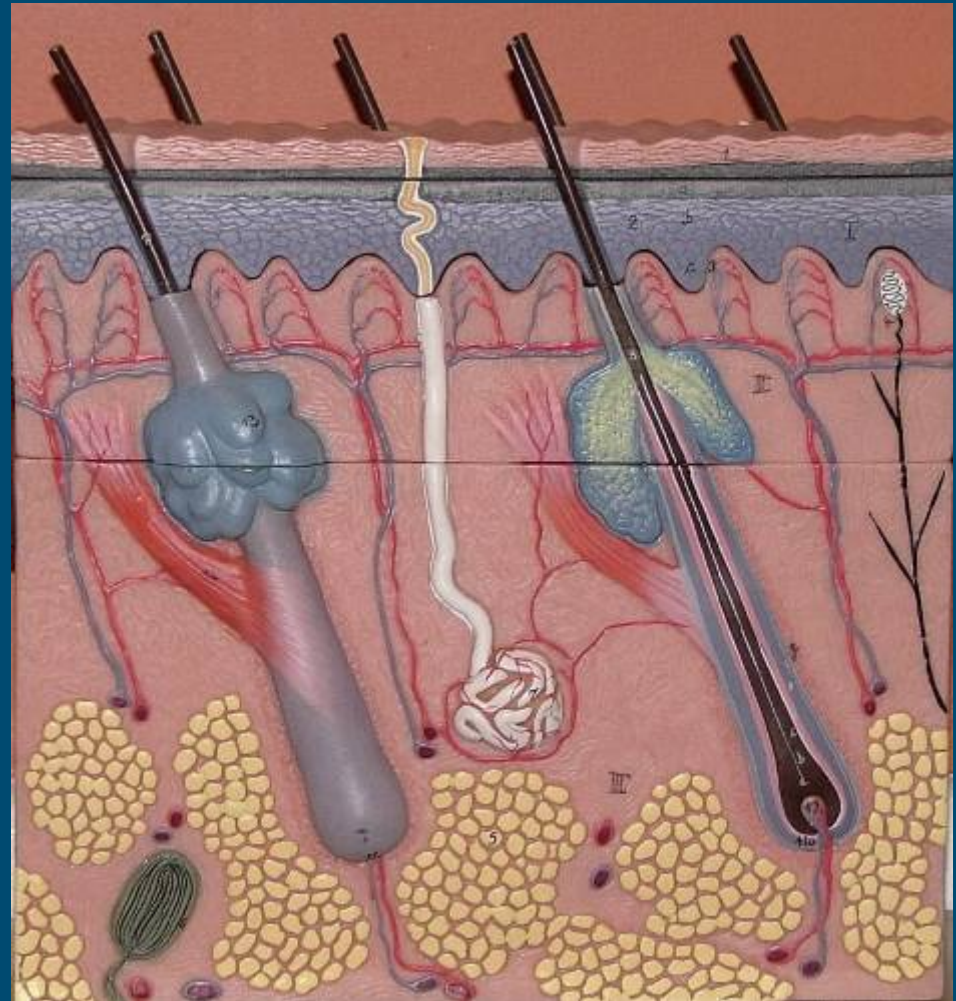
- Chronic feeding study in rats (Sasser 1989)
 - Endpoint was hyperplasia of the forestomach
 - Local effect produced by dosing with gavage
 - NOAEL = 0.03 mg/kg/day for 90 days

Dermal

- Dose in $\text{mg}\cdot\text{min}\cdot\text{m}^{-3}$ for exposure to vapour.
- Dose in $\text{mg}\cdot\text{kg}^{-1}$ or $\text{mg}\cdot\text{m}^{-2}$ for liquid contamination.
- Intake from contact with clothing and the environment
 - Liquid or vapour phase.
- Key question – are primary toxic effects local or systemic?

Dermal

- Skin is a barrier to diffusion.
- A depot can be formed in the skin during absorption.
- Absorption into the blood takes place in the superficial dermis.
- Exposure standards normally derived from systemic toxic effects, but Sulphur mustard produces severe local effects.



