BIOASSAY PROGRAMS

Program Design

Statistical Considerations

Laboratory Quality Assurance

Learning Objectives

- Explain the process for designing a worker bioassay program
- Define the statistical quantities used in monitoring programs
- Identify quality assurance procedures for bioassay

Purposes of Bioassay

Routine Bioassay:

- Confirm adequacy of workplace controls on radioactive material.

Confirm compliance with regulatory limits on exposure.

Special Bioassay:

- Assess dose parameters following a known or suspected incident.

Regulatory Requirements
for monitoring internal dose

- NRC:

  Adult workers likely to receive in a year intakes greater than 10% ALI

  Minors and declared pregnant females likely to receive a CEDE greater than 0.5 mSv

  "likely to receive" ?????

- Can be determined from average air concentrations of radioactivity or quantity and handling of radioactive material in workplace

Determining Intakes

- NRC:

  If exposure is by inhalation only, intakes may be calculated from DAC-hours of exposure, otherwise from bioassay measurements.

- DOE:

  Intakes must be based on bioassay measurements if measurement technology permits.

Bioassay Methods

- Whole-body Counting
  - "Direct Bioassay"
  - "In-Vivo Bioassay" Direct measurement
  - Photon emitters only
  - Can get distribution data
  - Can measure retention
  - Calibration problems
  - Surface contamination
- Excreta Analysis
  - "Indirect Bioassay"
  - "In-Vitro Bioassay"
  - More sensitive
  - Less accurate
  - Need biokinetic model
  - Excretable nuclides only
  - No distribution data
  - No direct retention data

Types of Bioassay Samples

- Excreta: urine, feces
- Body fluids: saliva, perspiration, blood, mucus (nose blows)
- Tissues: nails, hair, biopsy
- Routine samples: collected on a regular monitoring schedule
- Special samples: collected after an incident, known exposure, or follow-up to positive routine sample

