Touching lives, improving life. **P&G** ™

Designing Safety Into Products

A continuous analysis of alternatives

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Toxicologist

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Topics

- Fundamentals

- How is this applied at P&G?

- Examples

P&G's Business Scope

- **Approx 350 brands reaching over 4 billion consumers**

Household Care
Fabric Care, Home Care, P&G Professional, Baby Care, Family Care, Personal Power (batteries), P&G Chemicals

Beauty & Grooming
Female Beauty, Male Grooming, Prestige, Braun, Salon Professional,

Health & Well Being
Personal Health Care, Pet Care, Snacks, Oral Care, Feminine Care

Our policy is to ensure that such products are safe for both our consumers and the environment.
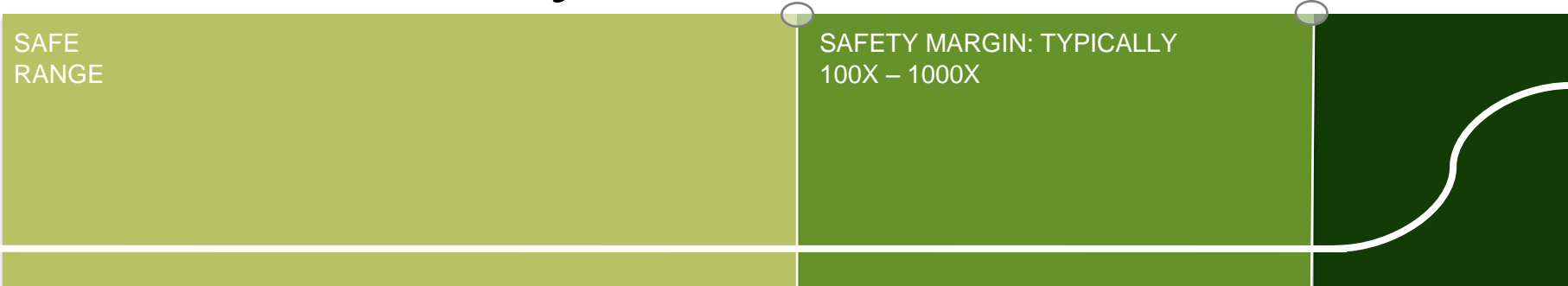
Principle

An ingredient is not safe or unsafe

- It's the use of an ingredient that can be judged as safe or unsafe

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Goal of Safety Assessment

SAFE RANGE

SAFETY MARGIN: TYPICALLY 100X – 1000X
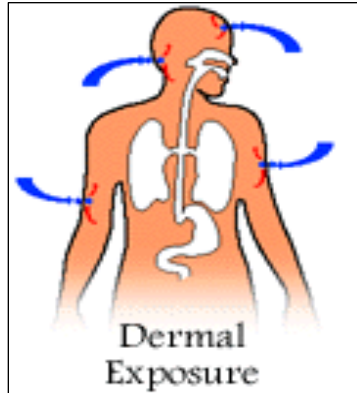
Amount used   <<   Amount that can cause harm

Exposure

- Route
- Duration
- Amount
- Other sources
- Unintended exposures

Hazard & Dose Response
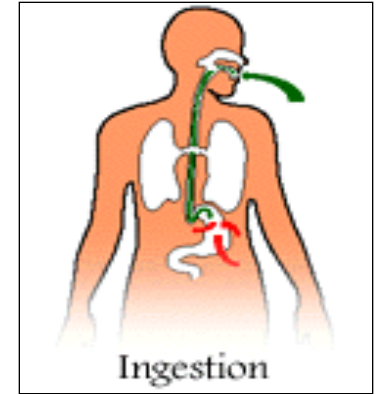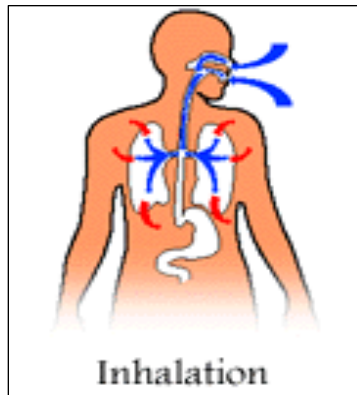
- Endpoints
- Dose-Response

