# Exposure to Multiple Chemicals

# Possible Interactions

- Independent
- Additive
- Antagonistic
- Potentiation
- Synergistic

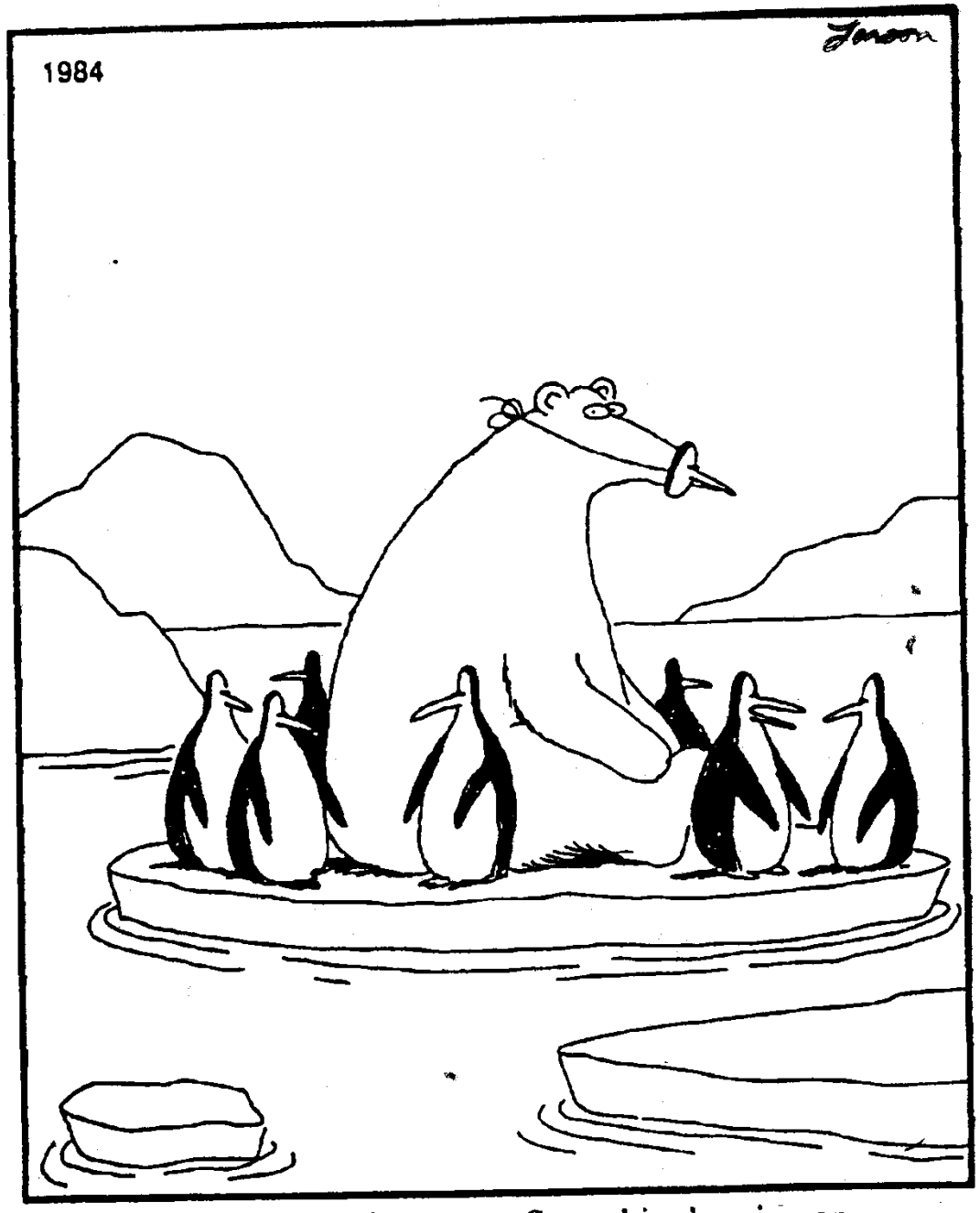
# Concurrent exposures

- Exposure to agents that have the same effect or act on the same target organ are additive

$$\frac{C_1}{T_1} + \frac{C_2}{T_2} + \ldots < 1$$

# Classic Example

- Worker exposed to both toluene and xylene
- Standardized exposures are “added” together




"And now Edgar's gone....Something's going on

# Additive effects – OK, OK. I know this one

- Methyl acetate and methanol
- 2-ethoxyethyl acetate and 2-ethyoxyethanol
- Ethylene glycol dinitrate and nitroglycerin

# Principle is easy but how to recognize additive chemicals

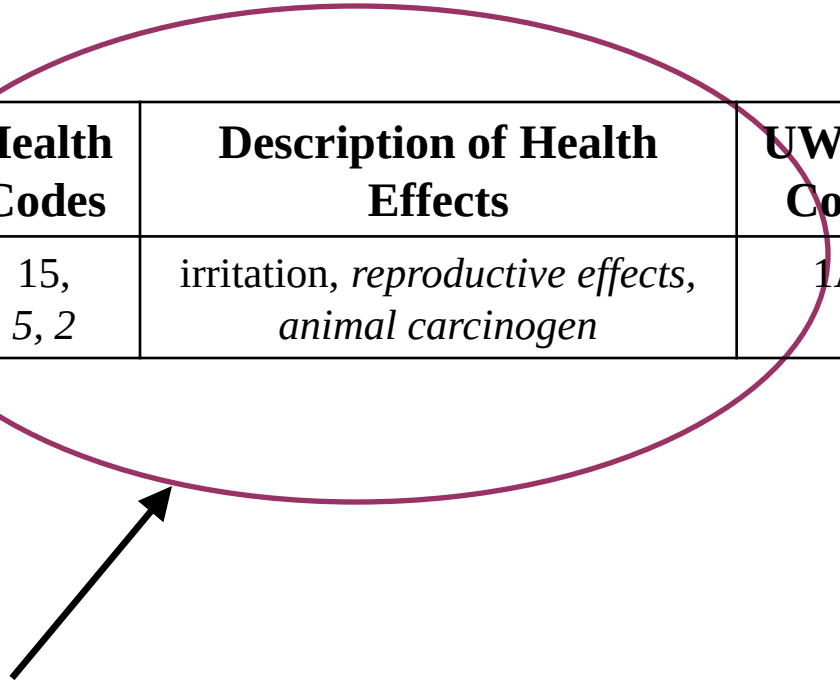
- TLV Documentation
- TLV booklet
  - –(TLV basis – critical effects)
- Toxicology references
- Our “Desktop Guide”

# Trichloroethylene documentation

- “50 ppm is recommended to control complaints of headaches, fatigue and irritability. STEL protects against anesthetic effects. This level should also provide a significant margin of safety from liver injury.”

# “Desktop Guide” in back of handout

| Chemical Name | Health Codes | Description of Health Effects | UWHA Code | Primary Data TLV is Based on |
|---|---|---|---|---|
| Acetaldehyde | 15, *5, 2* | irritation, *reproductive effects, animal carcinogen* | 1A | combination |



Primary Heath effect that TLV is based upon, *secondary health effect that occurs at higher exposures or perhaps is not fully understood at this time*

# Can provide hint of future health issues

**former Toluene entry**

| Chemical Name | Health Codes | Description of Health Effects | UWHA Code | Primary Data TLV is Based on |
|---|---|---|---|---|
| Toluene | 8, 15, *5 ,7* | narcosis/headache, irritation, *reproductive effects*, *CNS performance* | 2 | combination |

**current Toluene entry**

| Chemical Name | Health Codes | Description of Health Effects | UWHA Code | Primary Data TLV is Based on |
|---|---|---|---|---|
| Toluene | 5, 7, *7, 15* | Pregnancy loss, visual impairment, *irritation effects, CNS performance* | 4 | combination |

# Grain dust – but what about…

Cereal grain

Decomposition products of grain

Microorganism

Fragments of plant matter

Hairs, feathers and excrement of birds

Insects, insect parts

Fertilizer, pesticides, herbicides

Metal fragments, lubricating oil, paint chips

How do we allow for all these?

# Its built into TLV (within reason)

Cereal grain

Decomposition products of grain

Microorganism

Fragments of plant matter

Hairs, feathers and excrement of birds

Insects, insect parts

Fertilizer, pesticides, herbicides

Metal fragments, lubricating oil, paint chips

# TLV says what to consider

Diesel Fuel

“These limits apply only to fuels that do not contain significant levels of PNAs or hydrocarbons boiling outside the middle distillate range (175°– 338°C). Fuels that contain high-boiling ends (> 338°C) may have significant levels of PNAs, and are not covered in this TLV”

# Concurrent Exposure to Chemical and Physical Agents

- Not as widely considered
- Straight additive may not be best but that's the place to start

<u>Direct effects</u>

Vibration and lead

# Chemical and Physical

- Example is phototoxic or photoallergic
- drugs
- Perfumes, sunscreen
- celery (ingested)
- Coal tar

# Phototoxic case Study

Phytophotodermatitis commonly occurs in skin exposed to sunlight after contact with plants containing furocoumarins. While it is recognized that the consumption of plants or vegetables containing furocoumarins can potentially trigger a phytophotodermatitis, there have been no reports to date of a phytophotodermatitis triggered by an ingested herbal remedy. We describe the case of a 56-year-old farmer who developed an extensive photo-induced dermatitis after ingesting a herbal decoction prescribed for his chronic hand dermatitis.

# Noise and Solvents

Growing body of information that noise and solvents > noise alone

Toluene, mixed solvents, n-butyl alcohol

If a worker is exposed to noise and n-butyl alcohol, do you need to make an adjustment?

# N-Butyl Alcohol TLV Documentation (1992)

"In view of the apparent potential of n-butyl alcohol to increase hearing loss in the younger age group of workers, and to impair vestibular function at levels below 110 ppm, a 50 ppm TLV-Ceiling is recommended"

No adjustment (effect already built-in)

Chemical and Physical

Indirect Effects

Narcotic and Class II laser

- Are those health effects additive?
- Is there a problem with concurrent exposure?

# Now that we know Additive

- Dimethyl chickenwire raises COHb as does carbon monoxide
- Additive??
- CO = 0.6 TLV  DMC = 0.6 TLV
- Is this an overexposure??

