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MANAGING RISK

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What is risk?

- **The *likelihood* of an event that may adversely affect human health and the *severity* of the adverse effect**

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Risk Assessment

- **Risk assessment provides a formalized process to evaluate human, animal, and ecological responses associated with exposure to potential hazards**

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Risk Assessment

The purpose of risk assessment is to answer two related questions:

- **How likely is an adverse event to occur?**
- **If it does, how severe will the impact be?**

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Risk Assessment in the US

- The science of risk assessment evolved out of the necessity to make public health decisions in the face of scientific uncertainty

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Risk Assessment in the US

- Its basic propositions have been established over the past three decades and its applications have impacted virtually every aspect of public health and environmental protection

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History of Risk Assessment

- Qualitative assessment of the strength of the evidence or likelihood that agent A causes disease B

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Qualitative Risk Assessment

- **Koch's Postulates (1894)—defines the scientific evidence required to demonstrate causation for infectious diseases**

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Koch's Postulates

- An organism can be isolated from a host suffering from the disease
- The organism can be cultured in the laboratory
- The organism causes the same disease when introduced into another host
- The organism can be re-isolated from that host

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Qualitative Risk Assessment

- **Bradford-Hill Criteria (1965)—Criteria to be applied to establish causality between an environmental exposure to a noninfectious agent and a particular disease in humans**

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Bradford-Hill Criteria

- Is there a temporal relationship?
- How strong is the association between exposure and disease?
- Is there a dose-response relationship?
- Have the results been replicated?
- Is the association biologically plausible?

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Bradford-Hill Criteria

- Have alternative explanations been considered?
- What is the effect of ceasing exposure?
- Does the association exhibit specificity?
- Are the findings consistent with other relevant knowledge?

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Qualitative Risk Assessment

- Yes/No evaluation—does agent A cause disease B?

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Risk Assessment in the Federal Government

- Regulatory agencies had responsibility to protect human health from hazards due to exposures from food (FDA), medical products (FDA), the environment (EPA), the work place (OSHA), consumer products (CPSC)

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Risk Assessment and Risk Management

- Risk assessment—the characterization of the potential adverse effects of human exposure to hazards
- Risk management—the process of evaluating alternative actions to control risk and selecting among them

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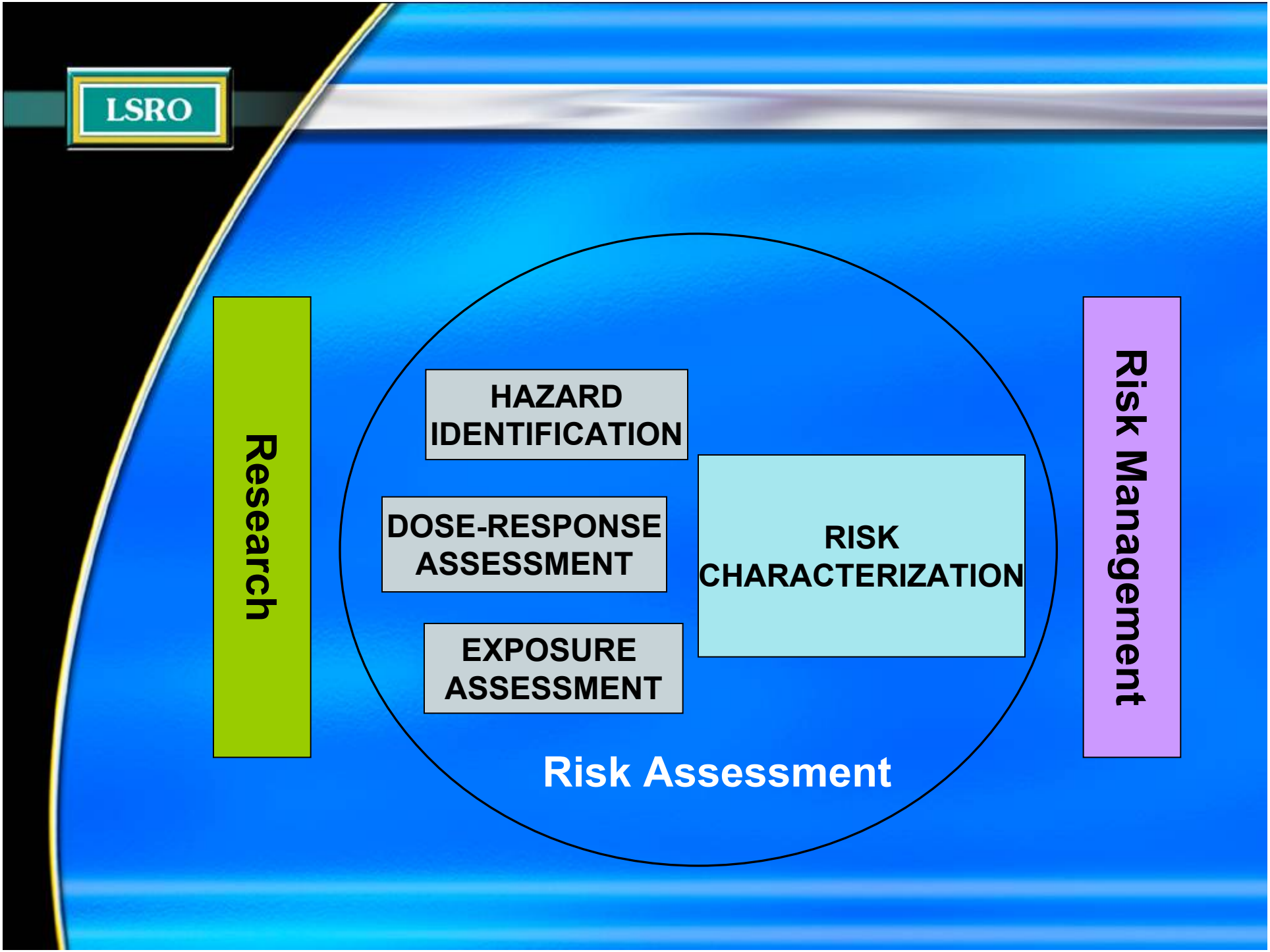
Steps in Risk Assessment

