

Biological Monitoring for Evaluating Occupational Exposure to Toxic Chemicals

An Introduction

This slide presentation was prepared by
The AIHA Biological Monitoring Committee
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Acknowledgements

in alphabetical order

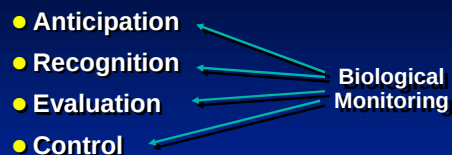
- Mark Boeniger, NIOSH, Cincinnati
- Tim Buckley, Johns Hopkins Univ., Baltimore
- Larry Lowry, Univ. of Texas Health Center, Tyler
- Shane Que Hee, Univ. Calif., Los Angeles
- Glenn Talaska, Univ. of Cincinnati
- Paul Ullucci, ESA Labs, Inc., Chelmsford, MA

Acknowledgements

Contributions are appreciated from
members of

***The American Conference of
Governmental Industrial Hygienists
Biological Exposure Indices Committee***

Scope of Industrial Hygiene and the Context for Biological Monitoring



**GOAL: PROTECT THE
HEALTH OF THE WORKER**

Means of Evaluating Exposure

- Air sampling
 - Skin sampling
 - Surface sampling
 - Biological monitoring –
- Measured outside the body
- measures inside body



Strengths of Air Sampling

- Long-standing tradition
- Good worker acceptance
- Established standards & guidelines
- Good equipment
- Standard methods available

Weaknesses of Air Sampling

- Does not account for:
 - ♦ All routes of exposure, esp. skin
 - ♦ Workload
 - ♦ Individual differences in absorption of inhaled dose
 - ♦ Misuse or malfunction of PPE
 - ♦ Concomitant exposures
 - ♦ Sensitive individuals



Strengths of Surface Sampling

- Can identify potential for surface derived exposures
- Easy to obtain
- Minimally disruptive of operations
- Favored by OSHA, EPA, HUD



Weakness of Surface Sampling

- Highly variable results
- Surface transfer to skin is variable and poorly understood
- May overestimate absorbed dose