$$MOS = \frac{B_{RV}}{E_{xp}}$$
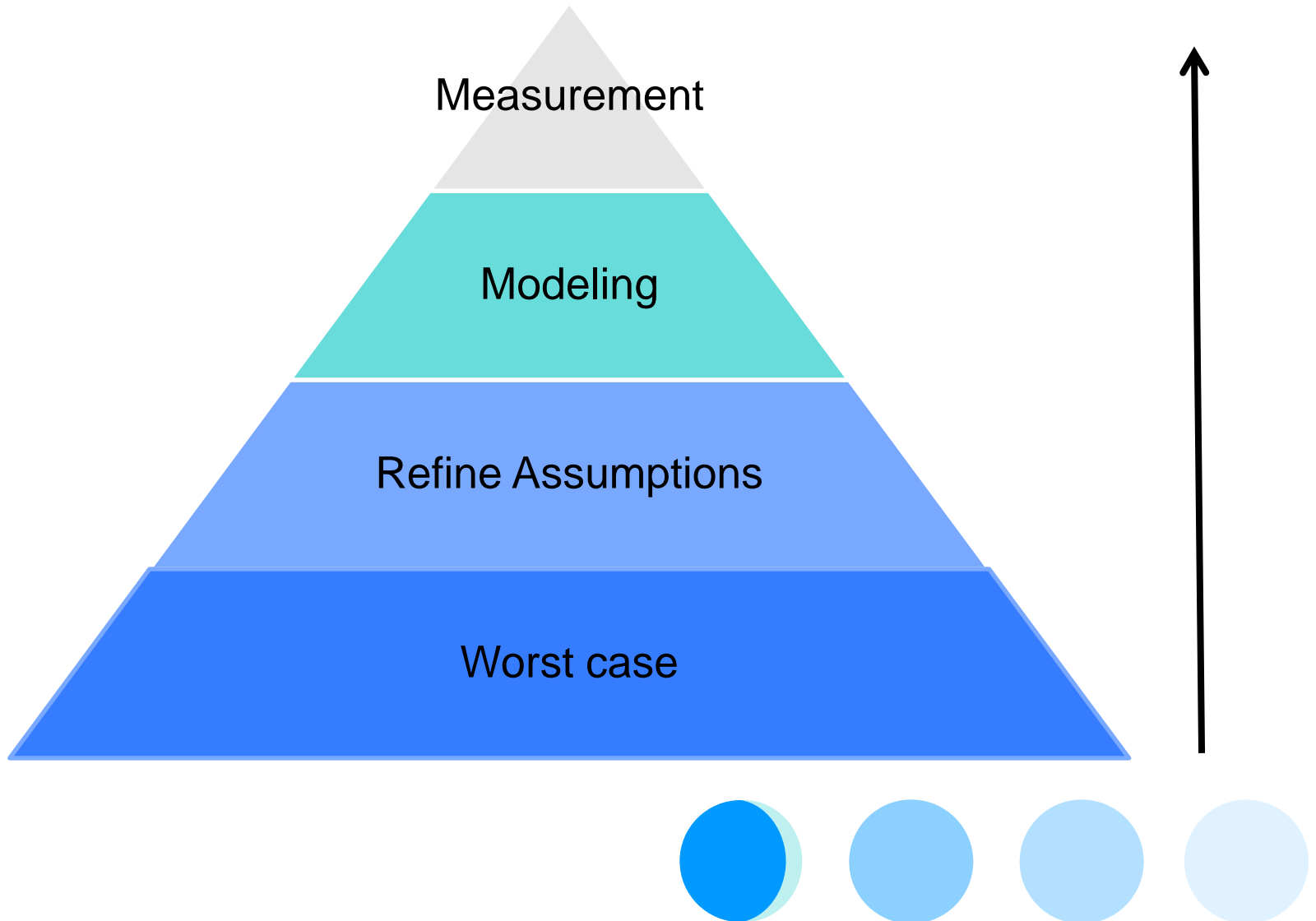
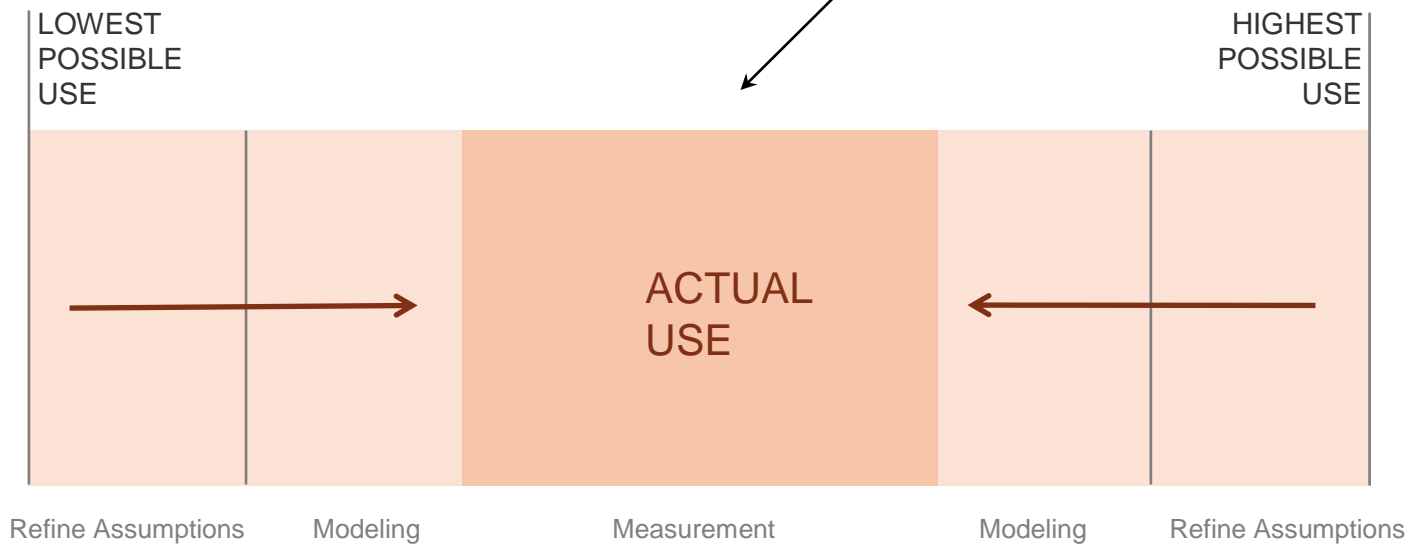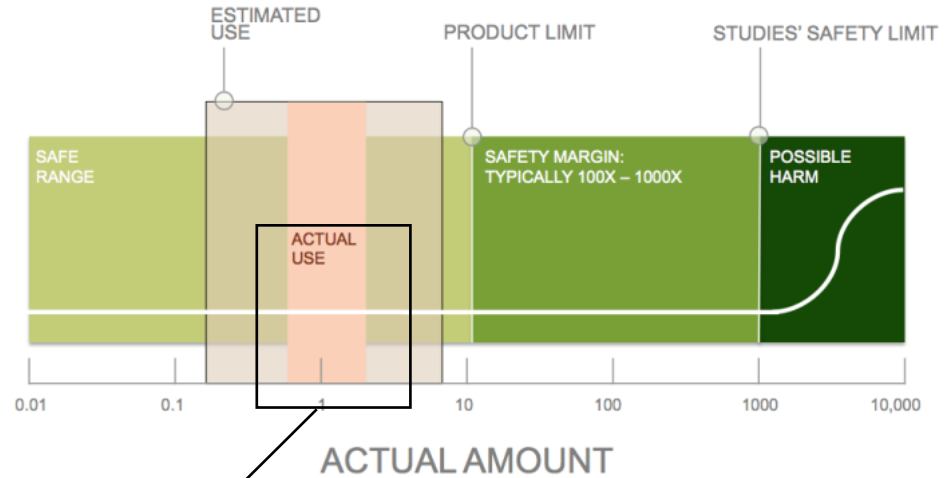# Routes of exposure