- **Hazard identification—does a substance cause adverse effects?**
- **Dose-response assessment—what is the relationship between dose and adverse effect(s)?**
- **Exposure assessment—What is the nature and degree of exposure to the substance?**
- **Risk characterization—Given steps 1-3, what is the level of risk?**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Research
HAZARD IDENTIFICATION
DOSE-RESPONSE ASSESSMENT
EXPOSURE ASSESSMENT
RISK CHARACTERIZATION
Risk Assessment
Risk Management

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1900-1970s: Risk Assessment/Management Zero Risk

- *Non-carcinogens*: Identify the "no-effect" dose level
- Apply appropriate "safety factor" to derive "safe/acceptable" dose for humans
- *Carcinogens*: Considered to have no threshold; poses risk at all dose levels
- No exposure permitted

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Quantitative Risk Assessment

- Necessary when a zero-risk approach is not feasible
- 1970's: FDA developed quantitative methods and policies based on the concept of *de minimis* risk
- Sensitivity of the method guidelines defined "not detected" as the level of a carcinogen in foods that posed $1X10^{-6}$ risk

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Quantitative Risk Assessment

- EPA's original approach to carcinogens in the environment was to ban them
- That is, the qualitative demonstration that a chemical is carcinogenic in animal studies was sufficient
- 1970's: Zero-risk was an "unobtainable" goal
- Acceptable risk of $1X10^{-6}$ was set

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Scientific Uncertainty

- Gaps in scientific information and/or understanding are encountered in risk assessment
- Scientific judgments are needed
- In the absence of ‘consensus judgments,’ policy is used to fill the gap—usually public-health conservative assumptions are used (reasonable worst-case)

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EPA Cancer Guidelines

- 1976—4 FR pages
- 1986—16 FR pages
- 1996-2005—52 FR pages

And OMB wants more….

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A New Paradigm

- The International Market Place
- ISO
- Terminology and Approaches

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Terminology

- **Risk Management: systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, and controlling risk**

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Terminology

- **Risk Analysis: systematic use of available information to identify hazards and to estimate the risk**

(= Risk Assessment in EPA paradigm)

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Terminology

- **Risk Evaluation: judgment of whether a risk is ‘acceptable’***

(Risk Management in EPA paradigm)

*** Safety is defined as freedom from unacceptable risk**

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Terminology

- **Risk Assessment: overall process comprising a risk analysis and a risk evaluation**

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Terminology

- **Risk Control: process which identifies and implements measures to reduce or maintain risks at a specified level**

(Risk Management in EPA paradigm)