Strengths of Skin Sampling

- Indicates individual skin contamination



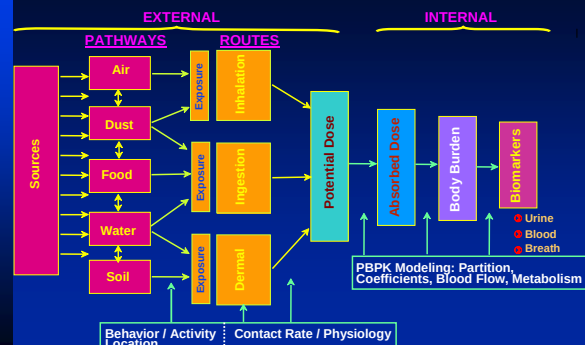
Weakness of Skin Sampling

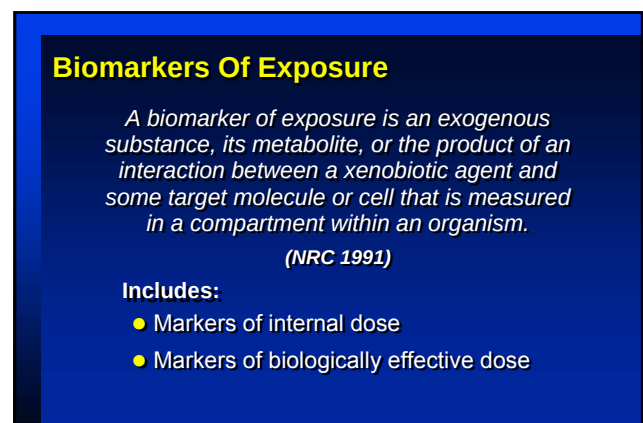
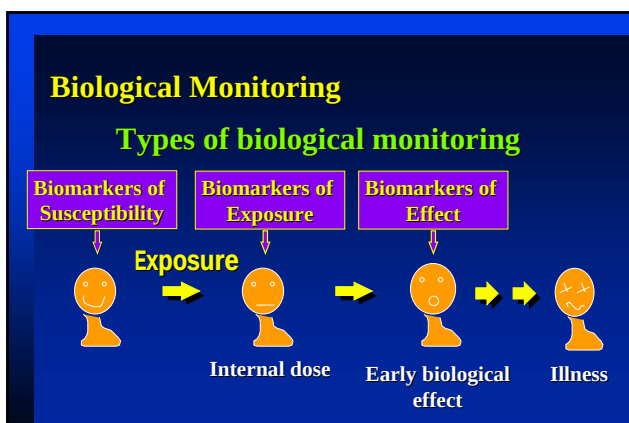
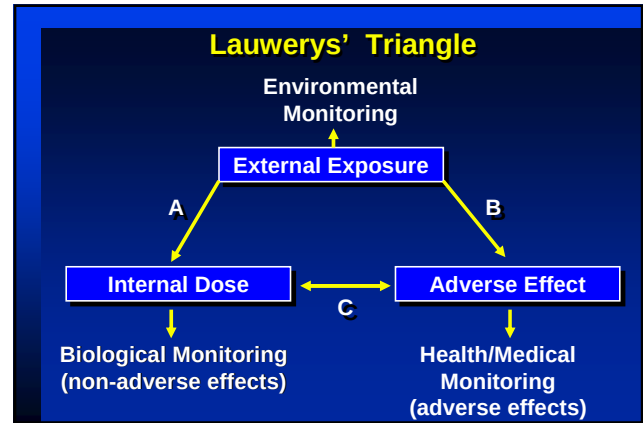
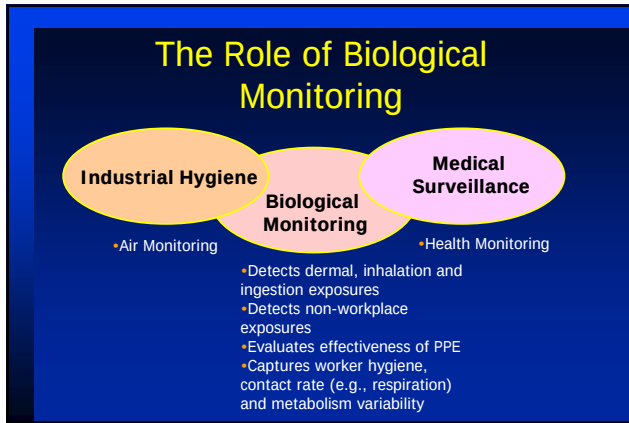
- Differences between techniques, some overestimate or underestimate exposure
- Relevance to biologically available or absorbed dose uncertain

Biomarkers

Measure of exposure, effect, or susceptibility by analyzing biological sample media

Exposure to Effect Continuum





Markers of Internal Dose

Some Examples

- Lead, cadmium, mercury, etc.; blood
- Trichloroethylene; trichloroacetic acid; urine
- Phenol; urine
- Toluene; o-cresol, urine
- Xylene; methylhippuric acid, urine
- Methylenedianiline, urine
- Toluene; expired air

Markers of Biologically Effective Dose

- Carboxyhemoglobin (carbon monoxide reversibly binds to RBC); Blood
- 2,5-Hexanedione (metabolite of 2-hexanone and hexane); Urine
- DNA Adducts (chemicals bind to bases in DNA); Blood & Urine
- Hemoglobin Adducts
N-(2-hydroxyethyl) valine in Hb; Blood

Biomarkers of Susceptibility

A biomarker of susceptibility indicates an organism's inherent or acquired limited ability to respond to the challenge of exposure to a specific xenobiotic substance.

Biomarkers of Susceptibility

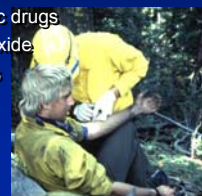
- Genetic, inherited:
 - Alpha-1-antitrypsin phenotype
 - Acetylator phenotype
 - P-450 2D6 polymorphism
- Acquired:
 - Antigens (hypersensitivity) in response to exposure to toluene diisocyanate or cotton dust
- Co-existing conditions:
 - Cirrhosis of the liver, renal deficiency

Biomarkers Of Effect

A biomarker of effect or response is a measurable alteration - biochemical, physiological, or other - within an organism that can be recognized, depending on its magnitude, as an established or potential health impairment or disease.