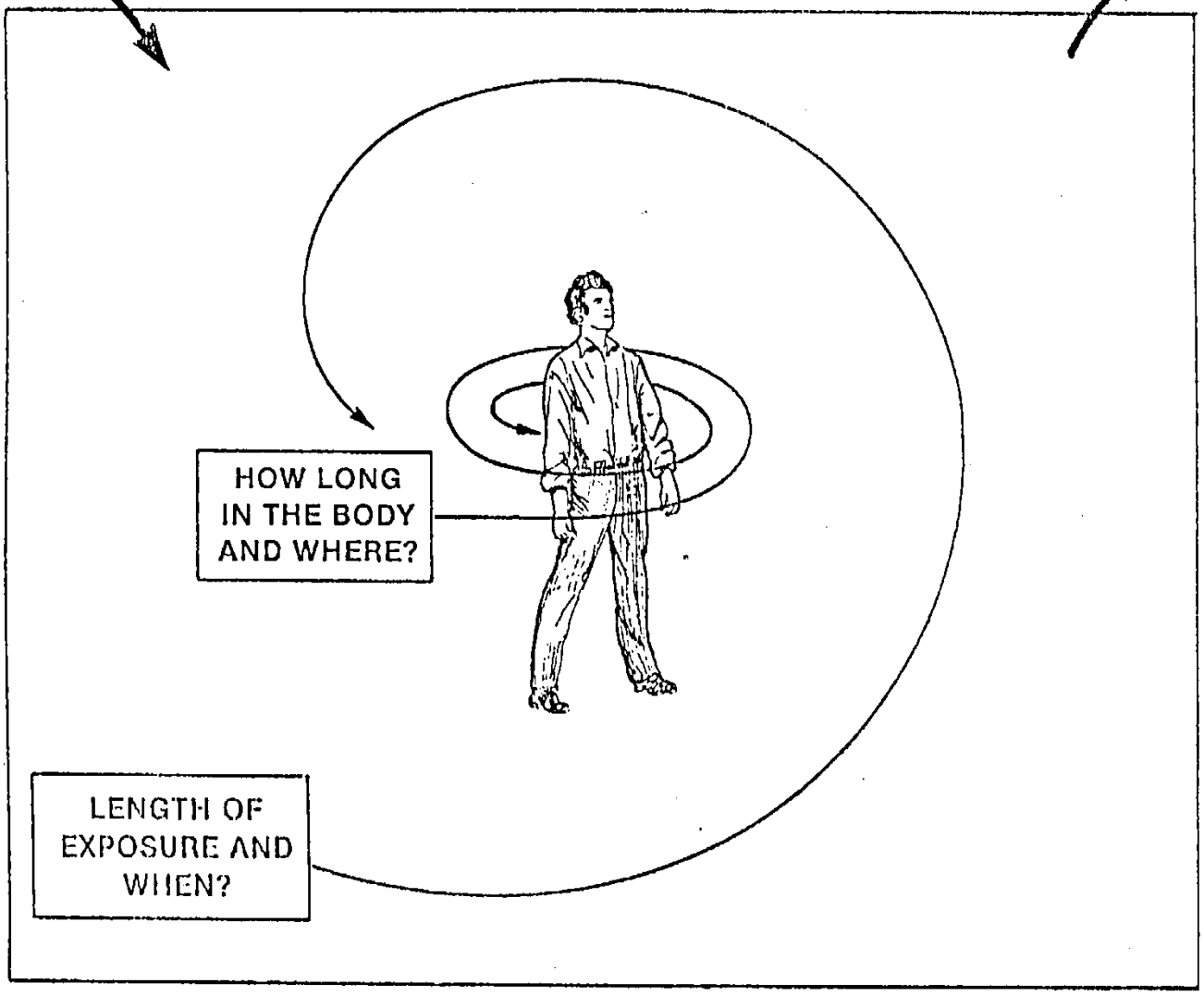
Choosing A Bioassay Sample

- Must consider:
  - Radionuclide (and matrix)
  - Physical properties
  - Chemical properties
  - Biokinetic behavior
  - Intake route
  - Workplace conditions
  - Time (when, duration)

WHY DO YOU WANT SAMPLES FOR THE NEXT THREE DAYS?

WHAT WAS IN THE WORK ENVIRONMENT?