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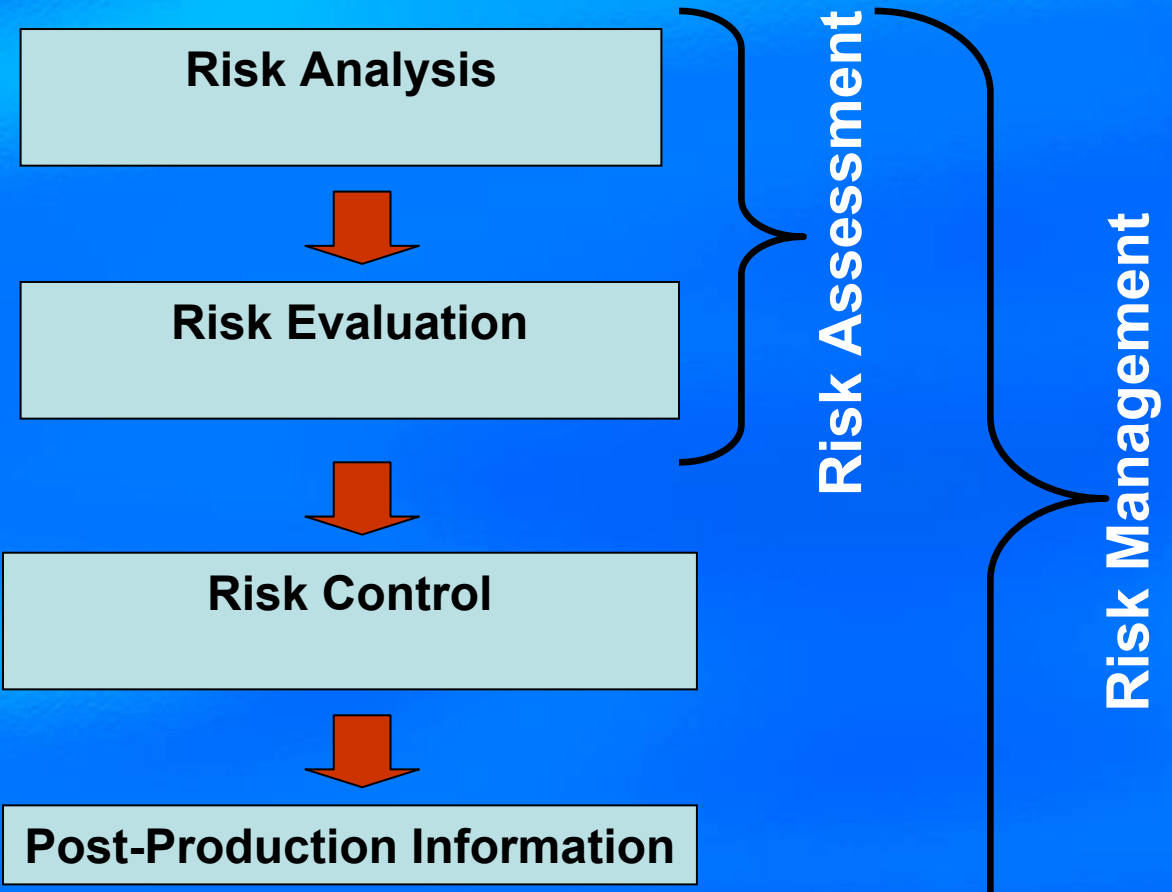
Risk Management Process



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Risk Analysis

- Identify intended use/intended purpose
- Identify hazard
- Estimate risk

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Risk Evaluation

- Is the risk acceptable?
- Does benefit outweigh risk?

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Risk Control

- Option analysis
- Implementation
- Residual risk evaluation
- Overall risk acceptance

