

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

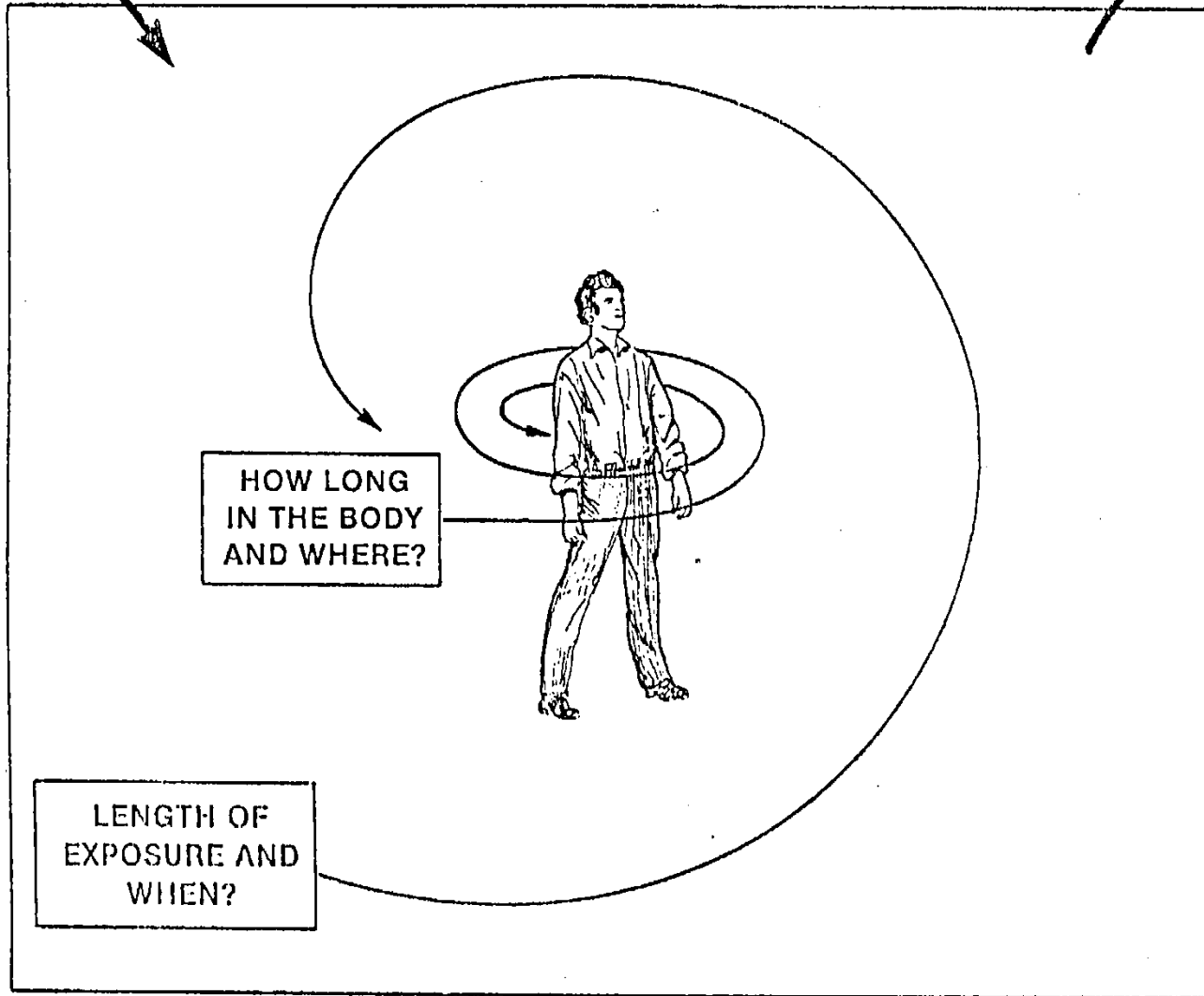
Choosing A Bioassay Sample

- 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?