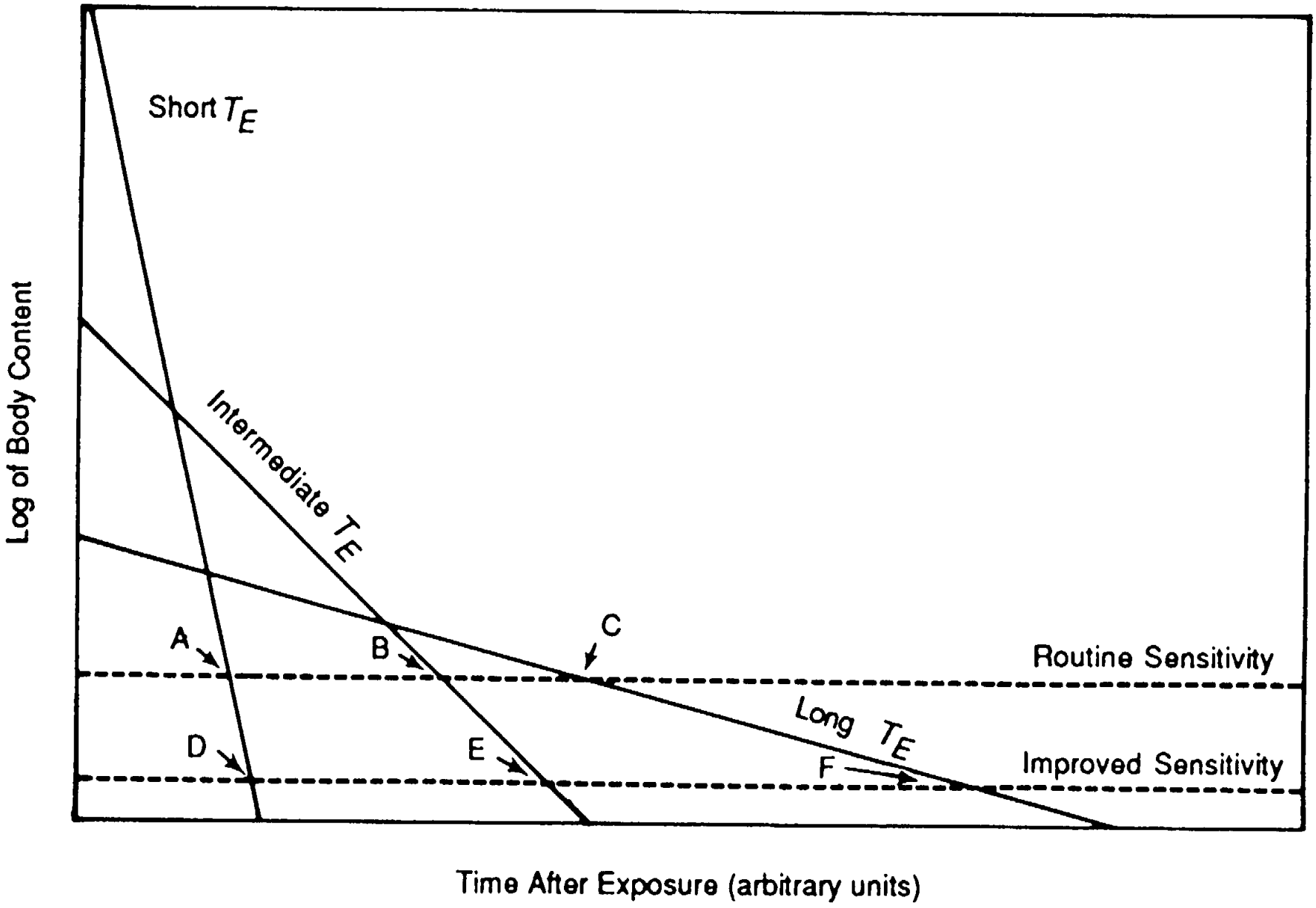
WHAT HAPPENED AFTER EXPOSURE?



Bioassay Scheduling

- The frequency of collection of bioassay samples should be based on the concept of “missed dose”

- At some time after an intake, the daily excretion will fall below the limit of detection of the analytical method, and so a sample collected after that time will be negative
- Consequently, the dose resulting from that intake will be missed.


Short T_E
Intermediate T_E
Long T_E
A
B
C
D
E
F
Routine Sensitivity
Improved Sensitivity
Log of Body Content
Time After Exposure (arbitrary units)

Missed Dose

- Missed dose is a function of:
  - radionuclide and matrix
  - route of intake
  - individual metabolism
  - acute or chronic intake
- Presumably, NRC licensees should set missed dose limits at or below 5 mSv--ALARA applies
- Scheduling frequency should be established in the technical basis document

Worker Selection for Bioassay

- No hard and fast rules for deciding how much activity in a work location triggers bioassay sampling except:
  - Time-weighted monthly average air concentration >10% of MPC (or DAC) or maximum >30% of MPC (or DAC)
- Several workers in same location should have sampling times staggered

Radiation Protection Dosimetry
Vol. 41 No. 1 p. 43 (1992)
Nuclear Technology Publishing

APPENDIX I

EXAMPLE FOR A RISK CARD IN NUCLEAR INSTALLATIONS

Information concerning the Installation
Legal Name of Company | Address | Site of Work

Information concerning the Worker
Name | First Name | Date of birth
Employee's No | Category

Working conditions
Working activities

Radiological risks: external exposure

X,γ<100 keV	X,γ>100 keV	β particles	α particles	Mixed radiat.	Thermal neutr.	Fast neutr. protons
○	○	○	○	○	○	○