Dermal
Exposure

Ingestion

Inhalation

Different uses may result in different effects

Exposure Tiered Approach

Tiered approach - Increasing precision

ESTIMATED USE

PRODUCT LIMIT

STUDIES' SAFETY LIMIT

SAFE RANGE

SAFETY MARGIN: TYPICALLY 100X – 1000X

POSSIBLE HARM

ACTUAL USE

0.01   0.1   1   10   100   1000   10,000

ACTUAL AMOUNT

LOWEST POSSIBLE USE

HIGHEST POSSIBLE USE

ACTUAL USE

Refine Assumptions   Modeling   Measurement   Modeling   Refine Assumptions

Consumer Exposure Assessment

How is data obtained to assess exposure?

❖ Habits & Practices data

- ◆ Consumer or laboratory testing to evaluate use and/or consumption
- ◆ Frequency of use
- ◆ Quantity of product used
- ◆ How product is used
- ◆ Identify sub-populations
- ◆ Simulated use sampling

❖ Product surveillance

- ◆ population data
- ◆ Unintended use scenarios

❖ Externally recommended/validated exposure assumptions (e.g., EU TGD, EPA Exposure Factors Handbook, SDA, CTFA/COLIPA etc.)

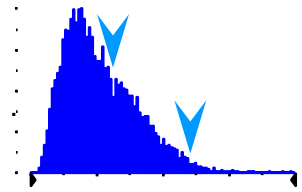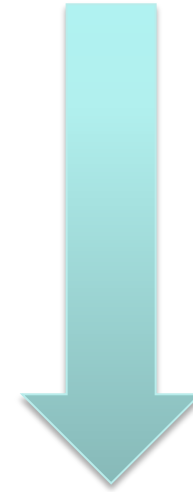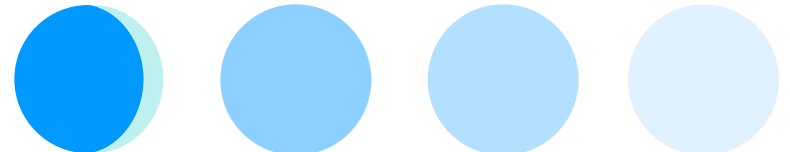❖ Work with Industry partners to publish large Habits & Practices datasets