# From the TLV documentation

| DMC ppm | DMC Standardized exposure | CoHB levels (%) | CO standardized exposure | CO (ppm) |
|---|---|---|---|---|
| 50 | 1 | 1.9 | 0.5 | 12.5 |
| 100 | **2** | **3.5** | **1** | 25 |
| 150 | 3 | 5.3 | 1.5 | 37.5 |
| 100 | 4 | 6.8 | 2 | 50 |

# Partially Additive

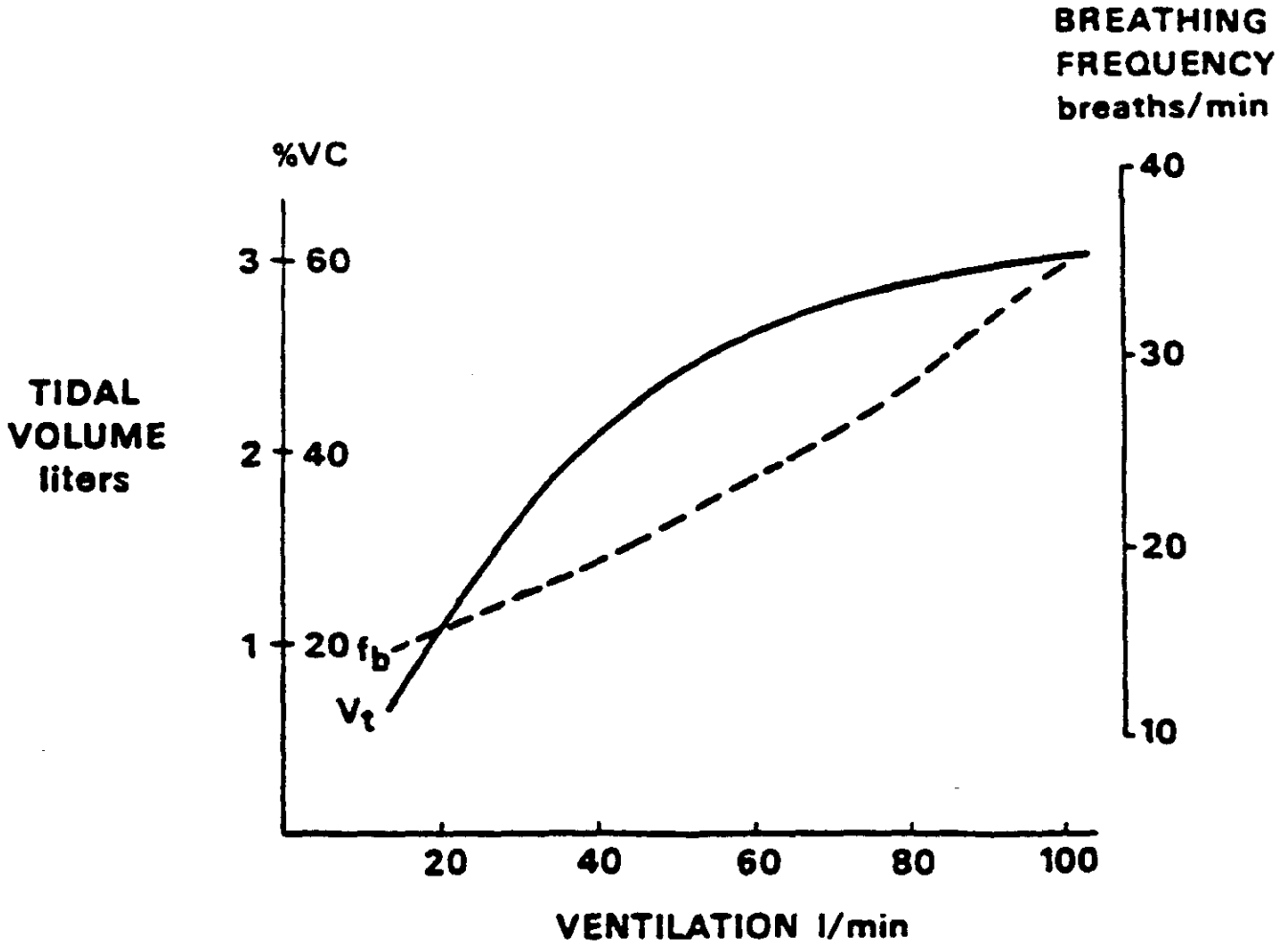
CO = 0.6 TLV  DCM = 0.6 TLV

- Is this an overexposure??
- C0 is at 0.6 x TLV
- DMC is half as good as producing COHb so 0.6 “becomes” 0.3 x TLV
- Combined exposure is 0.9 of the TLV for CO

# Summary

- Use available info
- TLV Documentation has info
- Consider total health effects
- Partially additive
- Be aware of synergism and potentiation