Radiological risks: internal exposure

^{3}H	○	^{125}I	○		○	^{210}Po	○	^{233}U	○	^{238}Pu	○
^{14}C	○	^{131}I	○		○	^{226}Ra	○	enrich.U<5%	○	^{239}Pu	○
^{32}P	○	^{137}Cs	○		○	natural Th	○	enrich.U>5%	○	mix.Pu	○
^{35}S	○	^{60}Co	○		○	^{228}Th	○	natural U	○	^{241}Am	○
$^{90}Sr/^{90}Y$	○		○		○		○		○	^{237}Np	○
^{45}Ca	○		○		○		○		○	^{244}Cm	○
^{36}Cl	○		○		○		○	Radon	○	^{252}Cf	○

Codes of exposure: 0 = None, 1 = Potential, 2 = Occasional, 3 = Frequent or Usual.
Additional information: Physico-chemical characteristics, presumed site- or material-specific ALIs, Work in areas of high natural radioactivity ($Bq.m^{-3}$).

Non-radiological risks

Infrared	○	Halogens	○	Hydrogen sulph.	○	Arom.HC	○	Ketones	○	Dioxines	○
Ultraviolet	○	Fluor	○	Carbon sulph.	○	Alicycl.HC	○	Acetone	○		○
Laser	○	Fluoric acid	○	Metals gen.	○	Benzene	○	Formalin	○		○
Microwaves	○	Mineral acids	○	Be dust	○	Alcan.non-fluor	○	Tributylphosp.	○		○
Low freq.EM	○	Caustic alkali	○	Na metal	○	Chloroform	○	Cyanides	○		○
Noise	○	Concrete	○	Chromic acid	○	Carb.tetrachl.	○	Arom.amines	○		○
Ultrasound	○	Metalloids	○	Ni & comp.	○	Trichloreth.	○	Other amines	○		○
Vibrations	○	Silica	○	Mercury	○	Freons	○	Diphenylamine	○		○
Animal dust	○	Asbestos	○	Lead	○	Hal.arom.HC	○	Chinones	○		○
Plant dust	○	Graphite	○	Used oil	○	Nitr.arom.HC	○	Silicones	○		○
Infect.agents	○	Carbon monoxide	○	Lubricants	○	Phenols	○	Thermoplast.	○		○
Sewage	○	Nitric oxides	○	Tars & prod.	○	Alcohols	○	Polyesters	○		○
Nuisance dust	○	Ammonia	○	Hydro.carb.	○	Aldehydes	○	Polyepoxides	○		○
	○	Sulph.anhydr.	○	aliph.HC	○	Ethers	○	Insecticides	○		○

Monitoring and bioassays required.

Clin. urine anal.	Alb.	○	Gluc.	○	Sed.	○									
Chem.urine anal.	Pb	○	Cd	○	U	○									
Radioact. urine	^{3}H	○	^{14}C	○	^{32}P	○	Ra	○	Pu	○	Am	○	^{233}U	○	^{235}U ○
Radioact. faeces	Pu	○	Am	○											
Internal radioact.	Total body	○	Thyroid	○	Lung	○	Pers.air-sampl.	○							
External exposure	TLD	○	Film	○	Finger dosim.	○									
Clin. blood	Ery.	○	Leuko	○	Thromb.	○	Diff.	○	Urea	○	Uric acid	○	Creat.	○	ALAD ○

Codes of frequency: 0 = None, 1 = Monthly, 2 = Quarterly, 3 = Semiannually, 4 = Annually.

Sample Collection Protocols

- Full 24-hour samples are preferable
- Sample collection away from the workplace is preferred to avoid contamination
- Worker training is absolutely necessary
- Procedures for sample control are required

Bioassay samples

- Samples collected for less than 24 hours must be scaled by volume (urine) or mass (feces)
- Reference Man values are 1.6 L/day urine and 125 g/day feces
- Reference Woman values are 1.0 L/day urine and 110 g/day feces

Statistical Considerations

- Terms such as “sensitivity,” “minimum detectable activity,” “detection limit,” etc. are used without much consistency.
- Whenever anyone uses such a term, ask what is meant, preferably by a statistical formula.
- Most regulatory agencies are using statistical measures based on the work of Altschuler and Pasternak, as modified by Currie.