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Percutaneous Vapour

- Unique data set of exposures of human volunteers in controlled chamber conditions.
 - Heinen et al 1946 (vapour exposures)
 - CDRE (India) publications 1930-1945 (liquid contamination)
 - Australian trials 1940-1945 (vapour exposures, concentrations and times not published)

Sulphur Mustard

Percutaneous Vapour

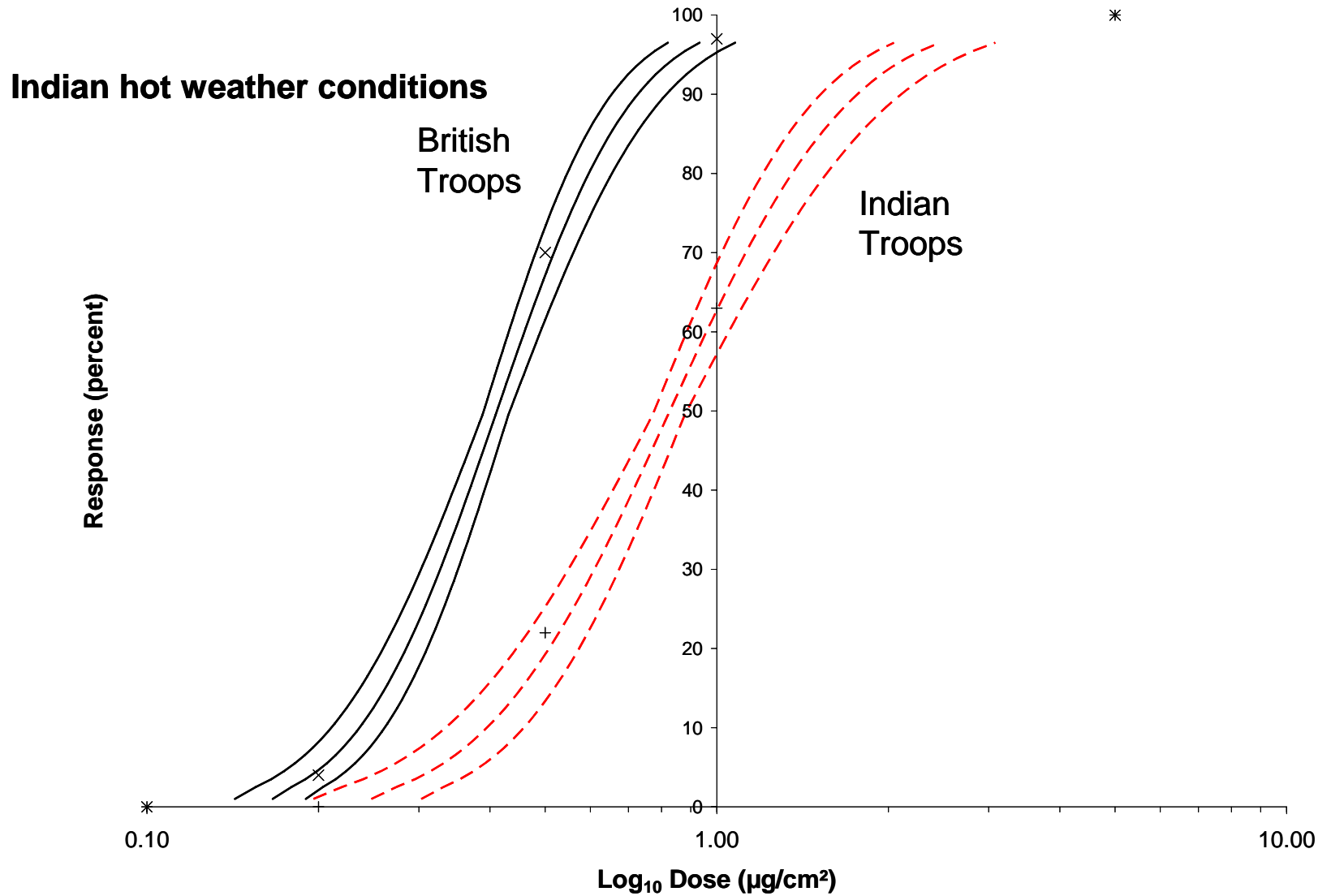
- Hienen
 - Ct's between $49.5 \text{ mg}\cdot\text{min}\cdot\text{m}^{-3}$ (t = 30 mins) and $695 \text{ mg}\cdot\text{min}^{-3}$ (t= 60 mins).
- CDRE (India)
 - Ct's between $69 \text{ mg}\cdot\text{min}\cdot\text{m}^{-3}$ (t = 5 mins) and $750 \text{ mg}\cdot\text{min}\cdot\text{m}^{-3}$ (t = 16 mins)
- LOAEL = $1.65 \text{ mg}\cdot\text{m}^{-3}$ for 30 mins