Multiple sources

Deterministic

$$Ag_{ex} = \sum_{1}^{x} prod_x(conc_x)$$

Probabilistic

$$Ag_{ex} = Prob \left[(prod_1(conc_1) + (prod_2(conc_2) + ...] \right.$$

Paraben

Preservative
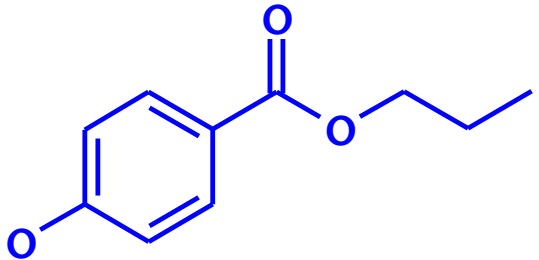
Propyl paraben
CAS# 94-13-3
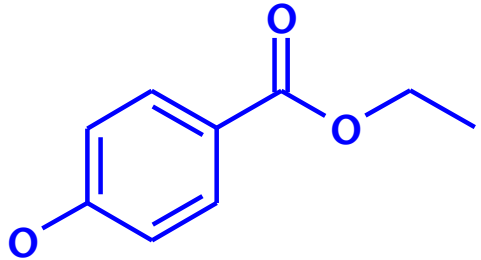
Ethyl paraben
CAS# 120-47-8
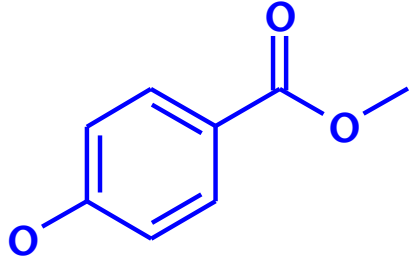
Methyl paraben
CAS# 99-76-3

Paraben

Estimate μg/kg/day
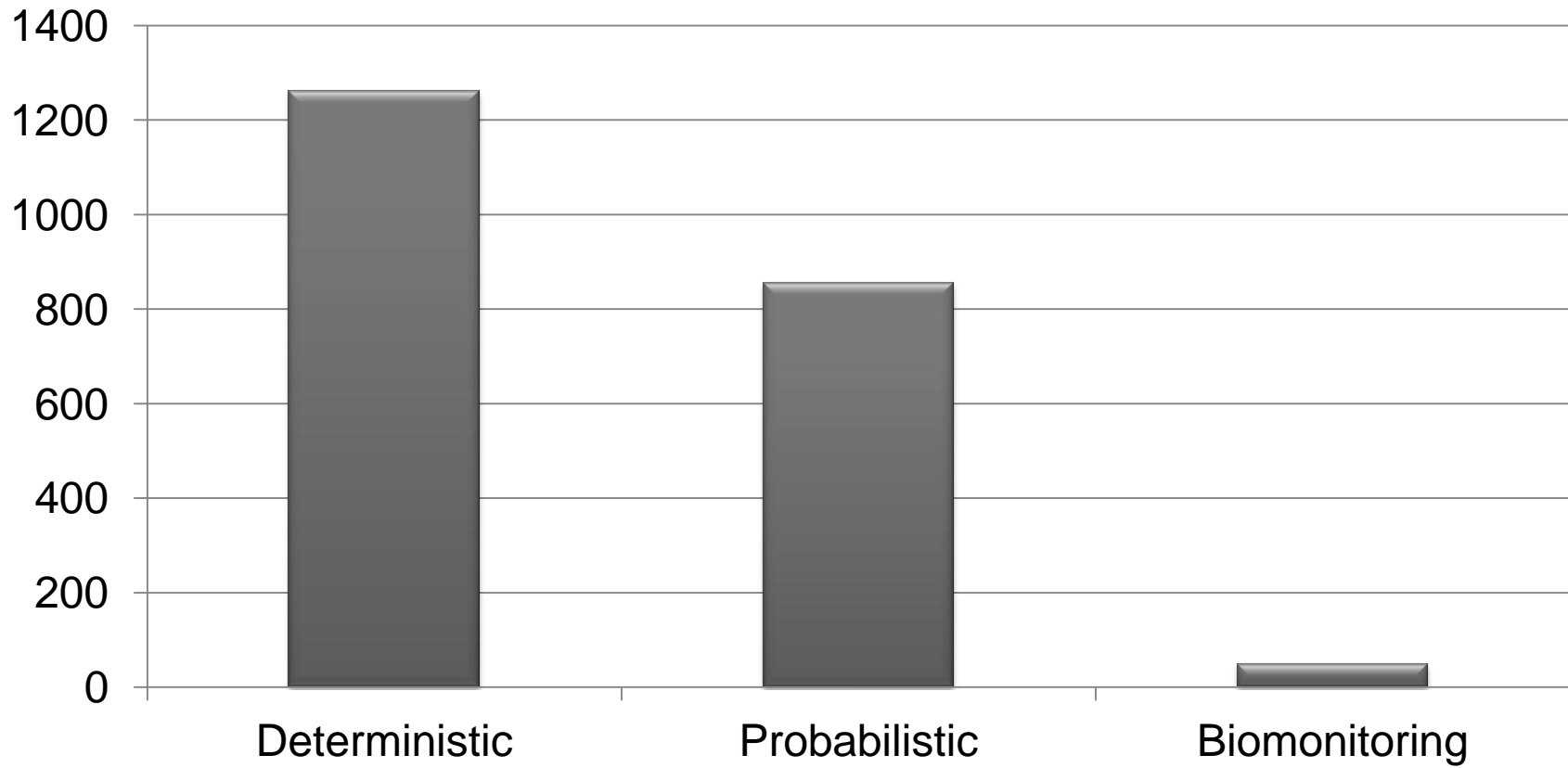
JECFA ADI of 10,000 μg/kg/day

Hazard: What happens and at what level?