Biomarkers of Effect

- Zinc protoporphyrin: lead
- Delta-aminolevulinic acid: lead
- Carboxyhemoglobin: carbon monoxide; methylene chloride
- Beta-2-microglobulin: cadmium
- Cholinesterase: organophosphorus pesticides
- Chromosome aberrations: antineoplastic drugs
- Sister chromatid exchanges: ethylene oxide
- Urine mutagenicity: antineoplastic drugs



Medical Monitoring Biomarkers — Liver

- Albumin, bilirubin, globulin, total protein
- Alkaline phosphatase (AP)
- Gamma glutamyl transpeptidase (GGTP)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Lactate dehydrogenase (LDH)

Medical Markers — Kidney

- BUN (Blood Urea Nitrogen)
- Creatinine
- Uric acid

Medical Monitoring — Blood Forming

- CBC
 - Differential
 - WBC, RBC
 - Hemoglobin & hematocrit
 - Reticulocyte count

Medical Monitoring — General

- Urinalysis
 - Appearance, color, ketones
 - Bile, occult blood, pH
 - Glucose, protein
 - Microscopic evaluation of sediment

Common Biological Monitoring Media

- Urine
- Blood
- Exhaled Breath

Creatinine Correction

- Normalization factor, dilution correction
- Calculation: $\text{mg/L} / \text{g/L} = \text{mg/g creatinine}$
- Typical Range: 0.5 – 3.0 g/L
- Specific Gravity in Field: >1.015 is OK
- Limitations: excretion mechanisms are complex and not absolutes

Sample Preservation of Metabolites in Urine

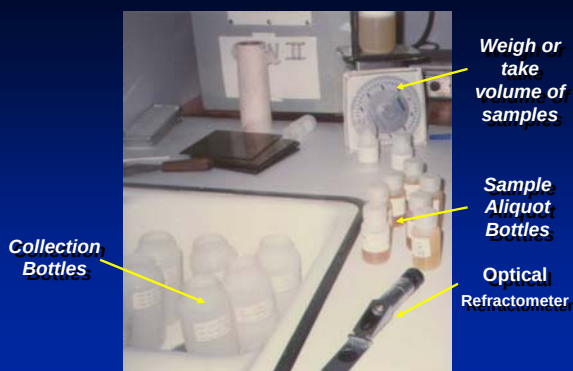
- Aromatic amines; aniline, MDA
 - citric acid added
- Glycol ether metabolites, mandelic acid, trichloroacetic acid, trichloroethanol
 - hydrochloric acid inhibits bacterial formation

Urine Collection

- 24 hour urine
- Spot urine
- Timing preferences:
 - End-of-shift
 - end-of-shift, end-of-week
 - prior to last shift of workweek
 - not critical



Processing Urine is Simple



Solvents in Blood

- Vacutainer tube, checked for contamination (hexane, toluene, xylene)
- Transfer to vial with Teflon® lined cap, fill to top, no headspace in tube
- Keep cold
- Ship overnight, cold
- Solvents in Urine : same as above

Trace Metals in Blood

- Special collection requirements
- Contamination from tube
- Contamination from needle
 - Chromium, nickel
 - Cobalt, manganese
 - Aluminum

Blood

Solvents

- Evacuated tube with anticoagulant; need a blank tube also to check for contamination (hexane, toluene, xylene)
- Transfer to vial with Teflon® lined cap, fill to top, no headspace in tube
- Ship overnight, cold (not freezing)



Blood

Metals

- Special collection requirements
- Contamination from tube stopper
- Contamination from needle
 - Chromium, nickel
 - Cobalt, manganese
 - Aluminum

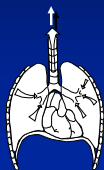


Transportation of Sample to Lab

- Place labeled sample in sealed bag
- Place in insulated shipping container
- Add frozen refrigerant
- Include proper requisition form
- Place insulated container in an appropriate labeled shipping box
- Ship next day or second day