Sulphur mustard

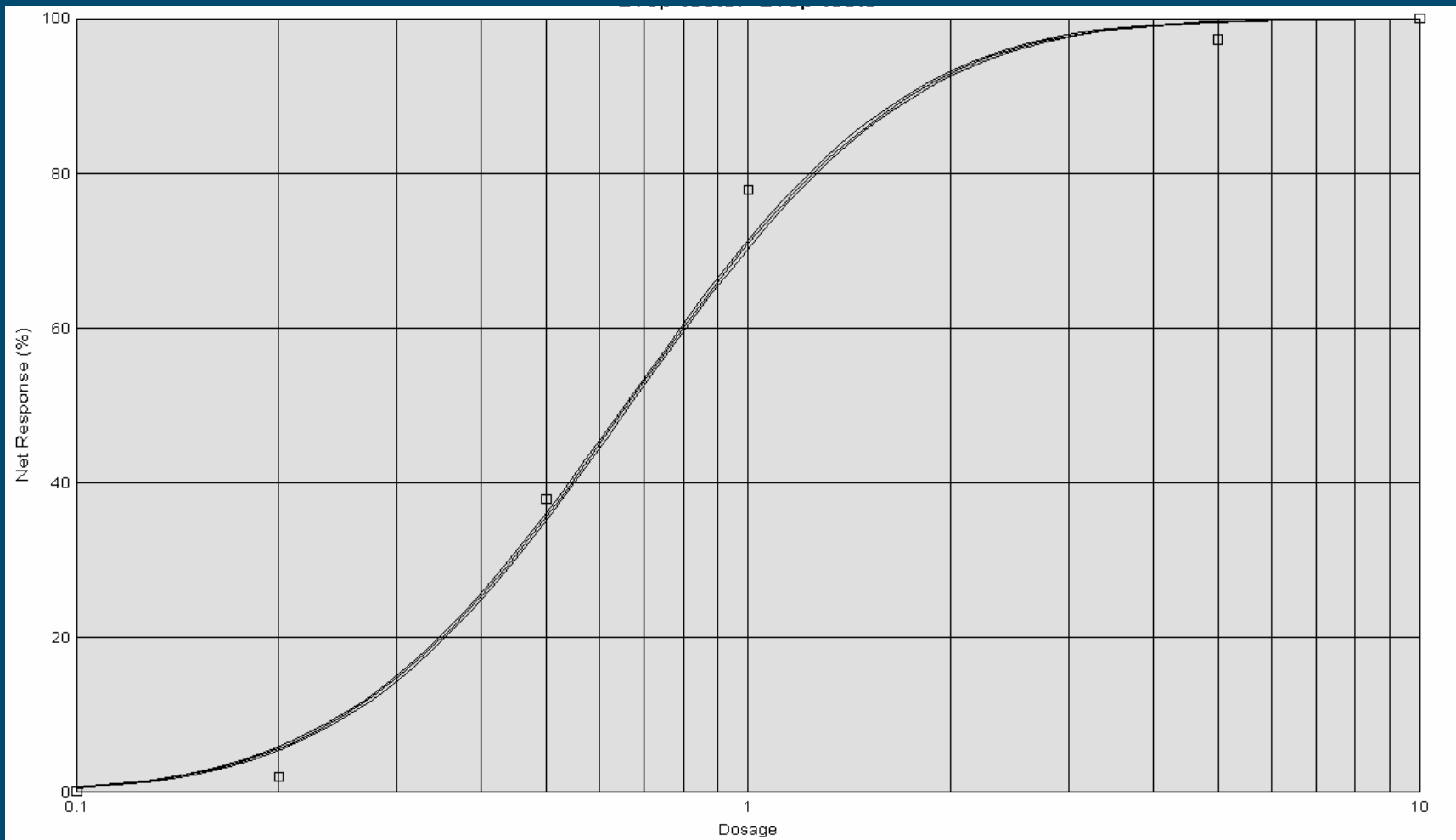
Percutaneous liquid

- Large numbers of volunteers exposed to HD in benzene droplets on the forearm.
- Studies carried out in UK (Porton Report 999) and India (CDRE (India) Reports 110 and 138)

Dose ($\mu\text{g}\cdot\text{cm}^{-2}$)	Tested	Responded
0.1	1,173	2
0.2	1,173	24
0.5	1,336	506
1	1,273	991
5	1,273	1,238
10	22	22