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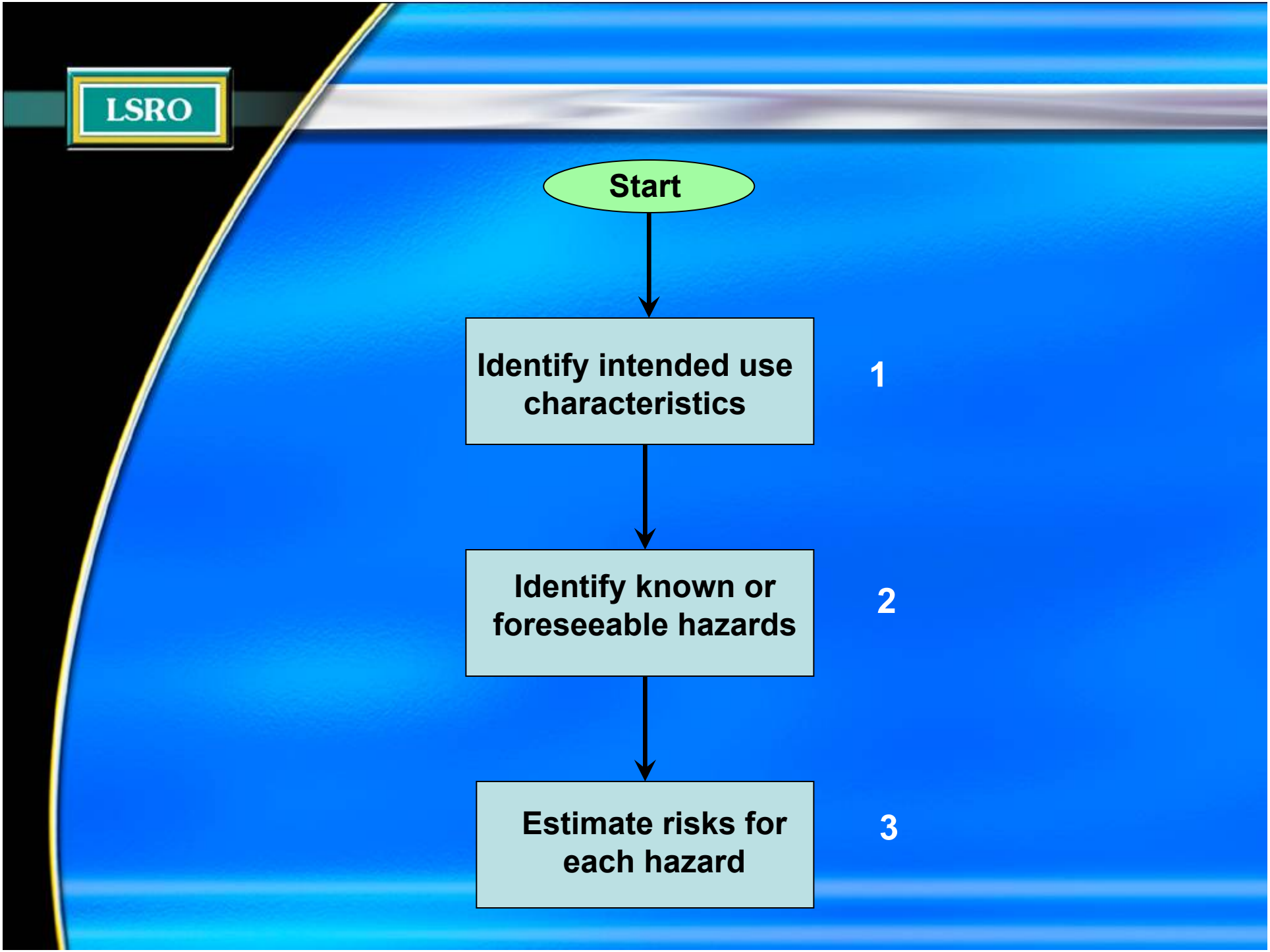
Post-Production Information

- Post-production experience
- Review of risk management experience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Start
Identify intended use characteristics
1
Identify known or foreseeable hazards
2
Estimate risks for each hazard
3

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Ranking Degree of Hazard

Type of data	High score	Medium score	Low score
Acute toxicity	Lethal dose ≤ 50 mg/kg	Lethal dose 50-500 mg/kg	Lethal dose ≥ 50 mg/kg
Chronic toxicity	NOEL ≤ 10 mg/kg	NOEL 10-1000 mg/kg	NOEL ≥ 1000 mg/kg
Type of chronic effect	Serious, irreversible	Major organ pathology	Minor biologic changes
Route of exposure	Same route	Only by other routes	No relevant routes
Source of information	Humans	Animals	Unconfirmed effects

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GHTF Risk Ranking Parameters

Severity of harm		*Probability of occurrence*	
S-5	Catastrophic	O-6	Always
S-4	Critical	O-5	Frequent
S-3	Serious	O-4	Probable
S-2	Minor	O-3	Occasional
S-1	Negligible	O-2	Remote
		O-1	Improbable
		O-0	None