Exhaled Air

- Inert compounds with low blood solubility
Good correlation with ambient levels
— n-hexane/2-hexanone
- Compounds of high blood solubility
Poor correlation with ambient levels
— acetone, MEK, toluene



Principal Advantages Of Biological Monitoring

- Individual variation in the absorption of contaminants can be assessed
- Measures total exposure including all routes of exposure



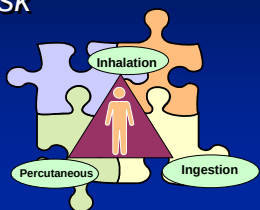
Principal Advantages Of Biological Monitoring - (continued)

- Effectiveness of PPE/work practices assessed
- Exposure outside of the workplace identified
- Individual absorption differences among workers identified
- Can confirm compound absorption when skin and/or oral exposure occur
- Provide powerful individual and group feedback and is an incentive for personal involvement in their own protection

Biological Monitoring Weaknesses

- Not as simple as air sampling
- Reflects total exposure, not just occupational
- May be invasive
- Workers may perceive themselves as guinea pigs
- Marker may not be agent specific, or only for workplace exposures
- Few standards or guidelines are available
- Analytical methods may not be available or costly
- Management/workers may fear this type of information

Biological monitoring is often best for estimating absorbed dose and risk

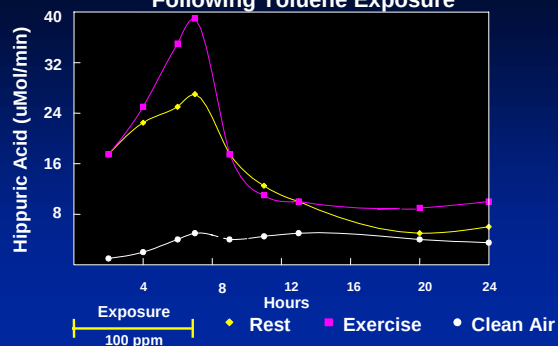


Individual Variation in Absorption of Airborne Contaminants Can Be Assessed

Pulmonary Absorption Rate Varies with the Ventilation Rate

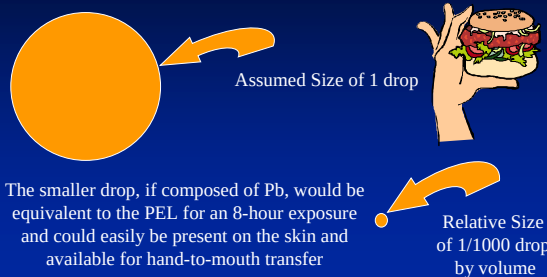
Physical Workload (W)	Alveolar Ventilation (L Air/Min)	Heart Rate (L/Min)	Increase Ventilation (vs. Light)
0 (Rest)	5.0	6.0	1.0
50 (Light Work)	16.0	9.0	1.0
100 (Moderate)	27.0	13.0	1.7
150 (Heavy)	38.0	19.0	2.4

Effect of Exercise on Excretion of Hippuric Acid Following Toluene Exposure

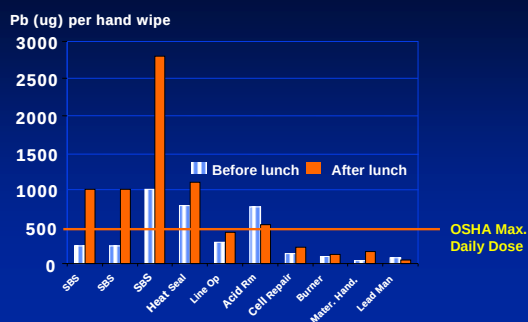


Example of Oral Ingestion via Contaminated Skin

Involving Hand-to-Mouth Transfer of Lead

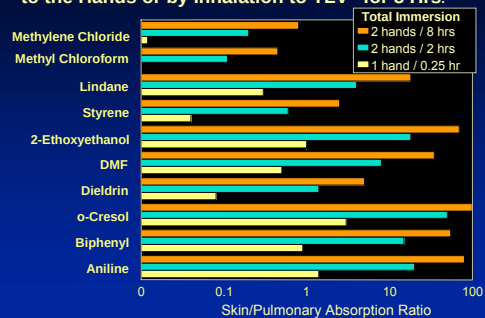


Lead on Hands Remaining After Washing and After Eating in Workplace Cafeteria



Skin can be an Important Route of Absorption

Relative Absorption of Chemicals from Exposure to the Hands or by Inhalation to TLV® for 8 Hrs.