Assumptions

- Counting rates are high enough that a Gaussian is a good approximation to the Poisson distribution of counts (e.g. N›50)
- Background counts are reasonably stable--there are no sources of variation other than counting statistics ($\sigma_b = \sqrt{N}$)
- Background and sample count times are the same (can adjust if not)
- Note: “background” means counts observed from a “suitable blank”

Definitions

- Accuracy: how well does a result agree with a known value--also called bias
- Precision: how closely do replicate results agree with each other--also called dispersion
- Decision Level: that value which has only a given probability of being a false positive
  - (Type I error): L_C
- Detection Limit: that value which has given probabilities of being a false positive or a false negative
  - (Type II error): L_D, also MDA (Minimum Detectable Amount/Activity)

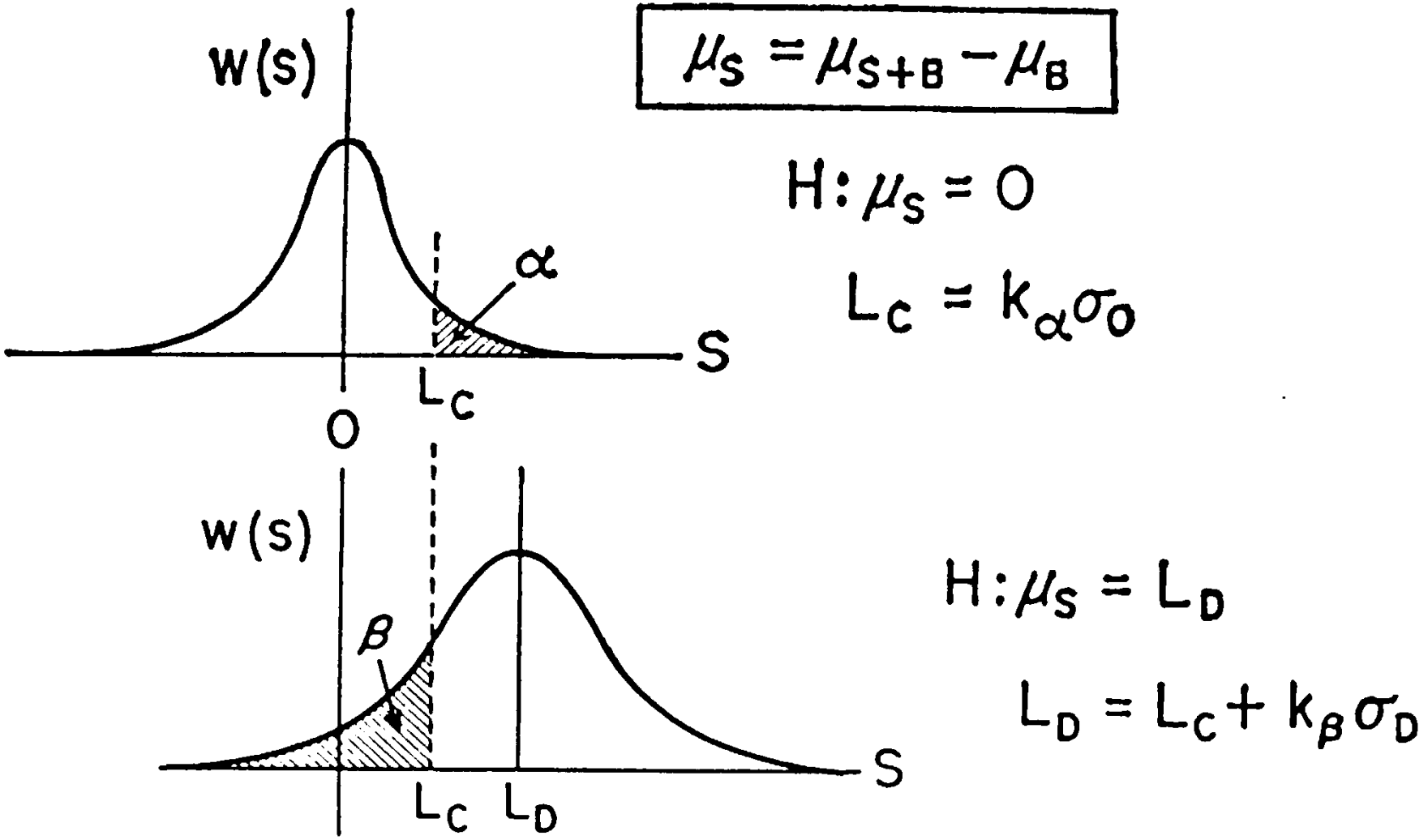


Figure 2. Hypothesis testing

Errors of the first and second kinds

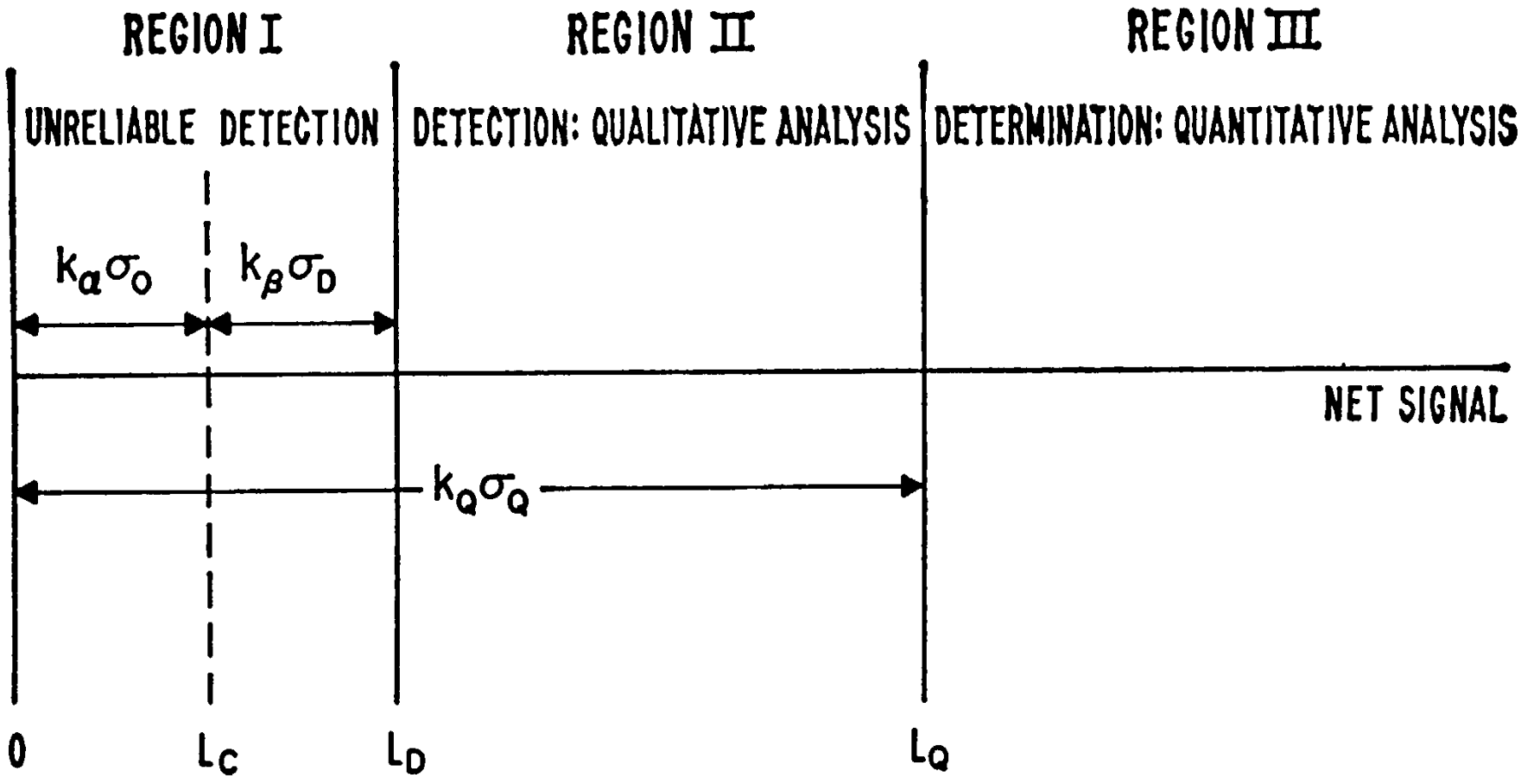