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GHTF Risk Chart

O-6					
O-5				HIGH	
O-4					
O-3			MID		
O-2					
O-1		LOW			
O-0					
	S-1	S-2	S-3	S-4	S-5

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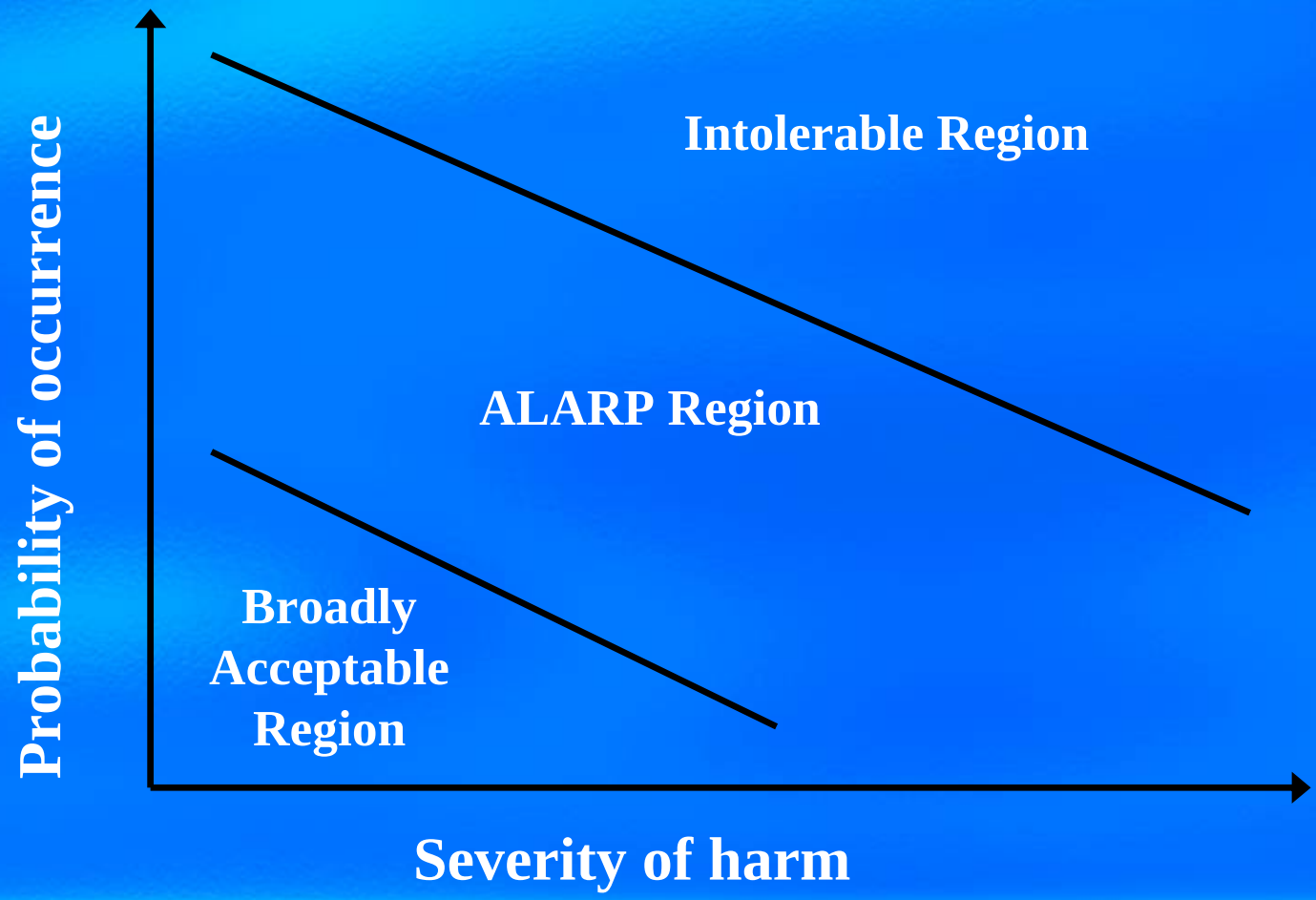
ISO Three Region Risk Chart



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Acceptable Risk

General rule of thumb:

Margin of safety ≥100-fold less than NOEL

Cancer risk ≤ 1 x 10-6

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MOS

- Chronic NOEL for chemical A is 5mg/d
- EPA derived a reference dose of 0.05 mg/d = 50µg/d
- Worst-case exposure is estimated to be 5µg/d
- MOS is 10
- If no ‘official’ acceptable dose available, use NOEL—MOS should be ≥100