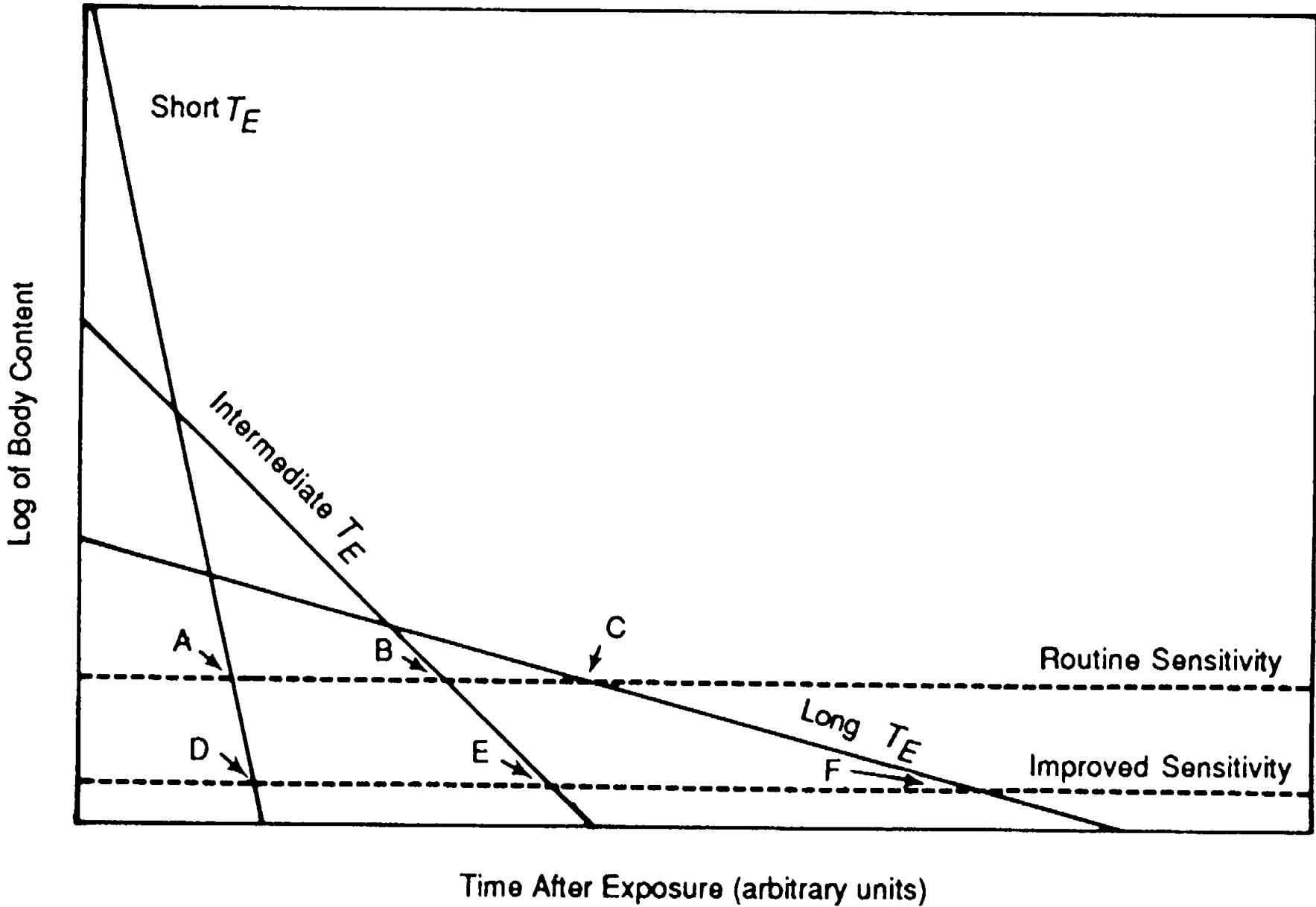
WHAT WAS IN THE
WORK ENVIRONMENT?

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

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

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 <input type="radio"/>	X, γ > 100 keV <input type="radio"/>	β particles <input type="radio"/>	α particles <input type="radio"/>	Mixed radiat. <input type="radio"/>	Thermal neutr. <input type="radio"/>	Fast neutr. protons <input type="radio"/>
------------------------------------------------	------------------------------------------------	--------------------------------------------	---------------------------------------------	----------------------------------------	-----------------------------------------	----------------------------------------------