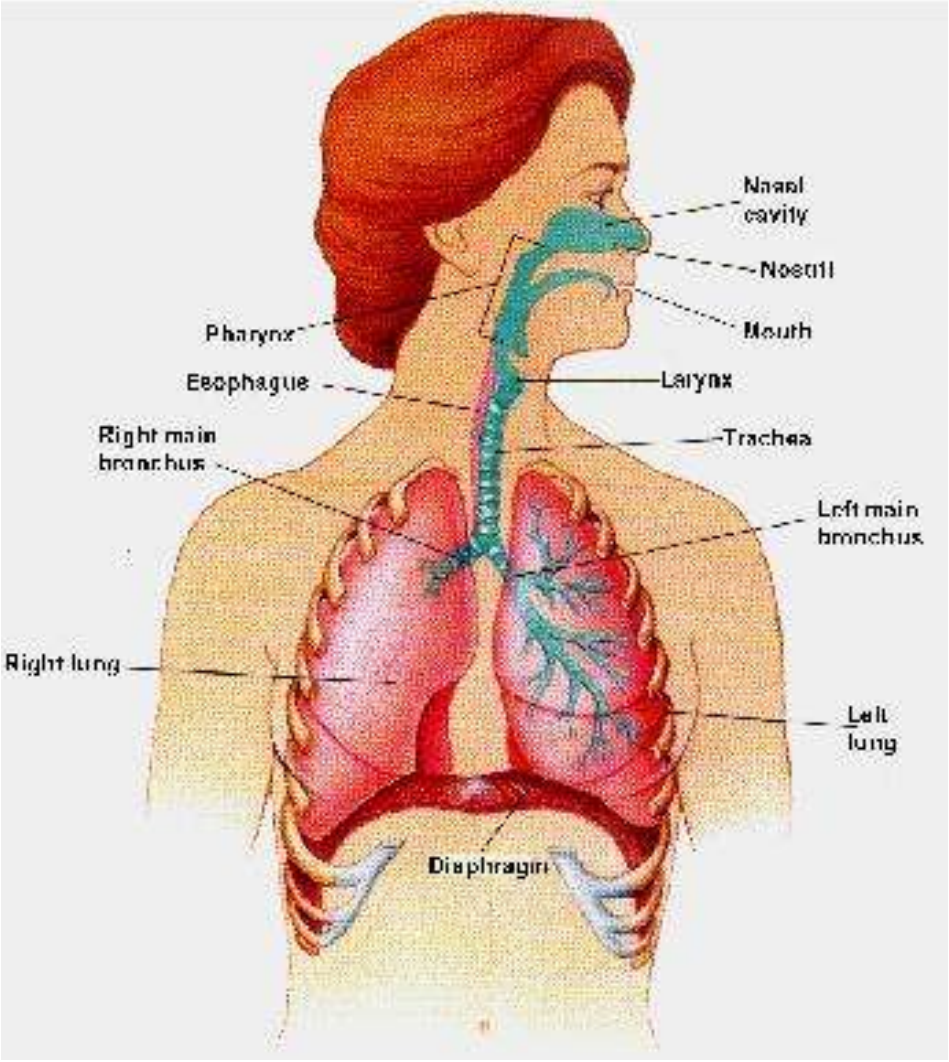
# Physical Exertion



# Whether it playing hockey


# Or just shoveling the sidewalk

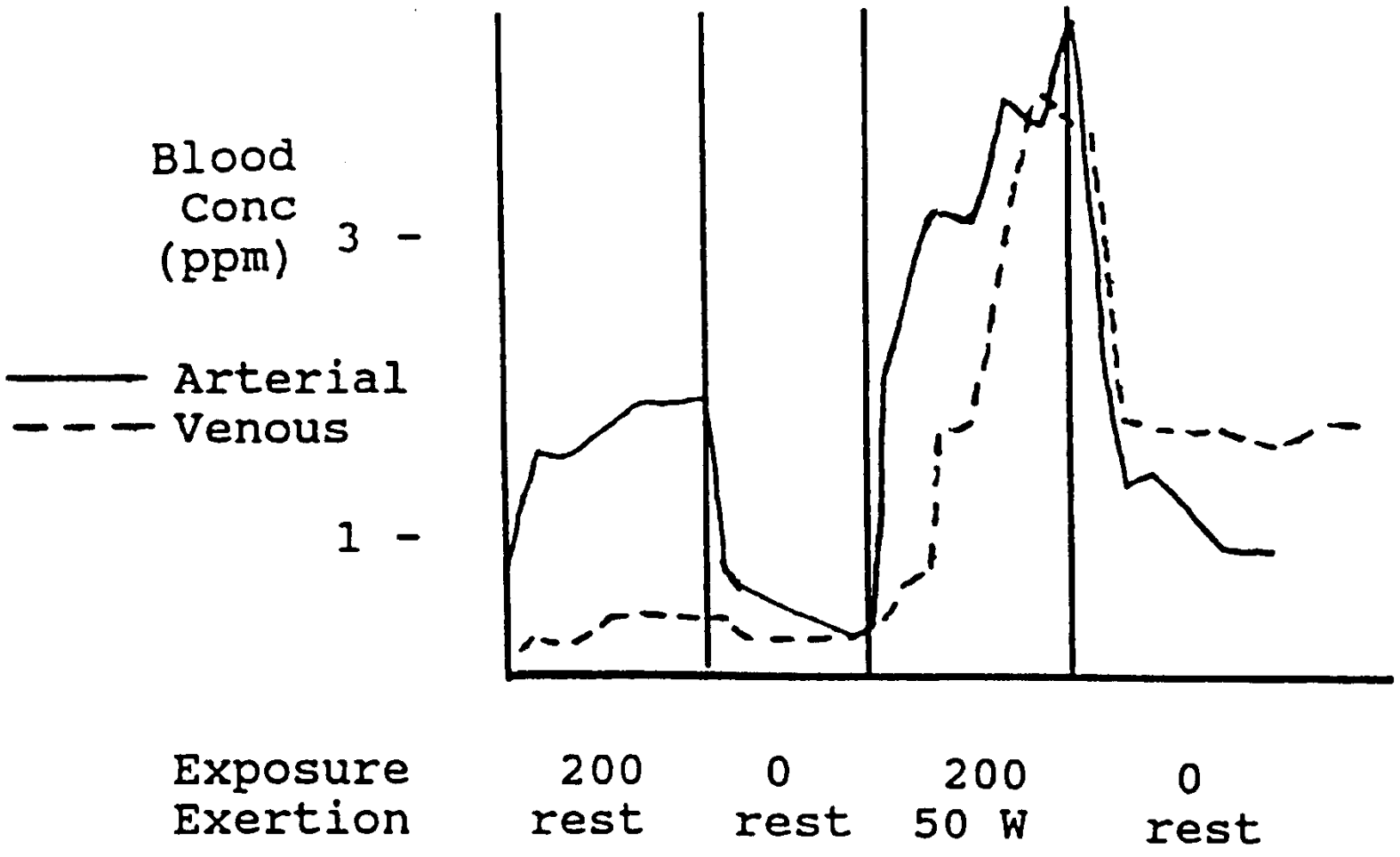
# You breath faster



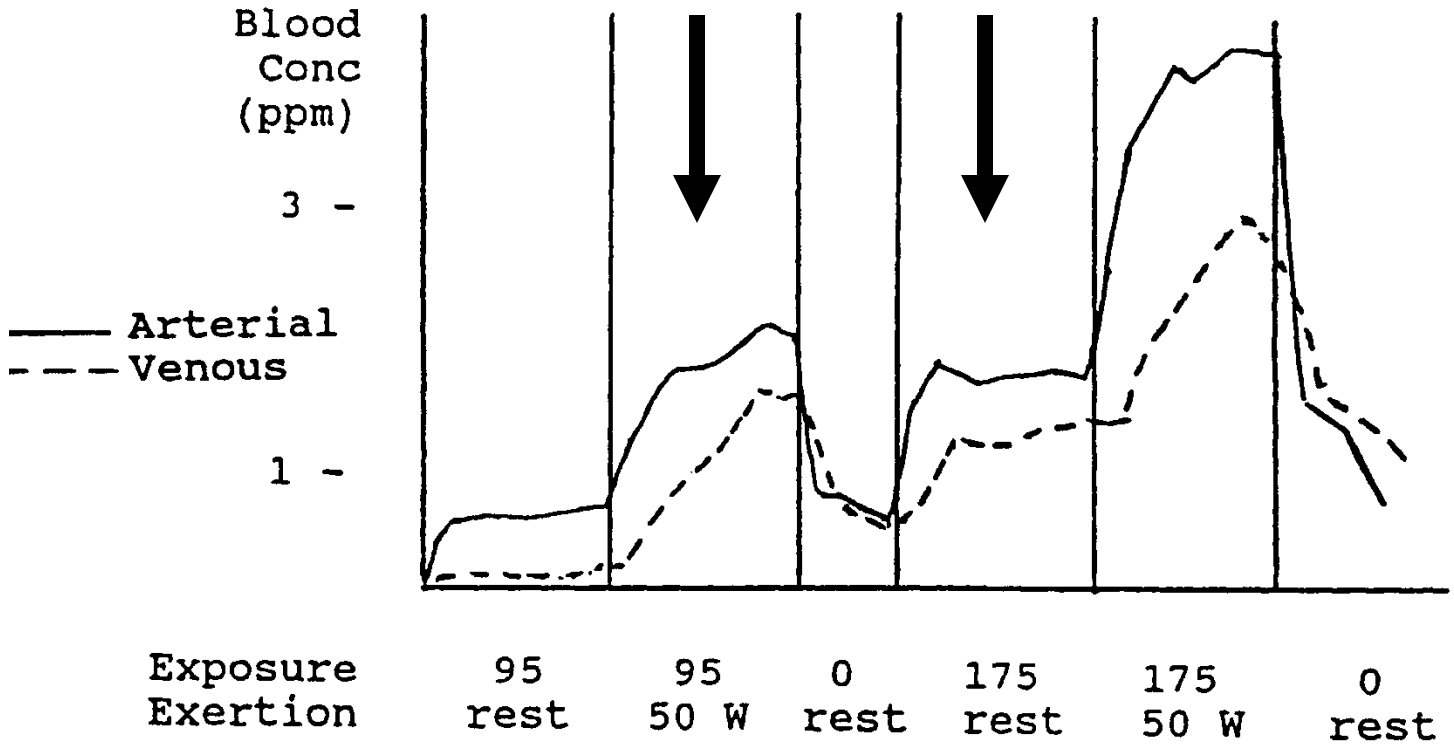
# Physical Exertion

- TLVS often assume that workers breath 10 $m^3$ ( 21 lpm) of air in 8 hour shift
- Exertion significantly increases ventilation rate
- Is this assumption always true?

# Blood concentration of toluene



# Blood concentration of toluene



# Absorbed dose rate

Inhalation dose depends on

Breathing rate (lpm)

duration

% retained

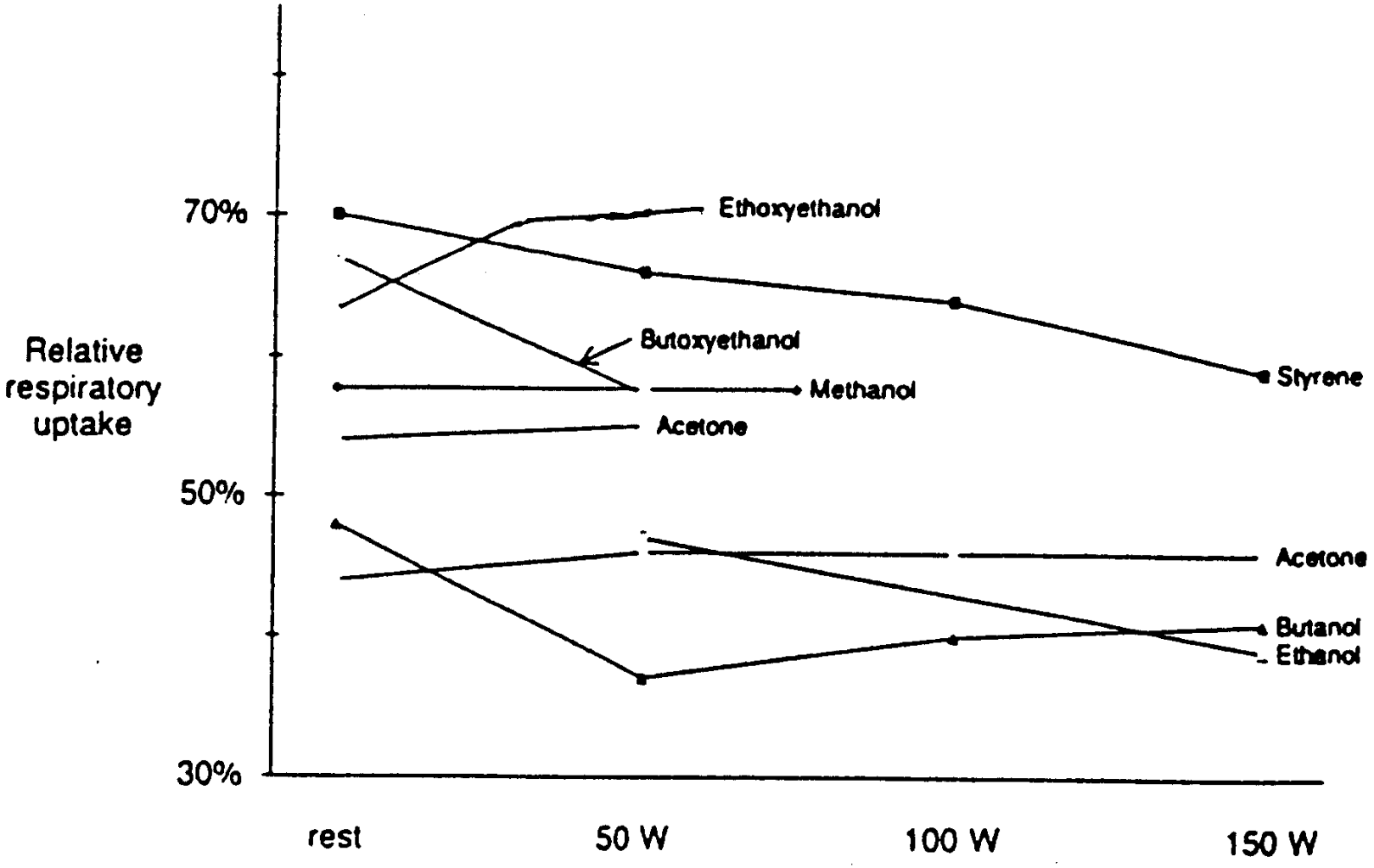
# Respiration increases with workload

| Workload (watts) | Ventilation (lpm) | Cardiac Output (lpm) | Liver Perfusion (lpm) |
|---|---|---|---|
| 0 | 5 | 6 | 1.5 |
| 50 | 16 | 9 | 1.3 |
| 100 | 27 | 13 | 1.2 |
| 150 | 38 | 19 | 1.2 |

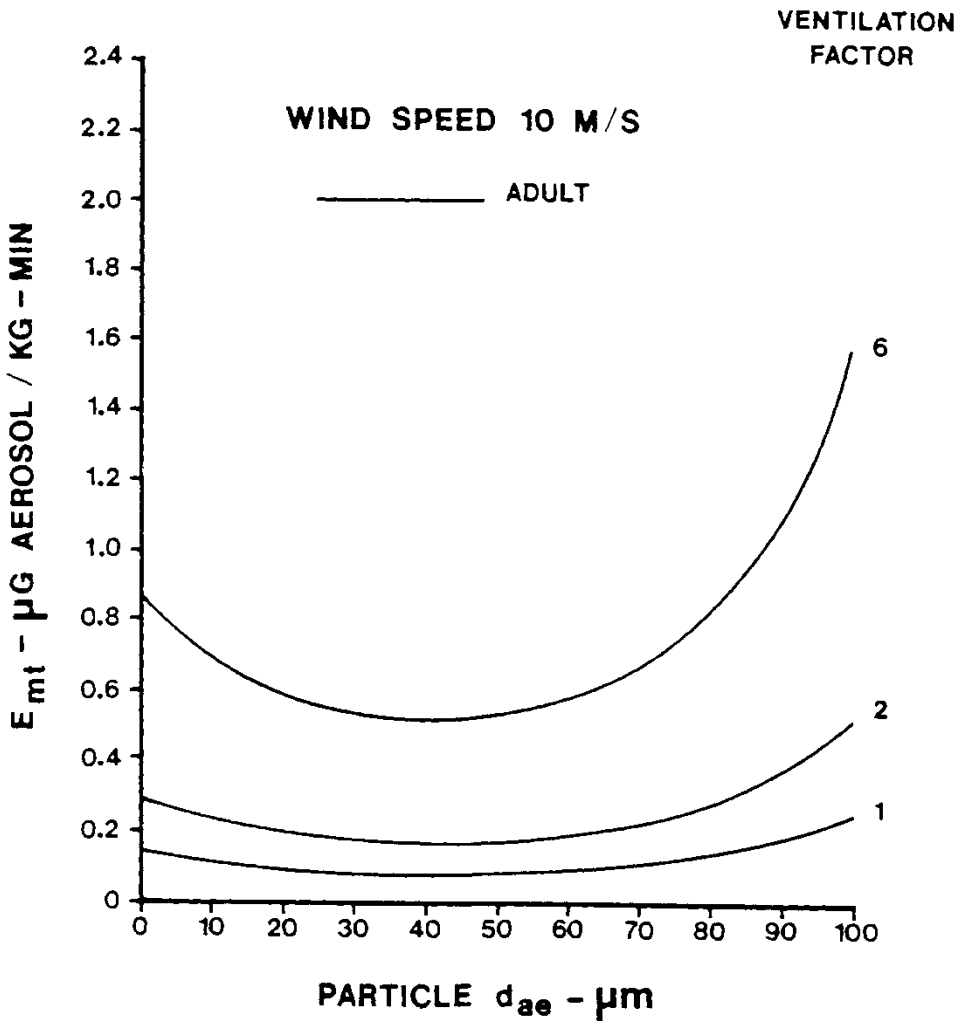
# What about % retention

- What % do I keep of what I breath in?
- A.k.a. Relative Respiratory Uptake
- Varies but 30 – 70 %
- Does it change with increased respiration

# % Retention solvents ≈ constant with increased respiration rate



# Particle deposition also proportional to ventilation rate




Deposition up 6x as ventilation rate up 6x

# Okay, so If

You “kept” the same percent of what you breathed at any ventilation rate

AND

Amount you breathed in doubled

Then that means that your absorbed dose ….