Dose-response

No effect range	Margin of safety	Effects
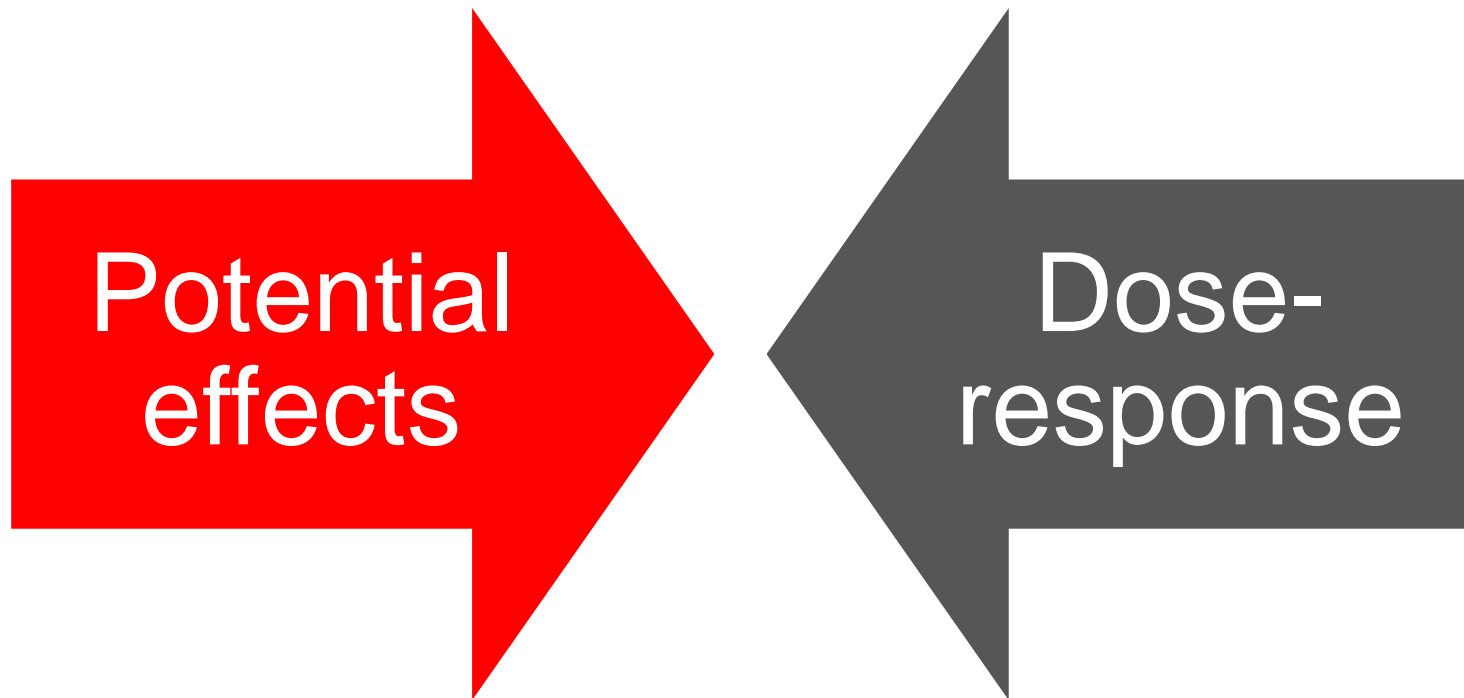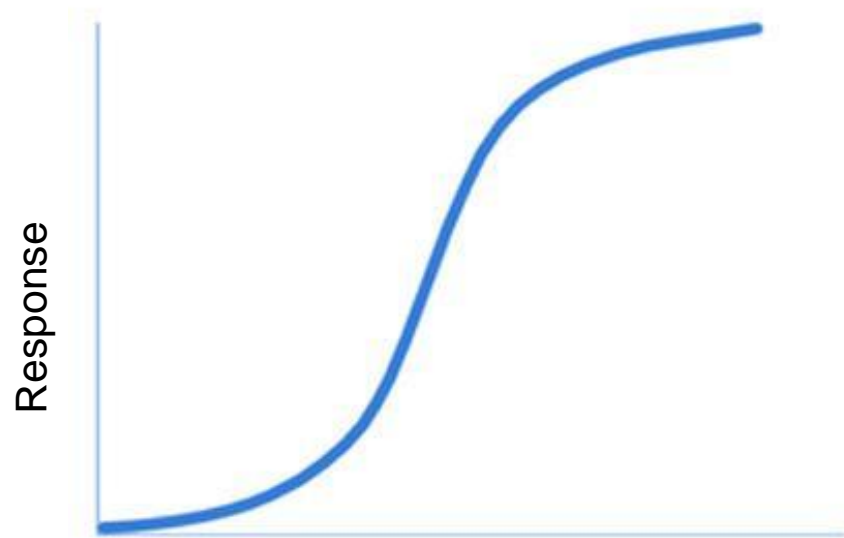
Response