Skin Absorption Versus Inhalation

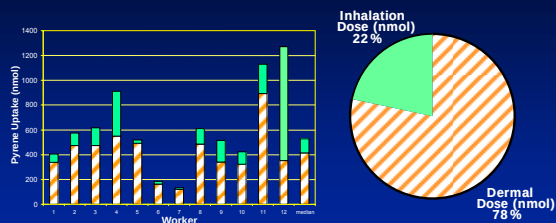
The Importance of Skin Exposure is Often Overlooked or Under-appreciated

PCBs

- 1 mg/m³ airborne exposure for 8 hours
— 8 mg
- One drop of 70% PCB on one hand
— 54 mg

Why Worry About Dermal Exposure?

Estimates of Pyrene Uptake During 5 Days



Van Rooij JGM; Van Lieshout EMA; Bodeller-Bade MM; Jongeneelen FJ (1993): Effect of reduction of skin contamination on the internal dose of creosote workers exposed to polycyclic aromatic hydrocarbons. *Scandinavian J. Work Environ. Health* 19:200-207.

The Skin & Percutaneous Permeation

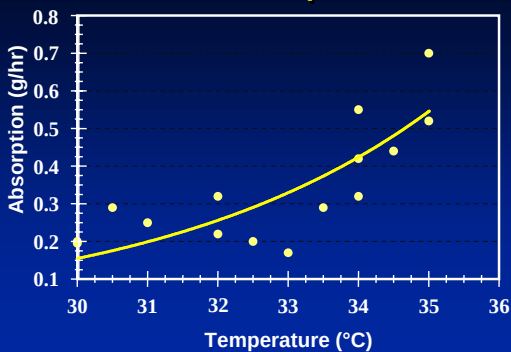
Chemicals that are somewhat soluble in organic oils and lipids as well as water are absorbed most readily through skin.

Those that are highly insoluble in either oils or water are poorly absorbed.

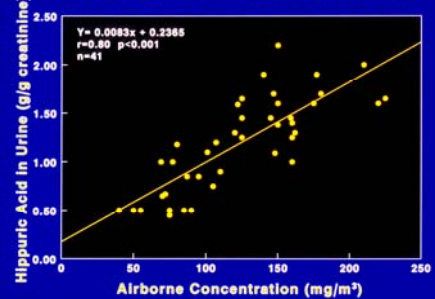
Factors Affecting Skin Absorption

- Location of skin on the body
- Hydration or wetness
- Temperature
- Skin condition