# If

% retained stayed the same

AND

Respiration rate doubled

Then that means that the absorbed dose also doubled

1 µg/l x 20 lpm x 50% RRU gives absorbed dose of 10 µg/min

1 µg/l x 40 lpm x 50% RRU gives absorbed dose of 20 µg/min

Twice the ventilation rate give twice the absorbed dose at the same air concentration

# Is this built into the TLV

- TLV based on several types of data
- Industrial experience
- Animal data
- Human volunteers
- Analogy
- Each has own assumptions

# Industrial Experience

Exertion likely built in

Exposures in mining and foundries would include exertion levels

If anything, exertion is down due to mechanization

# Animal Data

Typically assumes 10 $m^3$ breathed in a shift.

If ventilation rate is higher, adjustment should be made

# Human Volunteer

Mostly volunteers are “at rest”

Sometimes exercising on stationary bikes

should assume at rest and make an adjustment unless indication in documentation

HV often used for irritant testing where body burden is not an issue

# Analogy

- Based on or linked to another similar chemical
- Look up that chemical and see what primary data TLV is based on

# How will I know

How will I know what type of information the TLV is based upon

Read the documentation

Its not that hard

# How will I know

"Based on the controlled volunteer inhalation studies, …

Sulphuric acid documentation

# How will I know

"In chronic rat inhalation studies, exposure to high concentrations of titanium dioxide"

titanium dioxide documentation

# “Desktop Guide” in back of handout

| Chemical Name | Health Codes | Description of Health Effects | UWHA Code | Primary Data TLV is Based on |
|---|---|---|---|---|
| Acrylamide | 20, 7, *2* | dermatitis, CNS effects, *suspected carcinogen* | 4 | animal data |

Primary Data TLV is Based Upon

Tells you whether TLV is based on animal data, industrial experience, human, volunteers, analogy or combination

# Here is an example

- We have high exertion
- TLV not based on industrial experience but rather on animal data that assumes 10 m3 breathed in an 8 hour shift

# Ventilation Rates

- Ventilation rate (lpm) = 15.4 (kcal/min) +5
- Ventilation rate (lpm) = 0.22 (watts) + 5
- OK – need to know energy output

Light = 50 watts = 16 lpm

- Sitting or standing to control machines
- Performing light hand or arm work, writing, typing

Moderate = 125 watts = 32.5 lpm

- Walking around with moderate lifting or pushing, hammering nails, filing metal
- Planing wood, raking a garden, cleaning a floor

Heavy = 175 watts = 43.5 lpm

- Pick and shovel work, laying railroad tracks

(source ozone documentation)

# Heat Stress Documentation

| | | |
|---|---|---|
| Hand work | - light | - 0.4 kcal/min |
| | - heavy | - 0.9 kcal/min |
| One arm work | - light | - 1.0 kcal/min |
| | - heavy | - 1.7 kcal/min |
| two arms work | - light | - 1.5 kcal/min |
| | - heavy | - 2.5 kcal/min |
| Whole body | - light | - 3.5 kcal/min |
| | - moderate | - 5.0 kcal/min |
| | - heavy | - 7.0 kcal/min |
| | - very heavy | - 9.0 kcal/min |

# Examples of Activities

| | | |
|---|---|---|
| Hand work | - light | writing |
| | - heavy | typing |
| One arm work | - light | |
| | - heavy | hammering nails |
| two arms work | - light | filing metal |
| | - heavy | |
| Whole body | - light | |
| | - moderate | cleaning a floor |
| | - heavy | laying railroad ties |
| | - very heavy | |

# Ventilation Rates (again)

- Ventilation rate (lpm) = 15.4 (kcal/min) +5
- Ventilation rate (lpm) = 0.22 (watts) + 5

# Problems

- Exertion isn’t constant
- Exposure isn’t constant

# Exertion Example

- Worker files metal parts for 80% of day. Other 20 is putting parts on storage shelves.
- Calculate workload and ventilation rates for these activities
- Is TLV is based on 27 lpm, is an adjustment required??

# Hints

- Light work 2 arms: metal filing = 1.5 kcal/min
- Ventilation rate (lpm) = 15.4 (kcal/min) +5

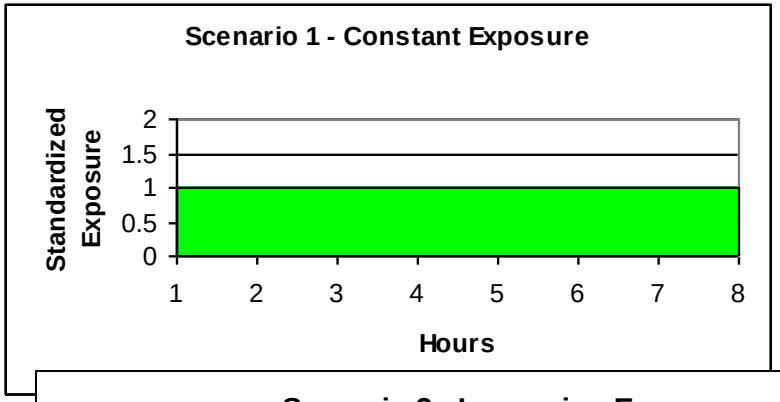
| | | |
|---|---|---|
| Whole body | - light | - 3.5 kcal/min |
| | - moderate | - 5.0 kcal/min |
| | - heavy | - 7.0 kcal/min |
| | - very heavy | - 9.0 kcal/min |

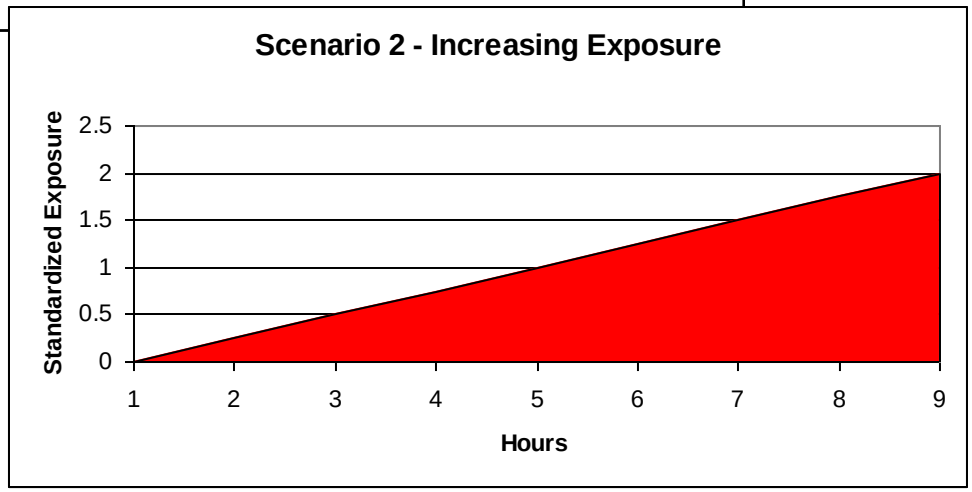
# Whew!!

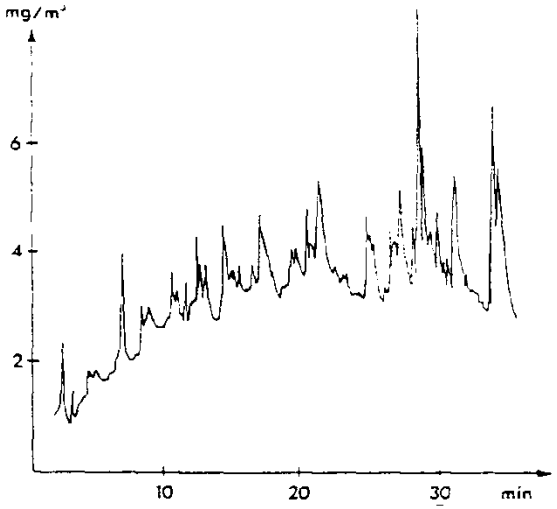
- That was hard work. Should we adjust the TLV for carbon dioxide in this room?

- Just kidding

# Exposure Profile




# What are we protecting

- TLVs are numerical
- Aimed at biological endpoints
- Worker are biological entities
- Biology overrules math

# Can misuse numbers

If the speed limit is 100 km/hour, can I drive 200 km/hr for ½ an hour?

Why not? After a one hour period, the car will only have traveled 100 km.

Doesn't that "equal" 100 km/hr"

# Key Points

- We ignore the biology and follow the math
- Blindly apply the TLVs numerically
- Don’t really understand TLVs we use every day

# Guidelines

- TLV – TWA
- TLV – STEL
- TLV - Ceiling

# TLV -TWA

- One number
- Exposure profile can be complex
- Can saturate pathways

# Examples of Saturation

- Metabolic Saturation
  - self–inhibition by excess drugs
  - insufficient metabolic enzyme
  - competition for co-enzyme or co-substrate
- Excretory Saturation
  - competition for tubular secretion or resorption mechanism
  - changed renal function
- Changed Drug Distribution
  - protein and tissue binding effect
  - overflow into new volumes