Dose

Hazard/Dose-Response

Tiered Approach

Measurement

Modeling

Existing information
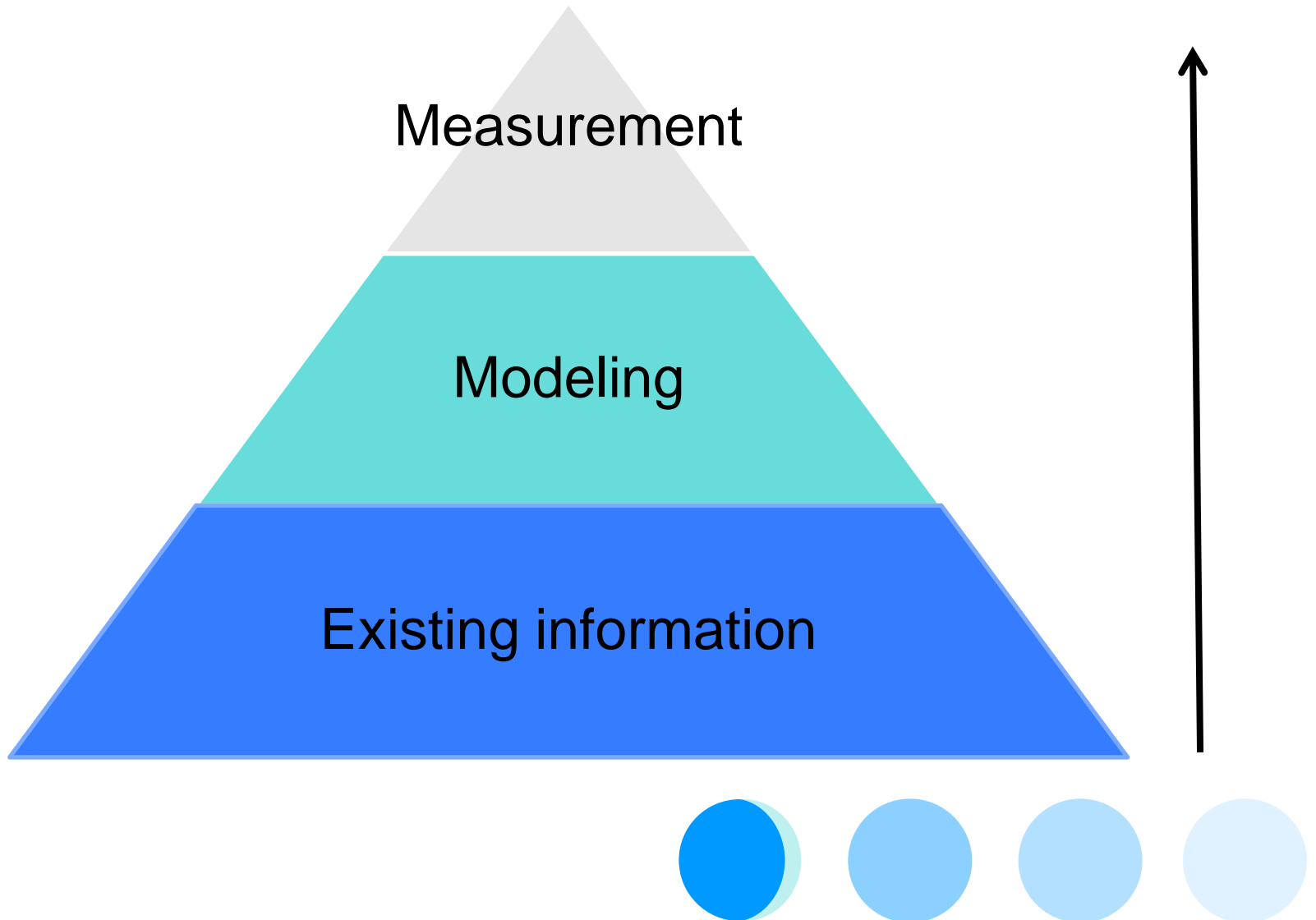
Possible Effects

- Cancer
- Allergies
- Repeat Dose (target organ toxicity)
- Reproductive & Developmental toxicity

- Irritation (ocular, dermal, pulmonary)
- Respiratory effects
- Photo-mediated effects
- Physical hazards

Existing information

Nomenclature
Structure
Literature Search

Indexing

What is known?