Figure 3. The three principal analytical regions

Table I. "Working" Expressions for L_C, L_D, L_Q.[a]

	L_C	L_D	L_Q
Paired observations	$2.33\ \sigma_B$	$4.65\ \sigma_B$	$14.1\ \sigma_B$
"Well-known" blank	$1.64\ \sigma_B$	$3.29\ \sigma_B$	$10\ \ \sigma_B$

[a] Assumptions: $\alpha = \beta = 0.05$; $k_Q = 10$; $\sigma = \sigma_0 = \text{const.}$

Table II. "Working" Expressions for Radioactivity

	L_C (counts)[a]	L_D (counts)	L_Q (counts)
Paired observations			
$(\sigma_B^2 = \mu_B)$	$2.33\sqrt{\mu_B}$	$2.71 + 4.65\sqrt{\mu_B}$	$50\left\{1 + \left[1 + \frac{\mu_B}{12.5}\right]^{1/2}\right\}$
"Well-known" blank			
$(\sigma_B^2 = 0)$	$1.64\sqrt{\mu_B}$	$2.71 + 3.29\sqrt{\mu_B}$	$50\left\{1 + \left[1 + \frac{\mu_B}{25}\right]^{1/2}\right\}$
Zero blank $(\mu_B = 0)$	0	2.71	100
Asymptotic ratio[b,c] (S/σ_B)	1.64	3.29	10

[a] Dimensions (counts) apply to the first three rows only.
[b] "Well-known" blank case; for paired observations, multiply by $\sqrt{2}$.
[c] Correct to within 10% if $\mu_B \geq 0$, 67, 2500 counts, respectively, for each of the three columns. For paired observations, $\mu_B \geq 0$, 34, 1250 counts, respectively.

MDA as Activity

- MDA formulas are based on counts
- To convert counts to activity concentration:

$$MDA = \frac{4.65\,\sigma(B) + 2.71}{a\,E\,R\,V\,T}$$

where:

a = unit conversion factor (e.g., dpm per nCi)

E = counting efficiency
R = chemical recovery
V = sample size
T = counting time

“POSITIVE” Sample

A Bioassay sample is considered “positive” when:

It exceeds the decision level

AND

It is confirmed by a follow-up sample

OR

It is associated with a known incident

OR

No follow-up sample is obtained

Ask your bioassay lab to:

- Report numerical values, even if less than zero, with total propagated error
- Specify number of standard errors reported
- Report if sample value exceeds L_c or L_D or your specified action level (if provided)
- Have a senior person review results before reporting

Don’t let your bioassay lab:

- Report values below MDA as “not detected”.
- Compute “sample-specific” values for MDA.
- Record values less than MDA as the MDA (censored data).