Radiological risks: internal exposure

^1H <input type="radio"/>	^{125}I <input type="radio"/>	<input type="radio"/>	^{210}Po <input type="radio"/>	^{233}U <input type="radio"/>	^{238}Pu <input type="radio"/>
^{14}C <input type="radio"/>	^{131}I <input type="radio"/>	<input type="radio"/>	^{226}Ra <input type="radio"/>	enrich. U < 5% <input type="radio"/>	^{239}Pu <input type="radio"/>
^{32}P <input type="radio"/>	^{137}Cs <input type="radio"/>	<input type="radio"/>	natural Th <input type="radio"/>	enrich. U > 5% <input type="radio"/>	mix. Pu <input type="radio"/>
^{35}S <input type="radio"/>	^{60}Co <input type="radio"/>	<input type="radio"/>	^{228}Th <input type="radio"/>	natural U <input type="radio"/>	^{241}Am <input type="radio"/>
^{90}Sr / ^{90}Y <input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	^{237}Np <input type="radio"/>
^{45}Ca <input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	^{242}Cm <input type="radio"/>
^{36}Cl <input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	Radon <input type="radio"/>	^{252}Cf <input type="radio"/>

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 ($\text{Bq}\cdot\text{m}^{-3}$).

Non-radiological risks

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

Monitoring and bioassays required.

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

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

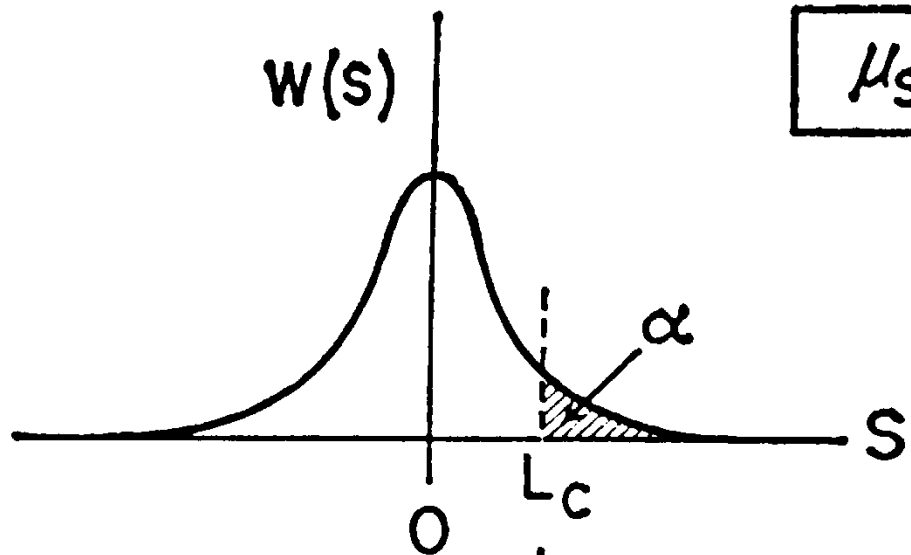
- Terms such as “sensitivity,” “minimum detectable activity,” “detection limit,” etc. are used without much consistency.
- Whenever anyone uses such a term, ask what is meant, preferably by a statistical formula.
- Most regulatory agencies are using statistical measures based on the work of Altschuler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

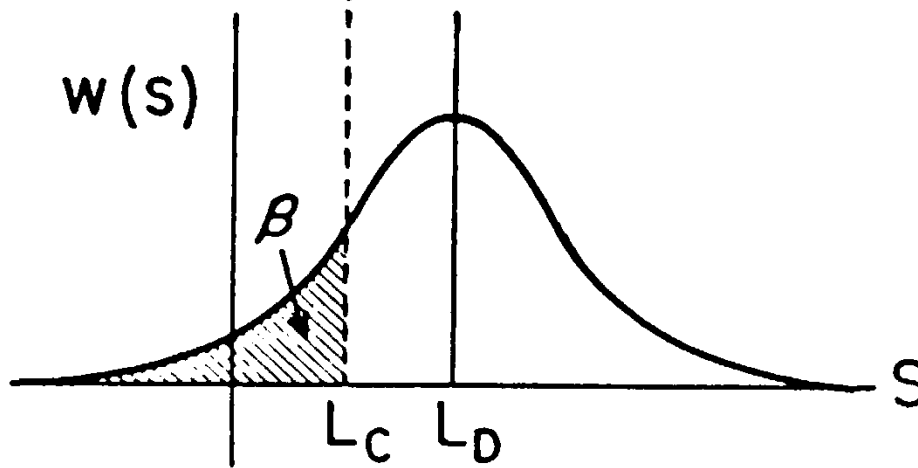
- Accuracy: how well does a result agree with a known value--also called bias
- Precision: how closely do replicate results agree with each other--also called dispersion
- Decision Level: that value which has only a given probability of being a false positive
 - (Type I error): L_C
- Detection Limit: 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)