Ingredient in question

Analogs
Sub-structures

Chemistry

Metabolism

Metabolites

Endpoints
Reference Doses

Assessment
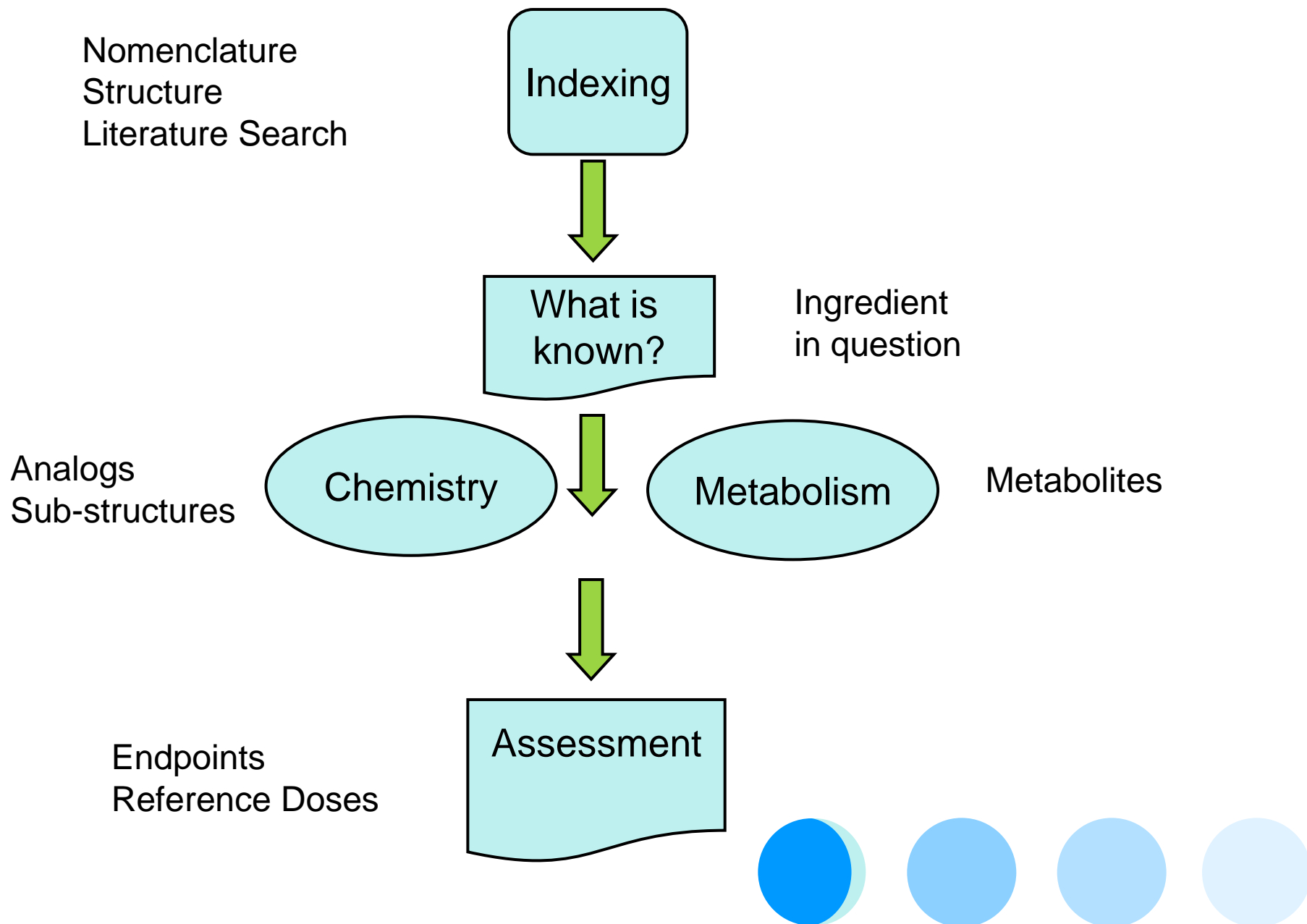
Connection with external DB

Substructure searching

- Genotoxicity (19,300)

- Carcinogenicity (15,800)

- Skin Sensitization (9,400)

- Skin Irritation (10,400)

- Reproductive/Developmental Toxicity (11,300)

- Subchronic/Chronic Toxicity (15,100)

- Acute Toxicity (68,500)

External Data Sources:
BIBRA, Cal Prop 65*, CTFA*, HERA*, HPV*, OECD*, IPCS*, NICNAS*, RIFM/FEMA*, SCCP*, WHO/JECFA*, SciFinder, ToxNet, ATSDR, CPDB, ECETOC, ECB, IARC , Thompson/MicroMedix, NTP, RTECS/NIOSH, Scopus, TSCATS, others*

Making a safety decision

$$MOS = \frac{RfD}{E_{xp}}$$

Endpoint	NOAEL	RfD	E_{xp}	MOS
Acute Oral	> 5 g/kg	50 mg/kg	0.001 mg/kg	1,000
91 day feeding	170 mg/kg	0.170 mg/kg		
Dermal Irrit.	36,000 μg/cm^2	360 μg/cm^2	1.2 μg/cm^2	300
Mutagenicity	Neg	-	-	-
Repro	Neg	-	-	-
Allergy – derm	Neg	-	-	-
Pulmonary Irrit	106,600 μg/g	1066 μg/g	2110 μg/g 70 μg/g 5 μg/g	0.5 15.2 213.2
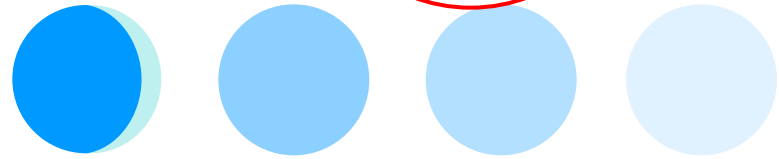
Product Development Process

Safety Assessment

Hazard

Possible Effects
Dose-response

Margin of Safety

What is the safe range?