Pooled dose response curve for skin irritancy of HD

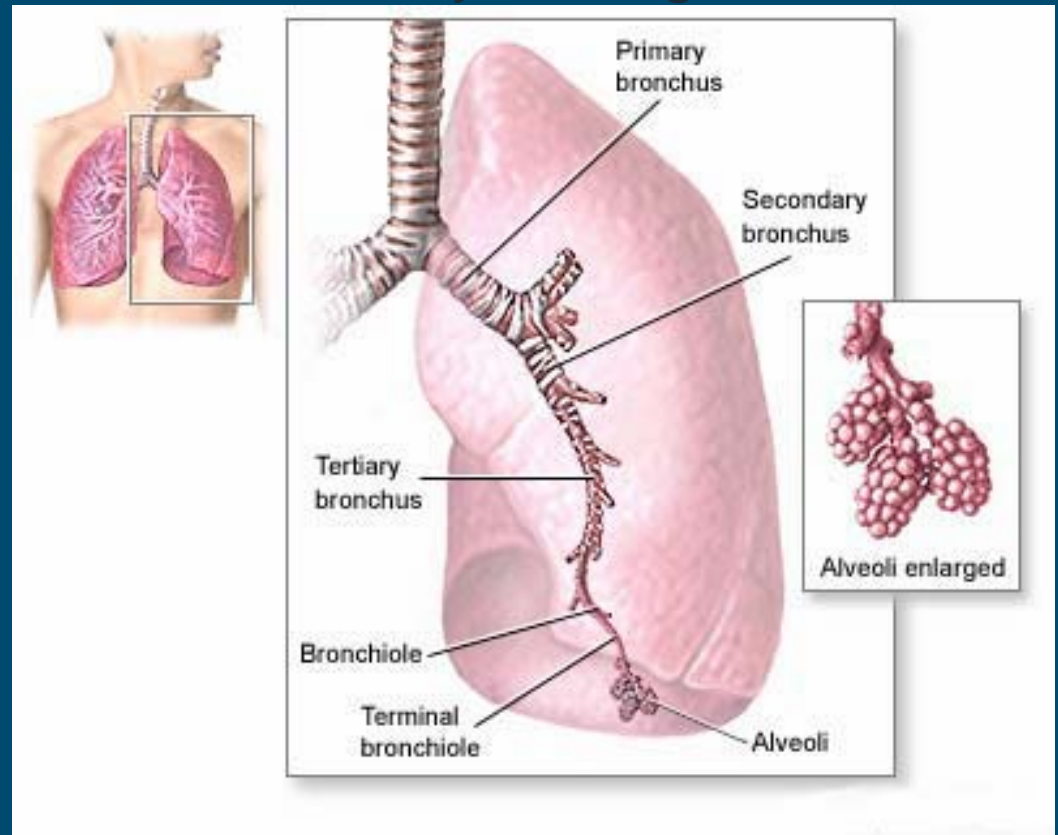


Inhalation

- Dosage in $\text{mg}\cdot\text{min}\cdot\text{m}^{-3}$
- Can also be expressed as a concentration with a reference period (e.g. $\text{mg}\cdot\text{m}^{-3}$ for 8 hours)
- Route of most concern
 - Everyone has to breath
 - Individual has little control over what is in the environment(?)
- Inhaled dose determined by:
 - atmospheric concentration.
 - breathing rate.
 - inspired fraction absorbed

Inhalation

- Very large surface area for absorption
- Membranes are very delicate and easily damaged
- Protected by the nasopharynx and muco-ciliary escalator