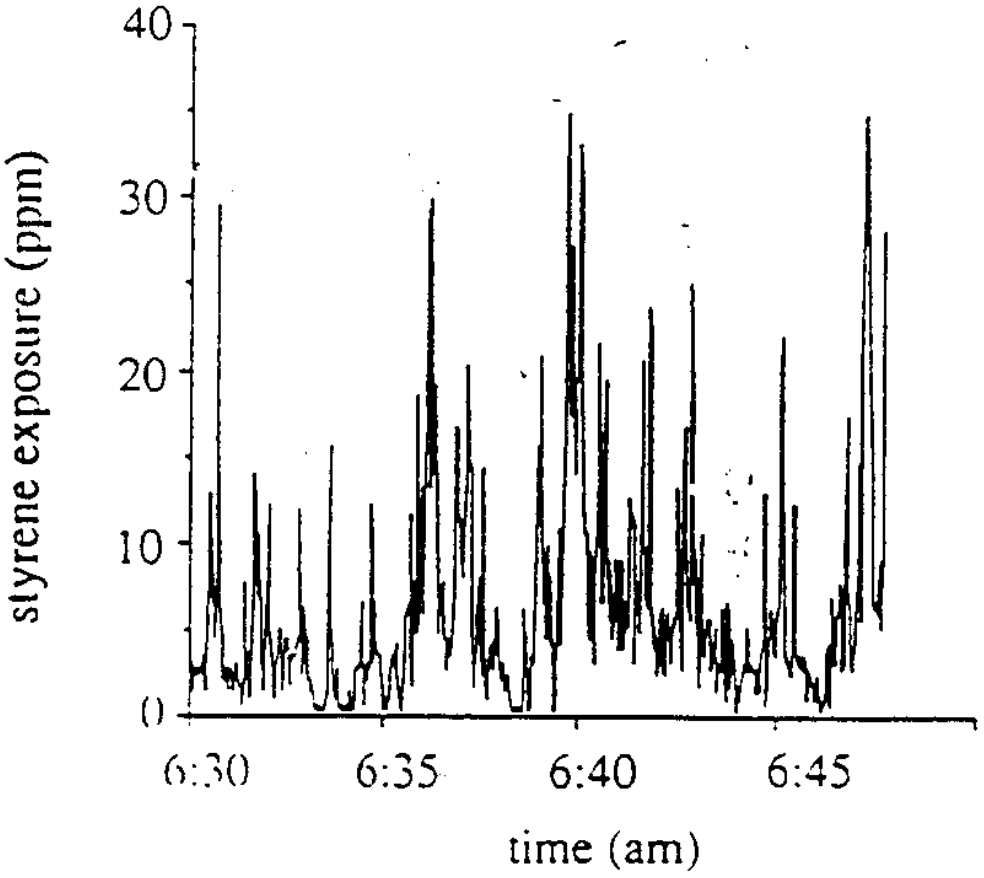
# Example

A worker is sampled for 4 hours. The exposure is collected on a single cassette. The lab results gives us one number which shows the time-wighted average airborne concentration during the sampling period.

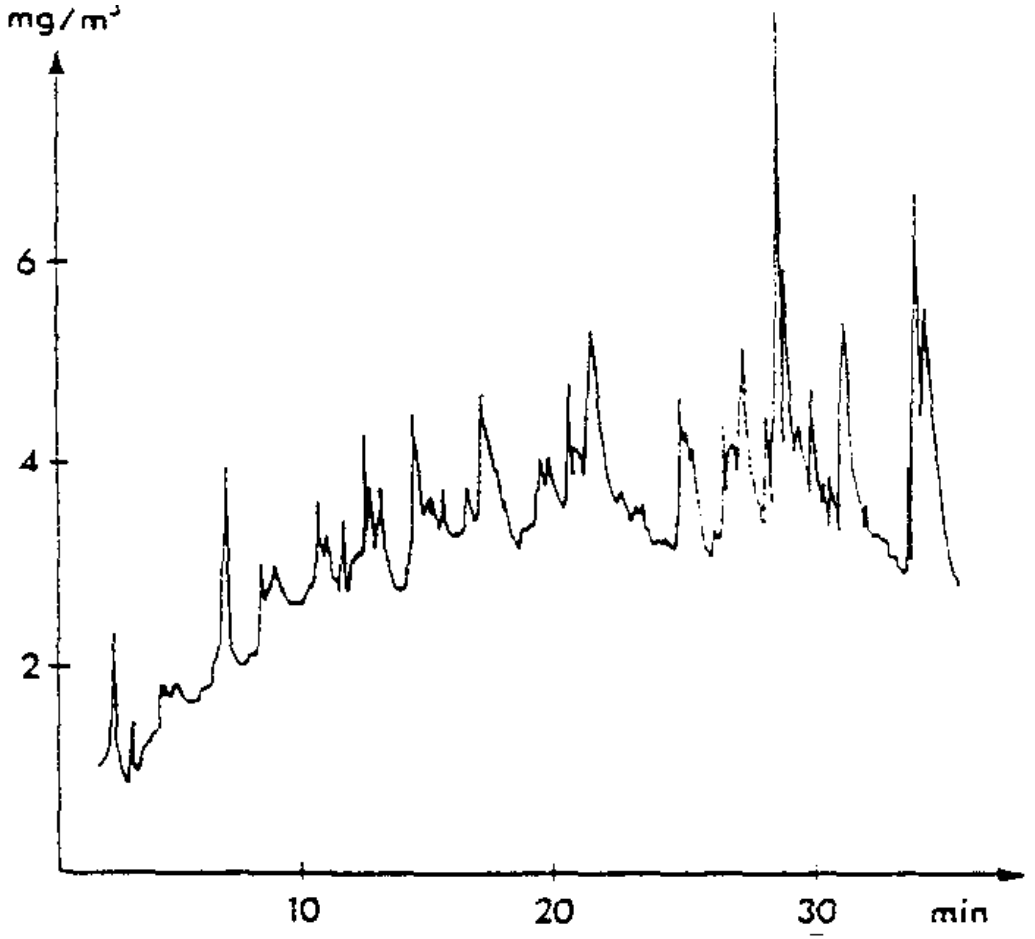
It is easy to think of this exposure being constant.

“He received an exposure of 0.4 times the TLV”

# Is This Constant Exposure?



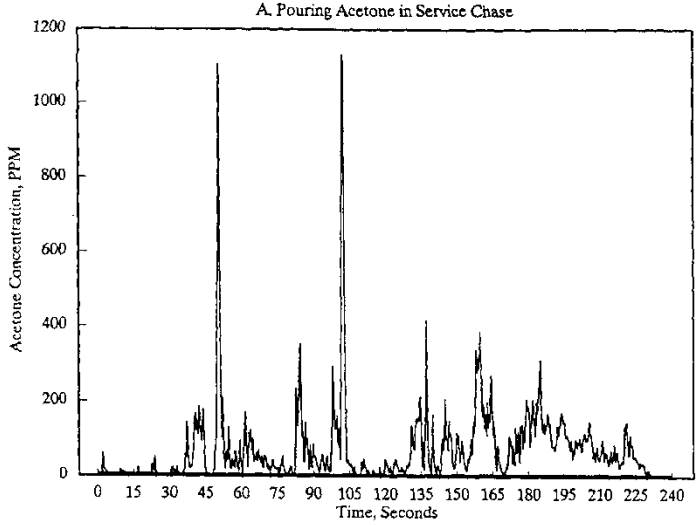
# Hot waxing of Skis

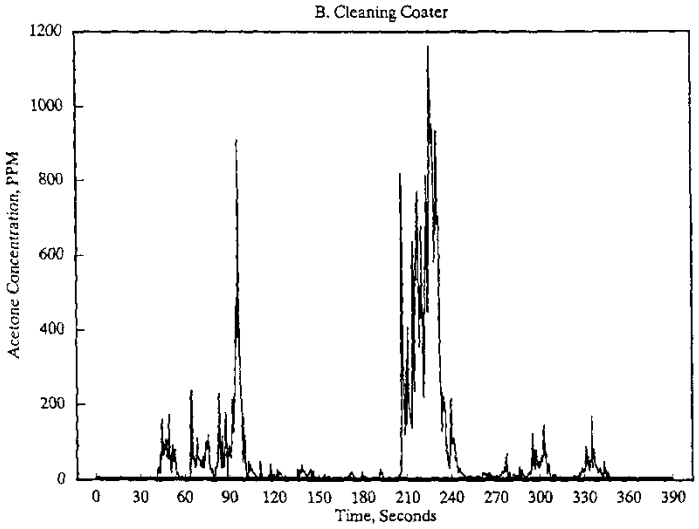


# Sound Familiar?

- Worker complains of irritation
- IH person samples
- Average exposure is low ( less than 10% of TLV)
- Conclusion = No Problem
- Perhaps irritation is caused by short term  but high exposure(s) that give a low average

# Acetone Levels in Microelectronics Fabrication



# Product dumped into Mill

Common Operation (powder blending)

Volume is small (2.5 kg)

Product is FDA-approved analgesic:

Oxycodone hydrochloride(OCH)

Activity is short

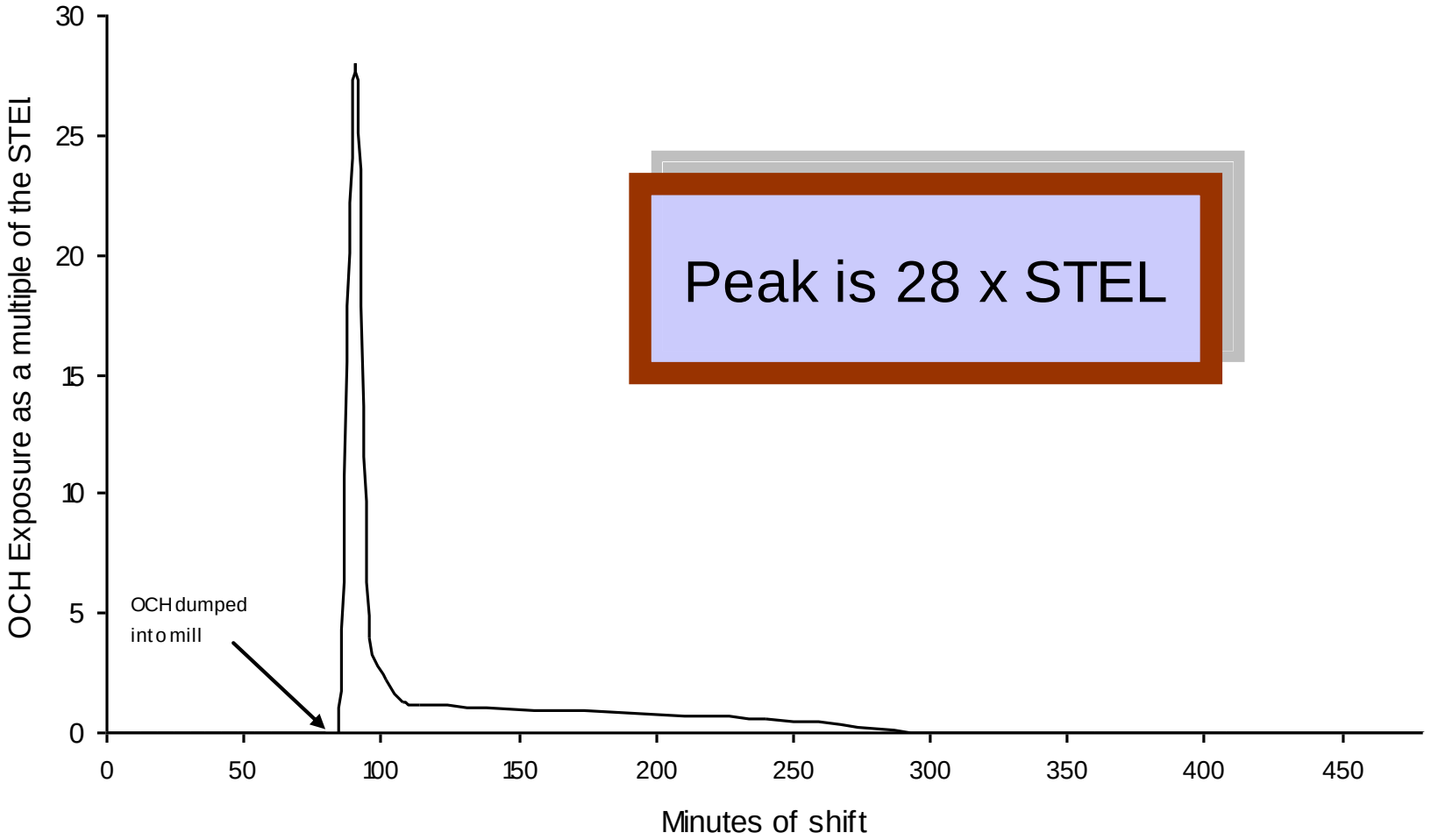
lasts 6.5 minutes (1.4% of shift )

