Section B

Biomarkers of Internal and Biologically Effective Dose
Biomarkers of Internal Dose

- **Internal dose/absorbed dose:** the amount of an environmental hazard that crosses one or more of the body’s membrane boundaries

- Direct measure of toxic chemicals or their metabolites in cells, tissues, or body fluids (e.g., blood, urine, breath, feces, milk, amniotic fluid, sweat, hair, nails, saliva)
  - Integrates multiple portals of entry
  - Integrates fluctuating exposures
  - Relates exposure to dose
### Biomarkers of Internal Dose

<table>
<thead>
<tr>
<th>Biomarker</th>
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</tr>
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<tbody>
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<td>Exhaled breath</td>
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<td>Blood levels</td>
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<tr>
<td>Fat concentrations</td>
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### Biomarkers of Internal Dose

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Biologically Effective Dose

- Amount of the internal dose and/or its metabolite that reaches and interacts with a molecular target

- The toxic action of a substance is a consequence of the physical/chemical interaction of the active form of that substance with a molecular target within the living organism

- The magnitude of the toxic effect will be a function of the concentration of altered molecular targets, which in turn is related to the concentration of the active form of the toxicant at the site where the molecular targets are located (biologically effective dose)
The Toxicological Process

Toxicokinetics
- EXPOSURE
  - Absorption
  - Distribution & metabolism of toxicant
    - Storage
    - Excretion

Initiation
- T + M → E1
  - Repair

Toxicodynamics
- E1 → E2
  - E3
    - E4
      - E5
      - E6
      - E7

Molecular level → Cellular response → Organ response → Organism response

Health ↔ Pathology
- Repair

Adapted by CTLT from In Vitro Toxicology, Vol. 3: 349-357 (1990).
Markers of Biologically Effective Dose

- **Biologically effective dose**: amount of the internal dose and/or its metabolite that reaches and interacts with a molecular target

- DNA adducts
  - Cellular DNA, e.g., benzo[a]pyrene-DNA adducts in peripheral lymphocytes of coke oven workers; $0^6$-methyl deoxyguanosine in GI mucosa from nitrosamine ingestion
Markers of Biologically Effective Dose

- DNA adducts (continued)
  - Urinary adducts, e.g., aflatoxin-$N^7$-guanine adducts in urine of individuals consuming $\text{AFB}_1$; oxidized DNA bases in urine following radiation and other forms of oxidative stress
Markers of Biologically Effective Dose

- **Protein adducts**
  - Hemoglobin: ethylene oxide, aromatic amines, tobacco-specific nitrosamines, cisplatinum, 4-aminobiphenyl
  - Albumin: aflatoxin $B_1$
DNA adduct assessment applied to tobacco smoke exposure

- Tissues and cells containing smoking-related DNA adducts
  - Lung, bronchial epithelium, alveolar macrophages, oral mucosa
  - Urinary bladder, exfoliated urothelial cells
  - Placenta, fetal tissues
  - White blood cells
4-ABP-Hemoglobin Adduct Levels

Non-smokers: $\bar{x} = 28$

Smokers: $\bar{x} = 154$
Smoking Cessation and 4-ABP-Hemoglobin Adduct Levels

Effect of Smoking Cessation on 4-ABP-Hemoglobin Adduct Levels (Five Different Individuals)