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Risk Calculation

Assumptions:

- EPA unit risk estimate = 7.8×10^{-6} µg/kg bw
- Worst-case average daily dose over lifetime (LADD) = 54 µg/day

LADD=54 µg/ 70 kg=0.77 µg/kg bw

- Lifetime cancer risk=7.8×10^{-6} µg/kg x $7.7 \times 10^{+1}$µg/kg
  $= 6.1 \times 10^{-5}$

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Application: Regulation-Driven

- **CALIFORNIA'S Proposition 65**

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Prop 65

- Ballot initiative—1987
- Anyone doing business in the state
- Carcinogens and reproductive toxicants
- Chemical lists
- Safe harbor numbers
- Warning requirements
- Enforced by AG
- Bounty hunter provision

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Compliance

- Each company
- Each product
- Manufacturing facility environmental releases
- Safe harbor numbers were average daily doses/exposures
  - Carcinogens: LADD equivalent to $1X10^{-5}$
  - Reproductive toxicants: Average daily dose on the day of exposure, 1000-fold safety factor required

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Risk Management Process

- Management responsibility
- Assemble a team
- Develop a systematic review process

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Phase I

- **Management**
  - **Quality Assurance**
  - **Law Department**
- **Team**
  - **QA and Legal**
  - **Analytical, purchasing, process engineers, risk assessors, toxicologists**

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Risk Management Process

- Identify Prop 65 substances of potential concern for products sold in CA
- Prioritize issues: product/substance pairs
- Develop a database
- Review available analytical data
- Determine regulatory limit to be used
- Perform risk assessments

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Steps 1 & 2: Product/Hazard Identification

- Systematic review process
  - Start with the Prop 65 list
  - Products that could possibly contain X

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Prioritize substance/product pairs based on presence in product:

- Known
- Likely
- Possible
- Unlikely
- N/A (drugs, e.g.)

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Substance	Known	Likely	Possible	Unlikely
C-1		X (product)	X (product)	
C-2	X (product)			
R-1				X

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Develop Parameters for RA

- Known and likely S/P pairs analyzed for presence of Prop 65 substance(s)
- Develop daily intake levels—LADD or ADD; product categories or specific products (USDA data)
- Identify ‘acceptable intake levels’ based on CA values, EPA values, other ‘official’ values, toxicological data

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Step 3 Sample Calculation

Concentration of S x Intake of P = (L)ADD

10 µg/kg x .056 kg = 5.6 µg

Is 5.6 µg/day ≤ Acceptable Daily Intake?