Worker wears protection

a HF AP (Protection Factor = 10)

Local exhaust ventilation (flexible trunk)

# Product dumped into Mill



# Product dumped into Mill

Common Operation (powder blending)

After correcting for respiratory protection, exposures to exposure to OCH is above its STEL

OCH = 28 x STEL (without respirator)

OCH = 2.8 x STEL (with respirator)

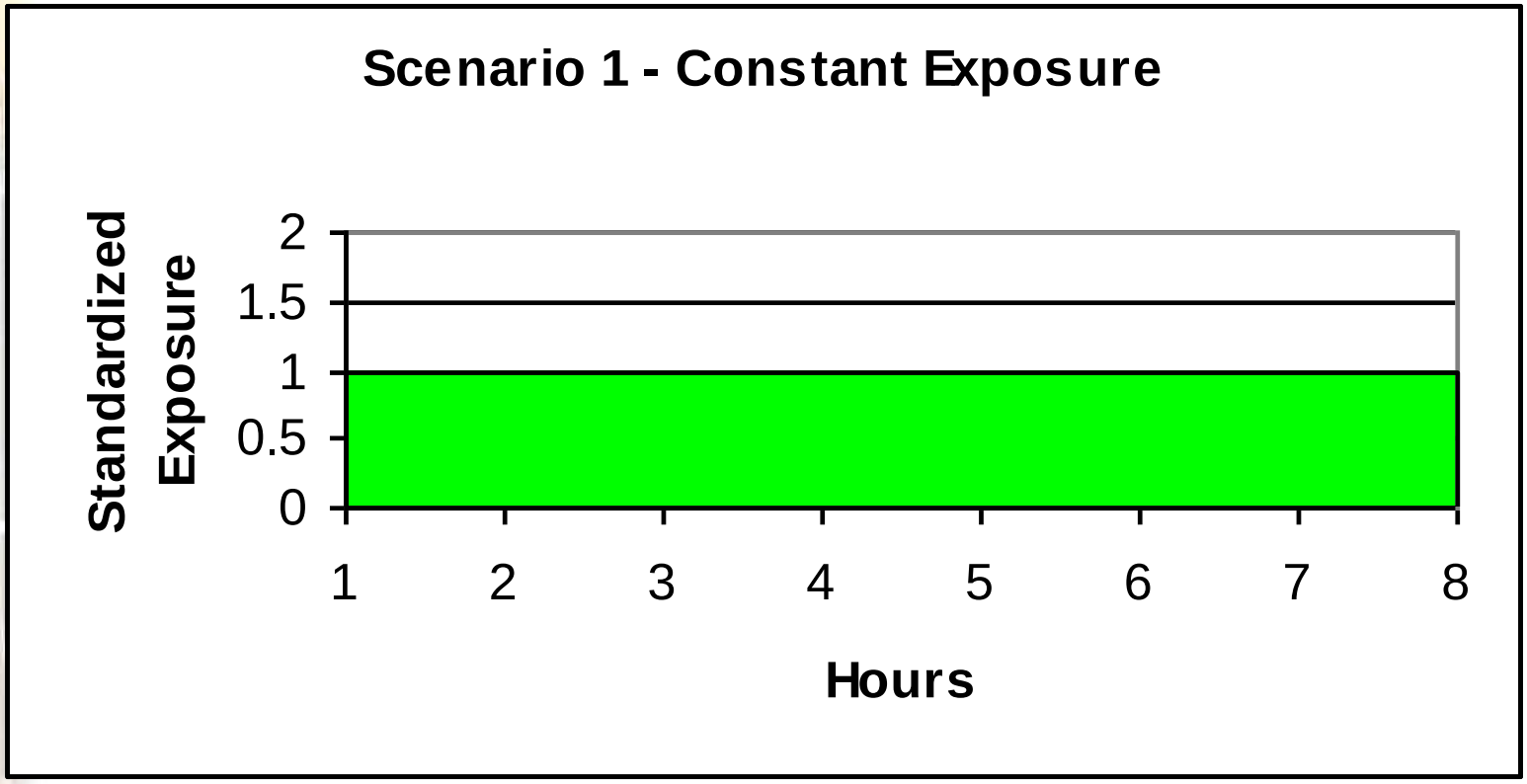
# The Point

- Exposure Profiles are complex
- Sometimes EP makes a difference
- Most IHs not aware of the issue

<u>Example</u>

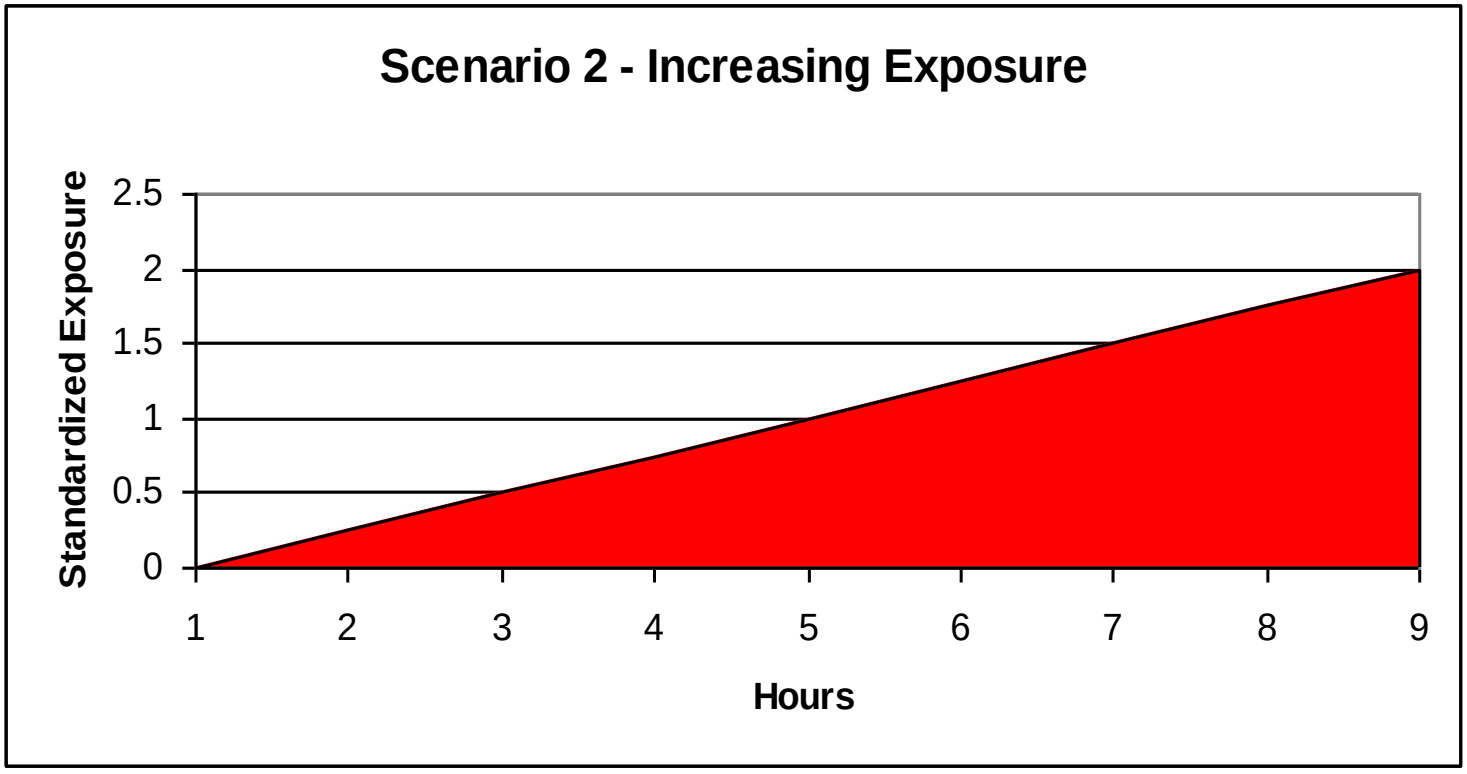
Average exposure to CO over 8 hour period = TLV