Aniline and Skin Temperature

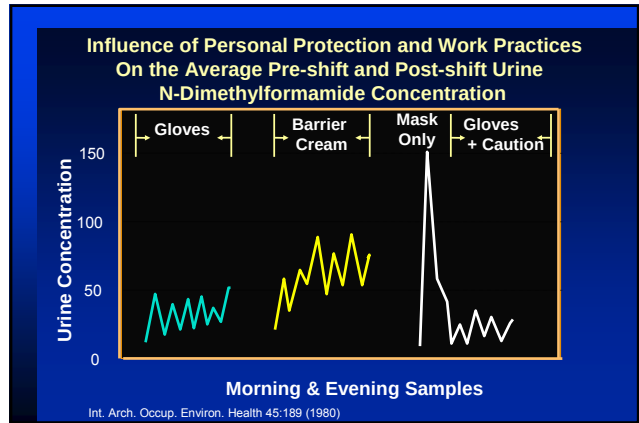


RELATIONSHIP BETWEEN TOLUENE IN AIR AND END SHIFT HIPPURIC ACID EXCRETION

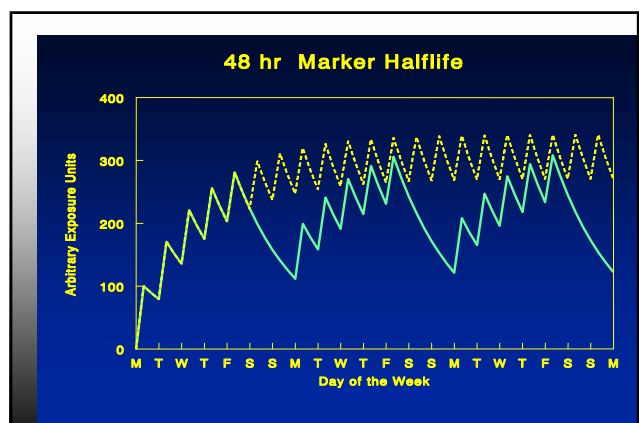


DEROSA, ET AL., INT ARCH ENVH OCC HLTH, 56, 135

Effectiveness of PPE and work practices can be assessed



Exposure outside of the workplace can be identified



Biological Monitoring Standards & Guidelines

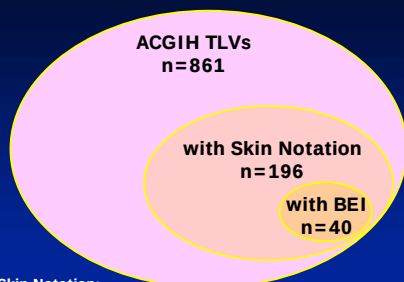
- OSHA Mandated Biological Monitoring
 - Lead
 - Cadmium
- ACGIH BEIs
 - Advisory only
- German BATs

BEIs - Biological Exposure Indices

- Definition

Reference Values of Biological determinants; the levels most likely observed when healthy persons are exposed to air concentrations at the TLV®.

The Dermal Exposure Gap



ACGIH TLV® Skin Notation:
"potential significant contribution to the overall exposure
by the cutaneous route . . . by direct skin contact with the substance."

BEIs

- Major Intended Uses

- Compare exposure from all routes of exposure
- Give absorbed dose relationship to individual's integrated air sampling
- Determine the effectiveness of PPE

BEIs

- Based on Human Data
 - Experimental and Field Studies
 - Relationship between external and internal doses at TLV® levels
 - Relationship between internal dose and reversible health effects

BEI Table

- Includes the following:
 - Chemical
 - Determinant
 - Specimen to collect
 - Time of collection
 - BEI
 - Notation

BEI - Time of Collection

- Biological Half - Life of Determinant
 - Short half-life indicates recent exposure
 - Long half-life indicates integrated exposure over time
 - Very long half-life, collection is not critical, cadmium half-life is 20 years!

BEI Notations

- “B” – Background: found in non-exposed population.
- “Ns” – Non-specific: the determinant detected in other chemical exposures.
- “Sq” – relationship is semiquantitative.
- “Nq” – monitoring is recommended, but no BEI available.
- “Sc” – increased susceptibility in some populations.

Issues in Biological Monitoring

- ✓ Why are you doing this sampling?
- ✓ Who are you going to sample?
- ✓ What are you going to measure?
- ✓ When and Where are you going to sample?
- ✓ How are you going to transport and store the sample?
- ✓ How will the samples be analyzed?
- ✓ How will the results be reported?
- ✓ What criteria will be used to determine what actions will be taken?

Biological Monitoring -- A Collaborative Effort



- Industrial Hygienists
 - exposure assessment
- Occupational Health Physician
 - interpretation of results
- Occupational Health Nurse
 - sample collection, coordination

Individual Differences Among Workers

- Absorption
- Distribution
- Storage
- Metabolism
- Excretion

Factors Influencing Absorption

- Route
- Physical form
- Solubility
- Physical workload
- Exposure concentration
- Exposure duration
- Skin characteristics

Factors Affecting Distribution

- Body size
- Body composition
- Protein binding
- Physical workload
- Exposure concentration
- Exposure duration
- Volume of distribution