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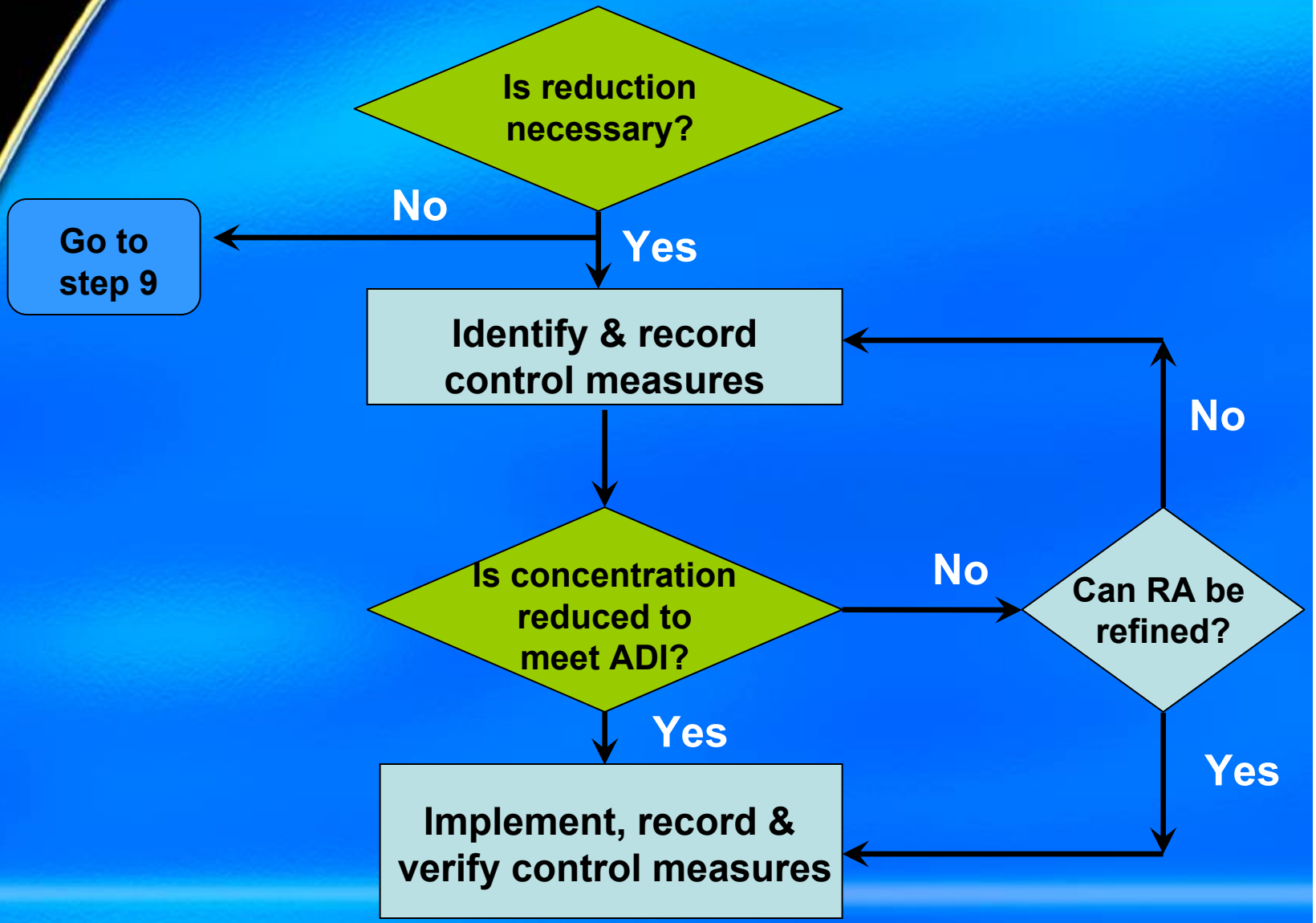
Is reduction necessary?
No
Go to step 9
Yes
Identify & record control measures
No
Is concentration reduced to meet ADI?
No
Can RA be refined?
Yes
Yes
Implement, record & verify control measures

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Identify & record control measures

What is the source of S?

- **Raw material?**
- **Ingredient?**
- **Processing?**

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Identify & record control measures

What changes can be made to reduce S?

- **Tighten specs on raw material?**
- **Substitute a different ingredient?**
- **Modify processing?**
- **Combination of above?**

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Implement, record & verify control measures