# Simple Example – Exposure to Carbon Monoxide




Average exposure = the TLV - TWA

# Simple Example – Exposure to Carbon Monoxide



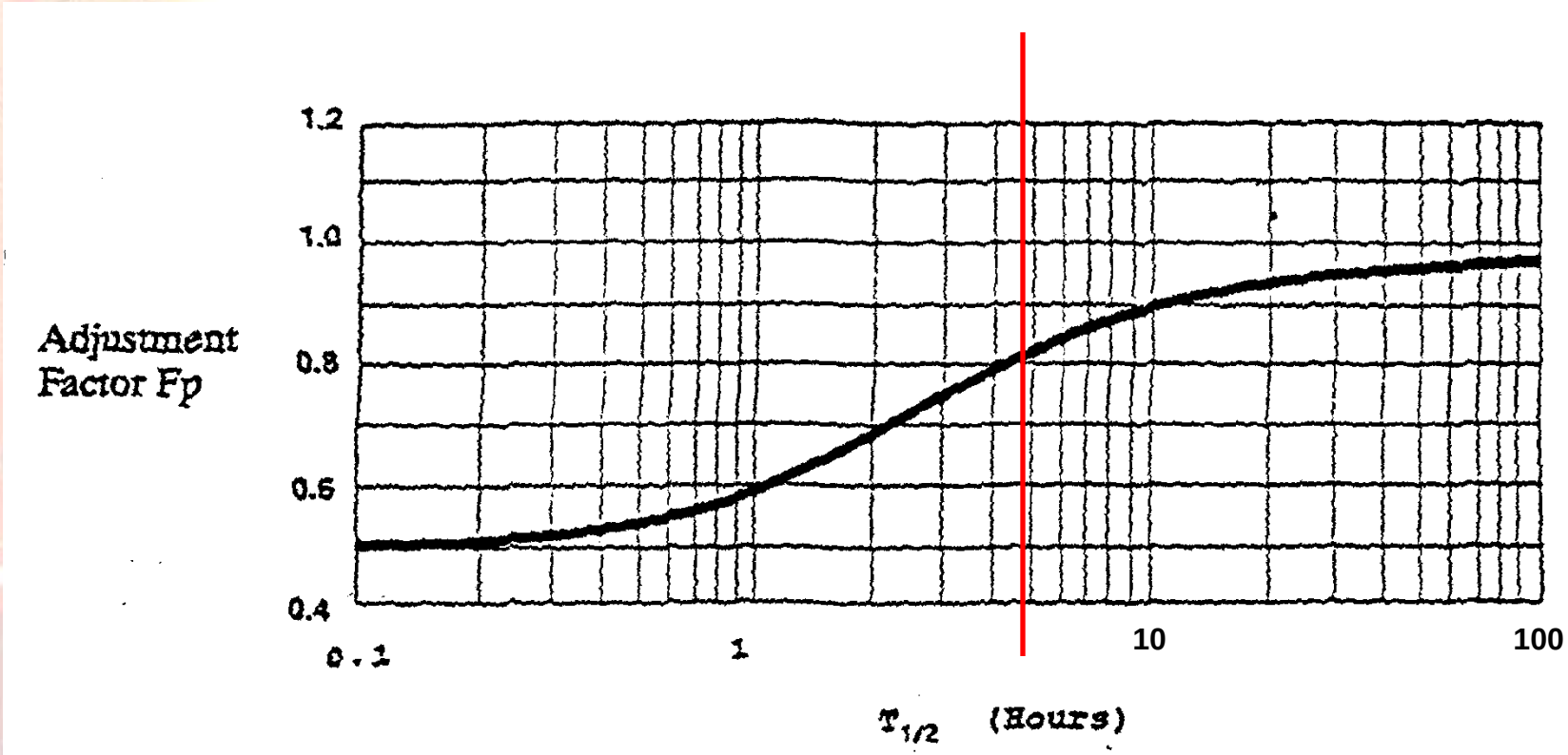

Average exposure = the TLV - TWA

# Body burden depends on Half-life

| Half Live (Hours) | PREDICTED RATIO OF PEAK BODY BURDENS | Required Reduction Factor |
|---|---|---|
| 0.25 | 1.92 | 0.52 |
| 5 | 1.20 | 0.83 |
| 20 | 1.09 | 0.93 |
| 100 | 1.02 | 0.98 |

# Pharmcokinetics (again)

## Graph for steadily rising exposure

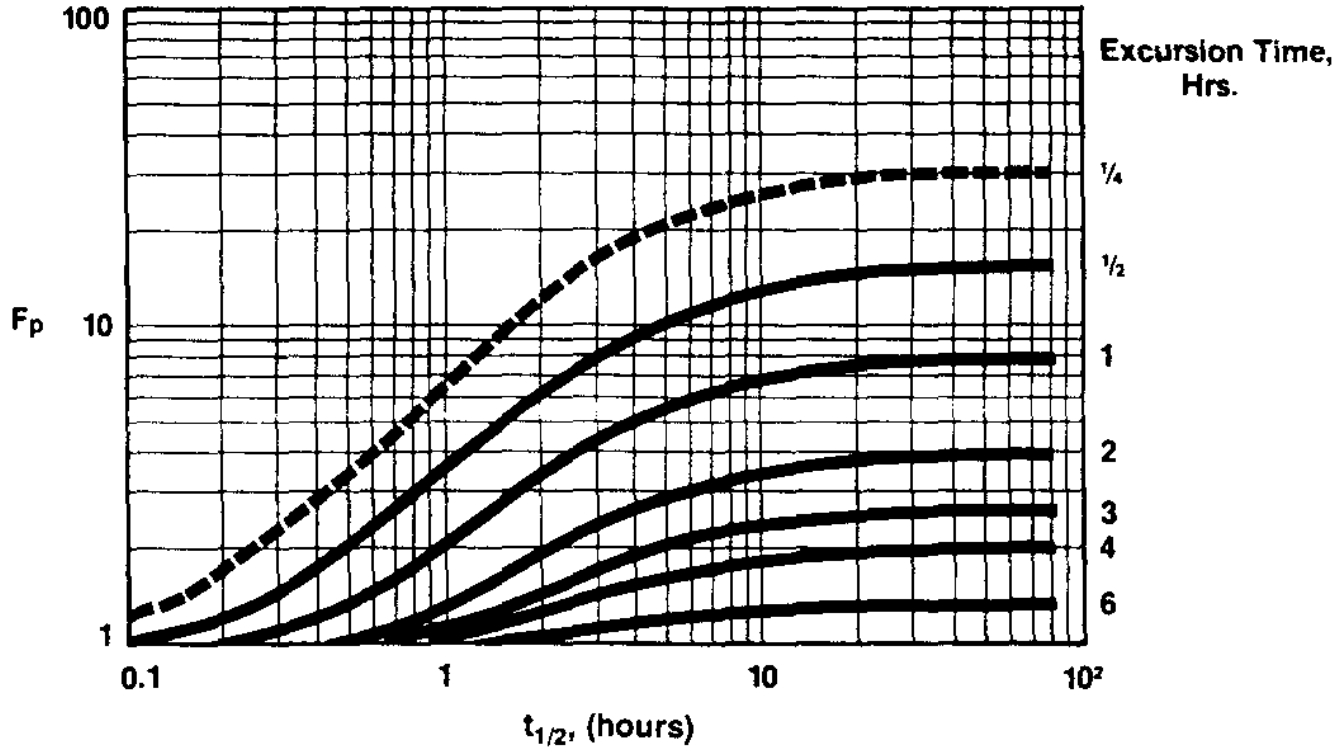



Source: Patty's

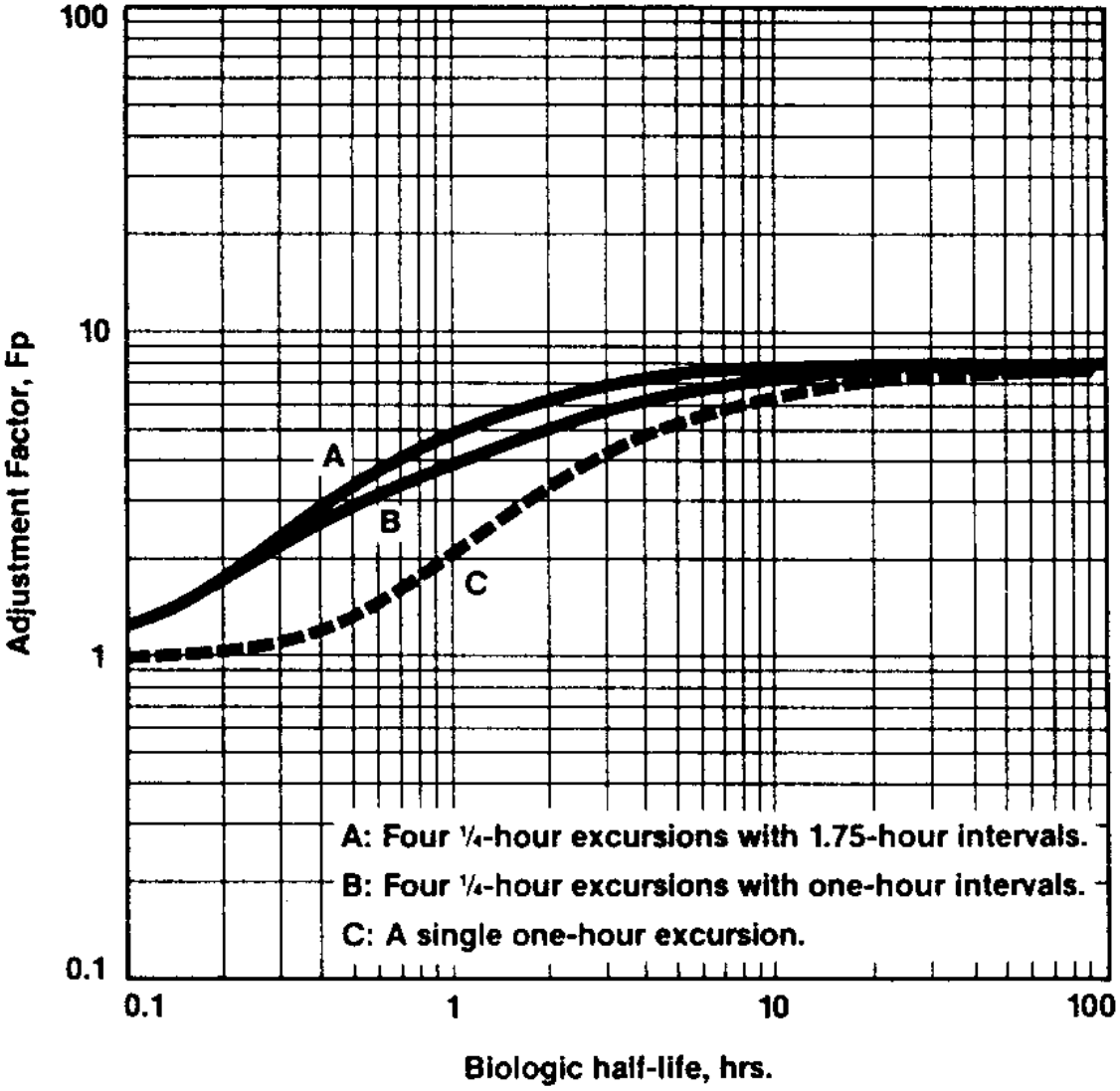
# Excursions

- A one time per shift event
- Again, half life is important
- Short half lives need low excursion limits
- Long half lives can have high excursion limits