$$\mu_S = \mu_{S+B} - \mu_B$$

$$H: \mu_S = 0$$

$$L_c = k_\alpha \sigma_0$$



$$H: \mu_S = L_D$$

$$L_D = L_c + k_\beta \sigma_D$$

Figure 2. Hypothesis testing

Errors of the first and second kinds

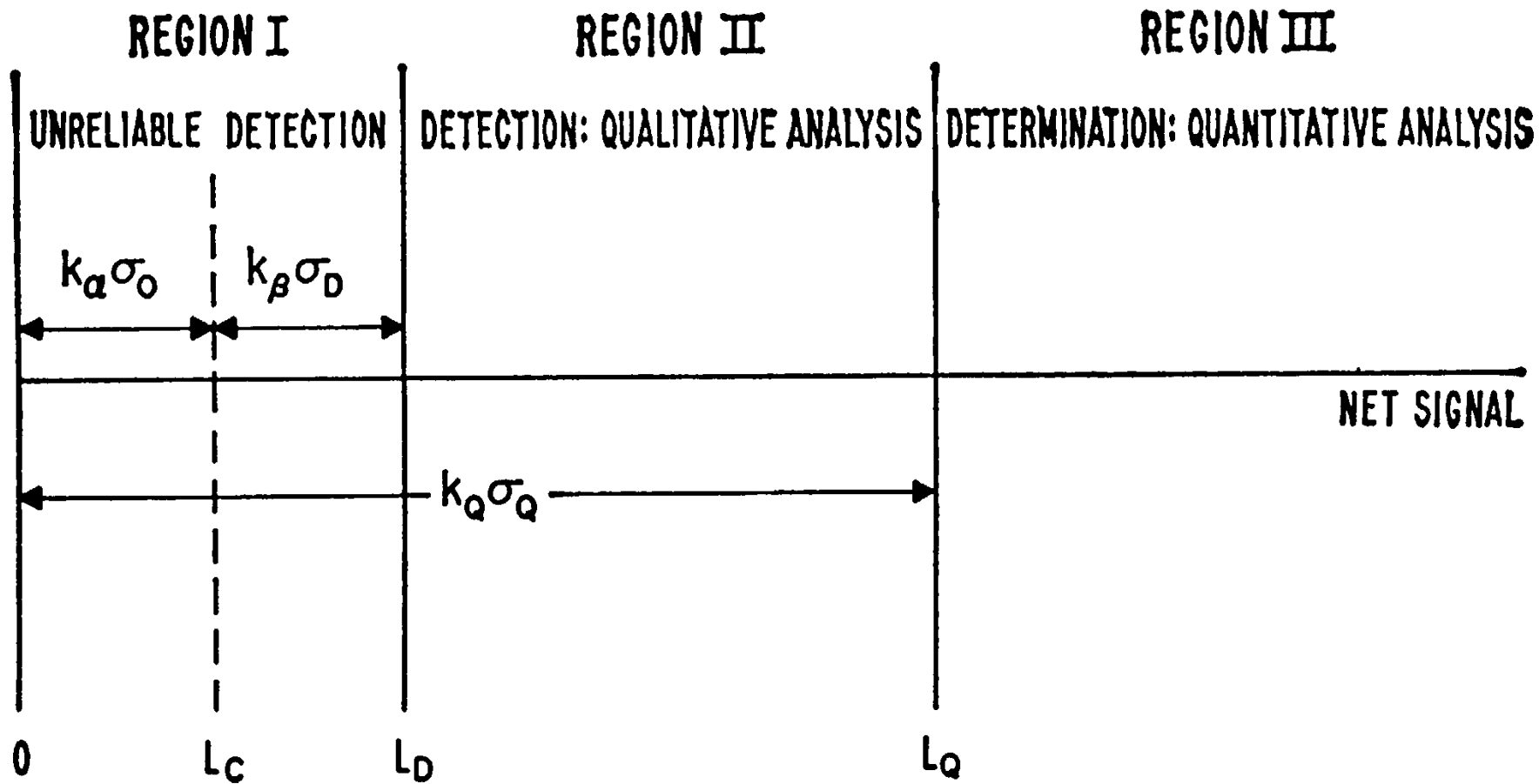


Figure 3. The three principal analytical regions

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:

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

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: $> 10 \times$ dose limit
Consider intervention at 1-10 \times 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: $\frac{\text{dose level} \times \text{intake retention fraction}}{\text{DCF} \times N}$
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