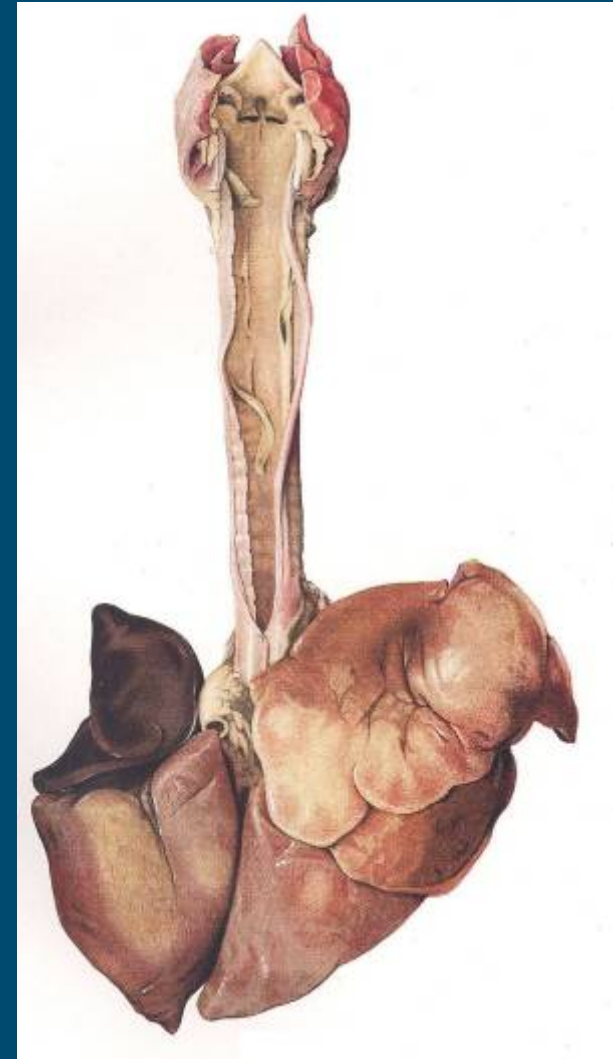
Inhalation

- Can also produce effects on the eyes.
- Local Irritation
- Toxicity directly to the eye
- Toxicity to the system after absorption.

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- No quantitative human data on inhalation.
- Some epidemiology without accurate dosimetry.
- Animals and humans react in a similar way.
- Very few animal studies on lethality.
 - LCt_{50} (mice) = 1000 mg.min.m⁻³ (10 min exposure).

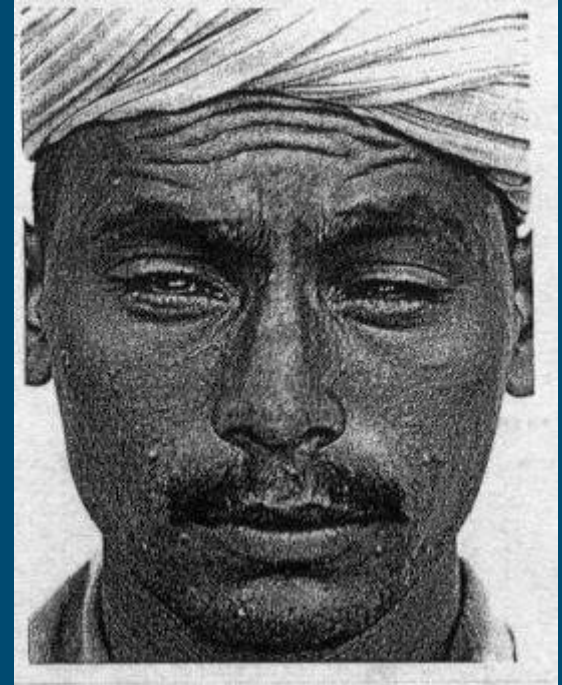
Inhalation - lungs



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- Two studies of effects on human eyes.
 - Guild and Harrison (1941)
 - Andersen (1942)
- Produces conjunctivitis photophobia and blepharospasm.
- LOAEL
 - Ct 12 mg.min.m⁻³ (claimed)
 - 0.06 mg.m⁻³ for 24 (8x3) hours.

Inhalation-eyes



5 mg.m⁻³ for 14 mins

CDRE (India) Report 241

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Inhalation

- H is a genotoxic carcinogen
- Local effects only useful to protect for short term emergency use.
- Only one study located to date of long term exposure to H where tumour incidence was recorded.
- 52 week exposure of rats to H vapour.
 - McNamara et al 1975
 - NOAEL = 0.001 mg.m⁻³

Multiple exposures

- If concerned about more than one route of exposure an exposure standard can be derived for each route and the sum of the exposures accounted for.

$$\frac{\text{Inhalation exposure}}{\text{Inhalation exposure standard}} + \frac{\text{Dermal exposure}}{\text{Dermal exposure standard}} + \frac{\text{Oral exposure}}{\text{Oral exposure standard}} < 1$$

Route to route extrapolation

- If data does not exist for a particular route it may be possible to extrapolate a dose from toxicology from a different route.
- If such a calculation is done, extra uncertainty factors should be included to account for the inadequacy of the toxicological database.

Other routes

- Injection
- Ocular
- Nasal
- Buccal

Summary

- The route of exposure is a critical determinant of:
 - The nature of the toxic effect
 - The dose required to produce a toxic effect
- For emergency service or military use the toxic end point may be different than for occupational exposure.
- Toxicity information is not always available via a relevant route of exposure. If so, route to route extrapolation should be explored with appropriate uncertainty factors to account for lack of appropriate data.