# Excursions



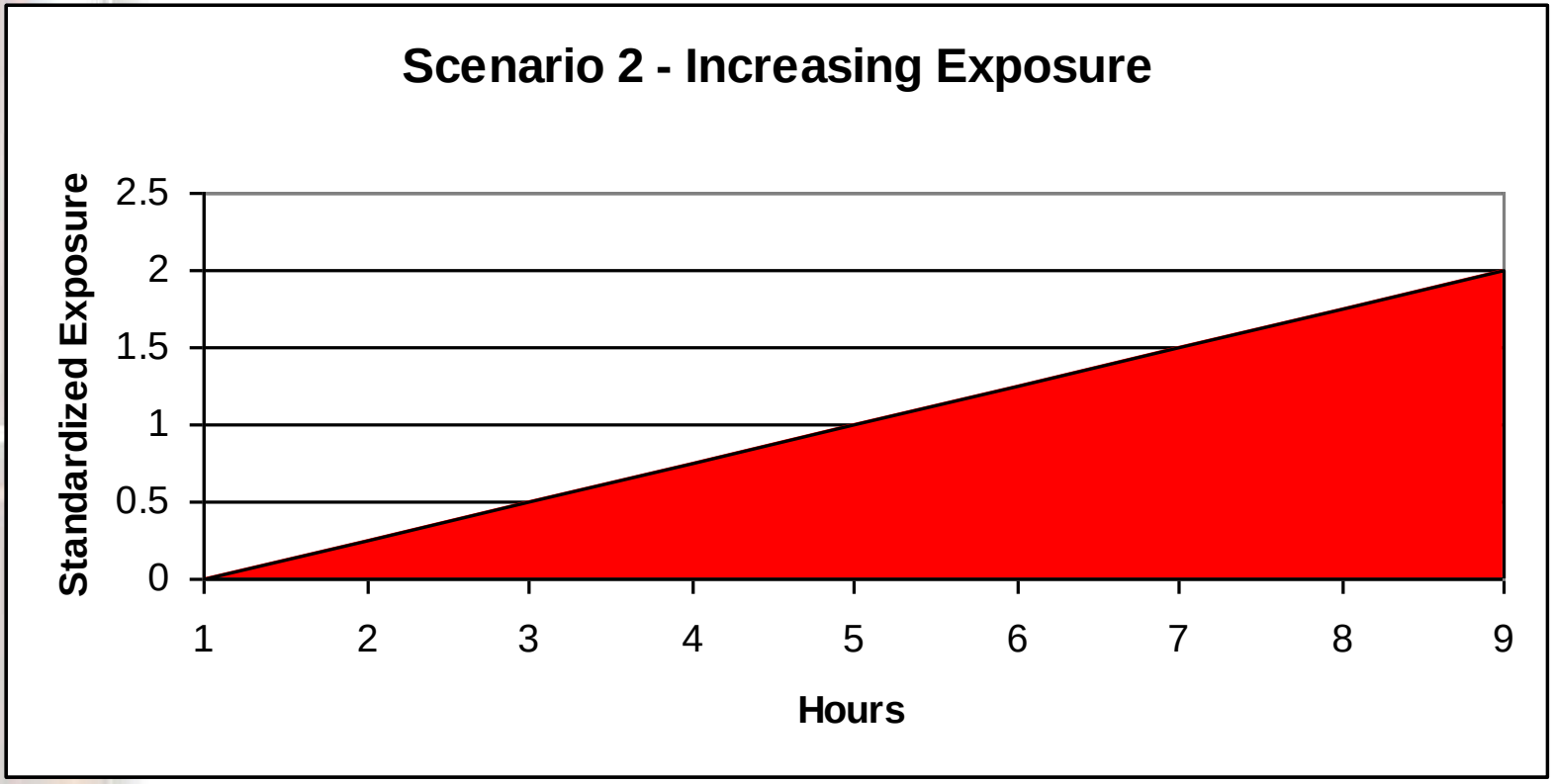
# Excursions


100
10
1
0.1
Adjustment Factor, Fp
A
B
C
A: Four ¼-hour excursions with 1.75-hour intervals.
B: Four ¼-hour excursions with one-hour intervals.
C: A single one-hour excursion.
0.1
1
10
100
Biologic half-life, hrs.

# Simple Example

Benzene TWA = 0.5 ppm STEL = 2.5 ppm

Does this scenario exceed the STEL?



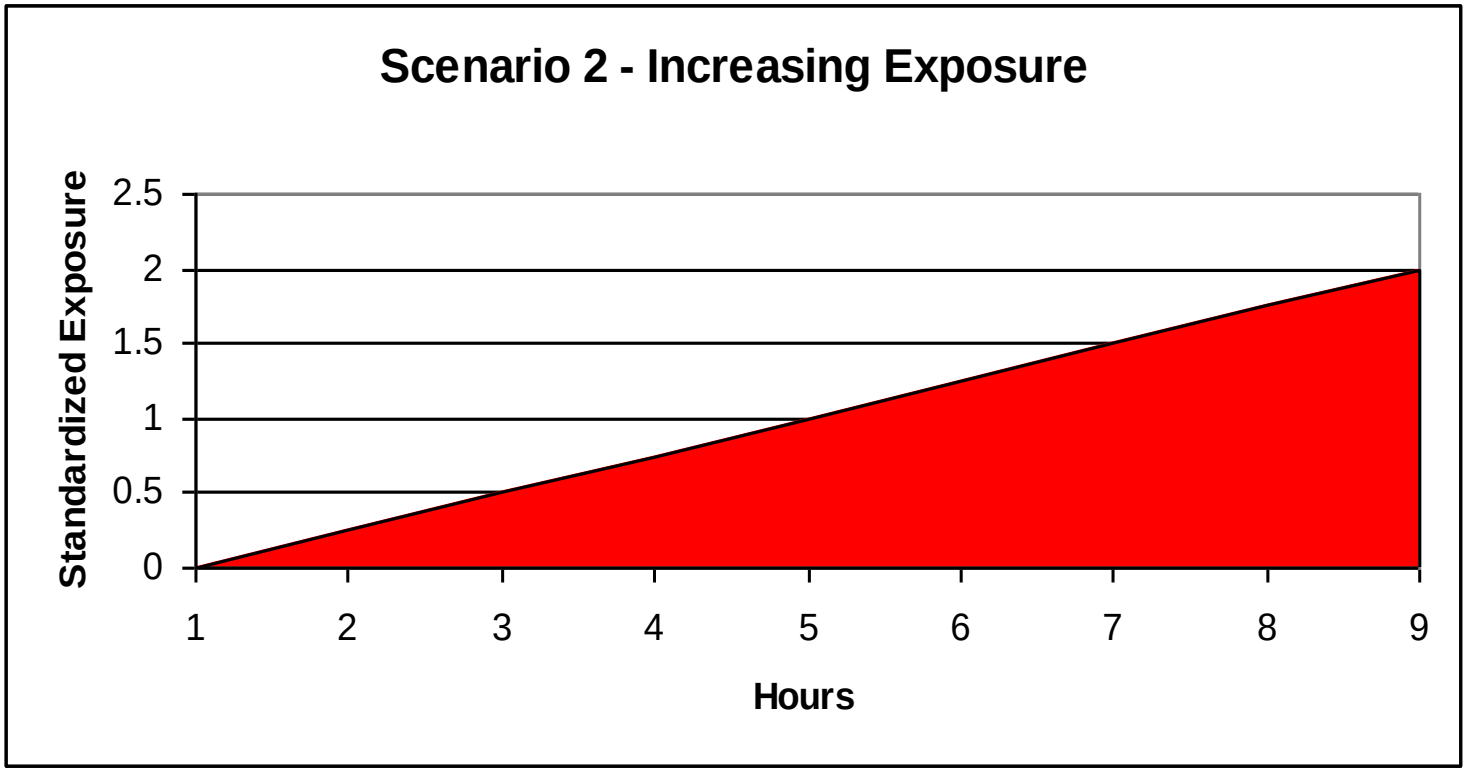
# STEL Rules

- a 15 minute exposure that should not be exceeded at any time during the day

AND

- Exposures above the TWA up to the STEL should be
  - less than 15 minutes
  - Should occur not more than 4 times per day
  - At least 60 minutes between successive exposures in this range

# Remember this Simple Example – Exposure to Carbon Monoxide

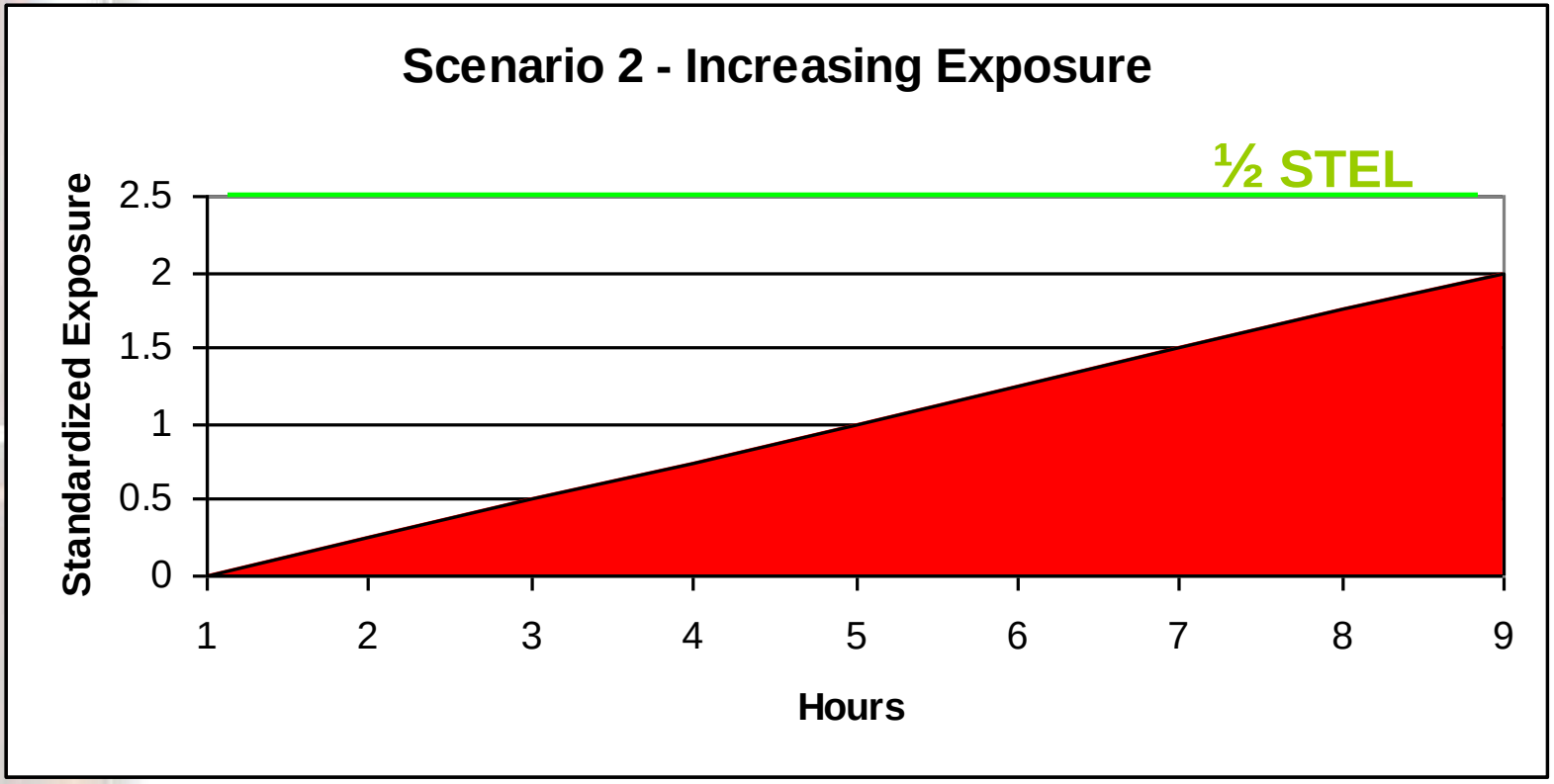



Average exposure = the TLV - TWA

# Lets Look Again at this simple example

Benzene TWA = 0.5 ppm STEL = 2.5 ppm

Does this scenario exceed the STEL?



# We Should Know This

Exposures above the TLV-TWA should be

- Less than 15 minutes; and
- Should occur not more than 4 times per day, and
- At least 60 minutes between successive exposures in this range

# We Should Know This

- This is basics info
- Its written clearly in the opening pages of the TLV Booklet
- Why don’t we know it?
- How many reports have you written based on what you thought a STEL was?

# Summary

Exposures are complex and the same average exposure can have different biological effects

For $ reasons, we don't explore EP often

When the average exposure doesn't explain things, consider exposure profile as part of the problem