Internal Distribution & Storage

- Fat
- Bone and teeth
- Target organs
- Plasma protein binding
- Free and bound

Acetone

- *Determinant:* Acetone in urine
- *Sampling Time:* End of Shift
- *BEI:* 50 mg/L
- *BAT:* 40 mg/L
- *Notation:* Nonspecific (NS)
- *Route:* Pulmonary, Dermal

Aniline BEI

- *Determinant:* Total p-aminophenol, urine
- *Sampling Time:* End of Shift
- *BEI:* 50 mg/g creatinine
- *Notation:* Nonspecific (NS)

Aniline — BEI

- **Determinant:** aniline, urine or Methemoglobin, blood
- **Sampling:** During or end of shift
- **BEI:** 1.5% Hemoglobin
- **Notations:** Background (B), non-specific (Ns), semi-quantitative (Sq)

Arsenic, Soluble Compounds, Arsine BEI

- **Determinant:** Inorganic arsenic and methylated metabolites, urine
- **Sampling:** End of shift at end of work week
- **BEI:** 35 µg/L
- **Notation:** Background (B)
- No BAT, air / urine values
- | <u>Air</u> | <u>Urine</u> |
|------------------------|--------------|
| 0.10 mg/m ³ | 50 µg/L |
| 0.05 mg/m ³ | 90 µg/L |

OSHA Inorganic Arsenic Subjects Monitored

- Employees over Action Level for at least 30 days per year
- Symptoms or signs of exposure
- Breathing difficulty during respirator fit-test

OSHA Inorganic Arsenic Monitoring Frequency

- At placement
- Yearly for those <45 years age <10 exposure
- Every six months for all others
- If symptoms appear
- At termination

Cadmium — OSHA

- *Determinant:* Cadmium in blood, urine
- *Sampling:* Not critical
- *Value:* Urine: <3 µg/g creatinine
Blood: <5 µg/L
- *Effect Marker:* Beta-2-microglobulin
- *Value:* <300 µg/g creatinine

Cadmium — BEI

- *Determinant:* Cadmium blood, urine
- *Sampling:* Not critical
- *BEI:* Urine: 5 µg/g creatinine
Blood: 5 µg/L
- *Notation:* Background (B)

OSHA Cadmium Monitoring Subjects

- Employees exposed at or above action level for 30 or more days per year
- Employees who wear respirators
- Employees acutely exposed due to emergency

OSHA Cadmium Monitoring Frequency

- Biological Monitoring
 - At placement and annually
 - Quarterly if levels raised, or on medical removal
- Medical Exam
 - Bi-annual
 - Semi-annual if levels raised, or on medical removal

Lead — OSHA

- *Determinant:* Lead in blood
- *Sampling:* Not critical
- *Value:* <50 µg/dL
- *Effect Biomarker:* Zinc Protoporphyrin (ZPP) in blood
- *Value:* <60 µg/L

Lead — BEI

- *Determinant:* Lead in blood
- *Sampling:* Not critical
- *Value:* 30 µg/dL
- *Notation:* Women of childbearing potential, >10 µg/dL, risk to child

OSHA Lead, General Industry Monitoring Frequency

- At placement
- Annually
- Every two months if Pb >40 µg/dL
- Monthly if on medical removal

OSHA Lead, General Industry Medical Monitoring Subjects

- Exposure at Action Level for >30 days per year
- If symptoms of exposure appear
- If concerns about past exposure or procreation
- Breathing difficulties

Benzene — BEI

- *Determinant:* S-phenylmercapturic acid
- *Sampling:* End of Shift
- *Value:* 25 µg/g creatinine
- *Notation:* Background
- *1996 Determinant:* Total phenol in urine
- *Value:* 50 µg/g creatinine

OSHA Benzene Subjects Monitored

- Employees at or above action level
- At or above PEL for 10 or more days per year
- At 10 ppm or above for 30 days per year
- Tire industry using solvents containing >0.1% benzene

OSHA Benzene Monitoring Frequency

- Prior to assignment
- Annually
- When symptoms occur
- In respirators for 30 or more days per year
- Exposed during emergency

OSHA Benzene Items Monitored

- Medical and work history
- Physical exam
- Hematology: CBC
- Urine Phenol (exposed in emergency)