- Implement controls
  - Supplier
  - Production
  - Product monitoring plan

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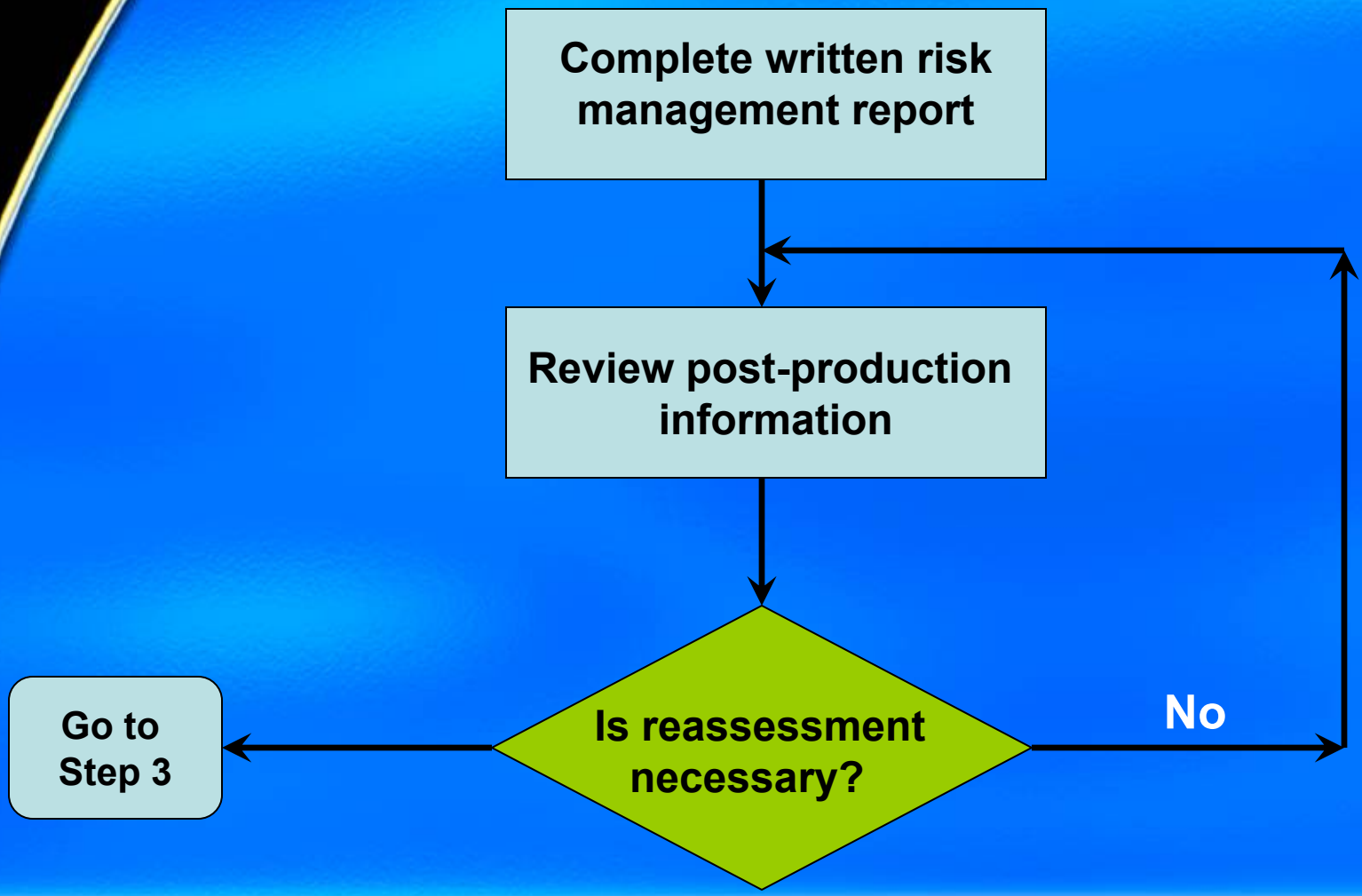
Complete written risk management report
Review post-production information
Is reassessment necessary?
No
Go to Step 3

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Are there new substances on Prop 65 list?

Are there new safe harbor numbers?

New products/process should trigger Prop 65 review

Changes affecting existing products (new supplier, reformulation) trigger Prop 65 review.

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Life Cycle Analysis

- Ensuring the health of the public throughout the total product life cycle
- Design
- Engineering
- Mode of action
- Clinical sciences
- Quality systems
- Post-marketing surveillance

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Life Cycle Analysis: Product

- Ensuring the health of the public throughout the total product life cycle
  - Design
  - Engineering
  - Mode of action
  - Clinical sciences
  - Quality systems
  - Post-marketing surveillance
  - Obsolescence

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Life Cycle Analysis: Environmental Issues

- **Product Applications and Release Diagram (PARD)**
  - **PARD depicts each step in life of a product: manufacture, storage and distribution, use, and disposal**
  - **Graphically reveals every point at which exposures to products and potential risks occurs**

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Environmental Issues

- Prioritize issues
  - Rank hazard/toxicity
  - Rank population exposures
- Human risks
- Ecological risks

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Ranking Degree of Hazard

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Population Exposures

Type of data	High score	Mid score	Low score
Monitoring	Frequent	Occasional	None
Production volume/Use	Major/ Widespread	Minor/No consumer	None/None
Phys/chem	Volatile, soluble	Poor vol, sol	Not vol, sol
Bioaccum	Fat soluble	Lo soluble	No soluble
Exp media	multimedia	One medium	Insignificant
Population	Most of pop	Subpops	None

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Human & Ecological Health

- If risks are excessive (exceed acceptable levels) at any point in the process—risk management begins
- If inadequate information exists, research should be considered

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Risk Communication

- Critical, beyond scope of this discussion
- Must be based on substantive risk assessment and management program
- Risk perceptions/nature of the risk

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Product Liability/Toxic Torts

- Demonstrate that all care has been taken to understand and manage a product's risks—'due diligence'
- Must be based on substantive risk assessment and management program