  - Reference: Chambless, Dubose & Sensintaffar, Health Phys. 63, 338 (1992)

Action Levels

(in increasing order of assigned dose)

- Recording level-- the dose is recorded and entered into worker's dose records
- Reporting level-- the dose is reported to supervisors, health physics, DOE, etc.
- Investigation level-- a formal investigation into the circumstances of the intake made
- Intervention level-- the worker is referred for medical evaluation/treatment

Numerical Values

- Recording level: 0.01--0.1 mSv
- Reporting level: 0.1--1 mSv
- Investigation level: 1 mSv

  (frequently same as reporting level)
- Intervention level: > 10 x dose limit

  Consider intervention at 1-10 x limit
- Remember the limits apply to dose from all intakes in a year, so a given (annual) dose limit needs to be divided by the number of sampling intervals in the year

Derived Action Levels

- A derived action level is that quantity of a radionuclide in a bioassay sample, that with the use of standard dosimetry models, indicates a dose at or above the corresponding action level.
- Thus there are
  - Derived recording levels
  - Derived reporting levels (DRL)
  - Derived investigation levels (DIL)
  - Derived intervention levels
- Should be listed in technical basis manual.

Derived Action Levels

- Numerical values depends on:
  - the radionuclide
  - the intake route
  - duration of intake (acute vs. chronic)
  - the sampling frequency
  - likelihood of multiple exposures
- Calculated as: $\frac{\text{dose level x intake retention fraction}}{\text{DCF x N}}$

  t = 0.5 x sampling interval

  N = number of sampling intervals/yr

Quality Assurance
in the Bioassay Lab

- “Quality” may be defined as conformance of a product or service to the customer’s needs.
- Some of those needs are:
  - meet regulatory requirements
  - provide defensible data
  - alert for workplace problems
  - timely results
  - prompt follow-up

QA Programs

- For NRC licensees, the QA program must meet the requirements of NQA -1 (18 points)
- The essential elements of your QAP should be the same whether an in-house lab or an outside contractor is used
- Note: a QA Plan is only part of a QAP

QA Documentation

- Technical basis document:
  what you're doing and why
- QA Plan
  how you are going to assure quality
- Procedure manual
  radiochemical methods, counting protocols, acceptance criteria, instrument calibration
- Analyst qualification
  education, certification, OJT,etc. (requirements given in QA Plan)

Essential Elements of QA Plan

- Description of program and objectives
- Personnel training and qualification
- Documents and records
- Work process controls
- Design control
- Procurement control
- Nonconformance management
- Self assessment
- Independent assessment

Quality Control Samples

- Possibly the most important aspect of QA
- QC samples are any samples analyzed specifically to assess the program
- Three types: spikes, blanks, splits
- QA samples should be at least single-blind i.e., analyst does not know “right” value
- May be double-blind, also: analyst does not know sample is QC --looks like routine
- Available from various sources

Laboratory Accreditation

- No national programs specifically for bioassay
- DOE has internal dosimetry DOELAP
- EPA certification for radioactivity in environmental samples (may also be administered by state)
- AIHA laboratory accreditation program

  (not for radionuclides)

Chain of Custody

- Absolutely vital for defensible data
- Bioassay samples frequently collected away from workplace
- Empty container should be sealed, seal to be broken by subject
- Subject should seal filled container
- Samples must be under positive control while being processed

QA Responsibilities
Laboratory Manager

- Directs laboratory operations, has responsibility for QA implementation
- Obtains necessary resources to satisfy QA requirements
- Participates in and resolves QA problems discovered by staff
- Reviews and approves plans and procedures
- Arranges internal and external assessments

QA Responsibilities
QA Coordinator

- Monitors compliance with QA plan through internal assessment
- Maintains and updates QA plan
- Manages document control system
- Conducts training on QA program
- Provides QA review of procurements, processes, and other operations that could affect quality

QA Responsibilities

Laboratory Analysts

- Prepare, use, revise written procedures
- Maintain copy of procedure manual and personal qualification records
- Apply QA requirements to all aspects of routine activities that could affect quality
- Detect and report nonconformances and document corrective actions.
- Suggest quality improvements