Exposure

How much?
How long?
What route?
Where does it go?

STOP

YIELD

Reformulate

Product Management

Labeling
Packaging
Distribution

Marketplace

New Information

Post marketing surveillance
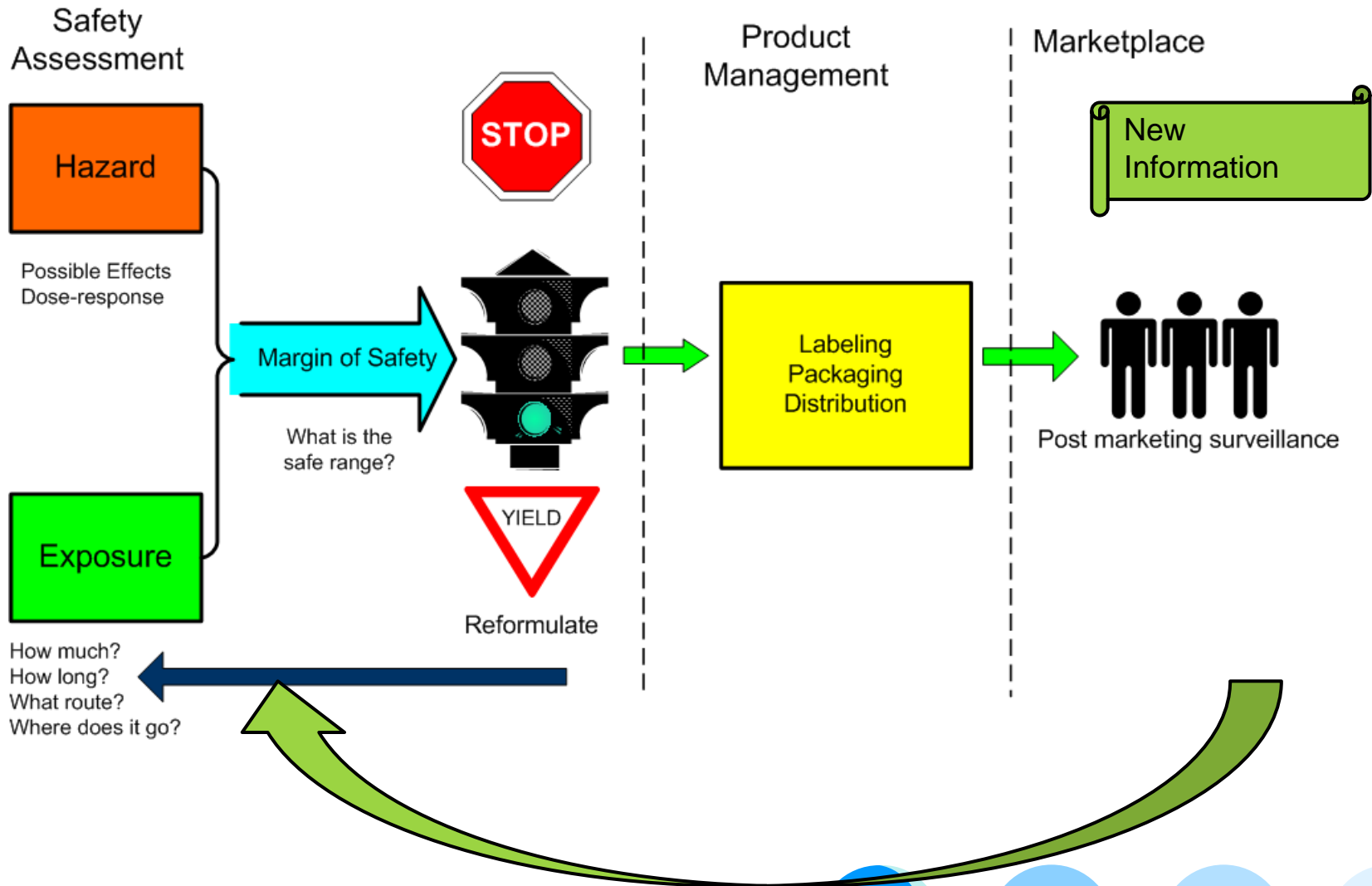
*Adopted from NRC 1983

Design Safety In – *Right from the start*

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ID showstoppers

Limited Exposure

Extended Use

Ad hoc use

1 – 5 year process

- •Hazard ID
- •Limit Exposure

Risk Assessment
Literature
Worse Case

Refine Assessment
Analytical
Safety studies
Consumer insight

Refine Assessment
Registrations

Surveillance
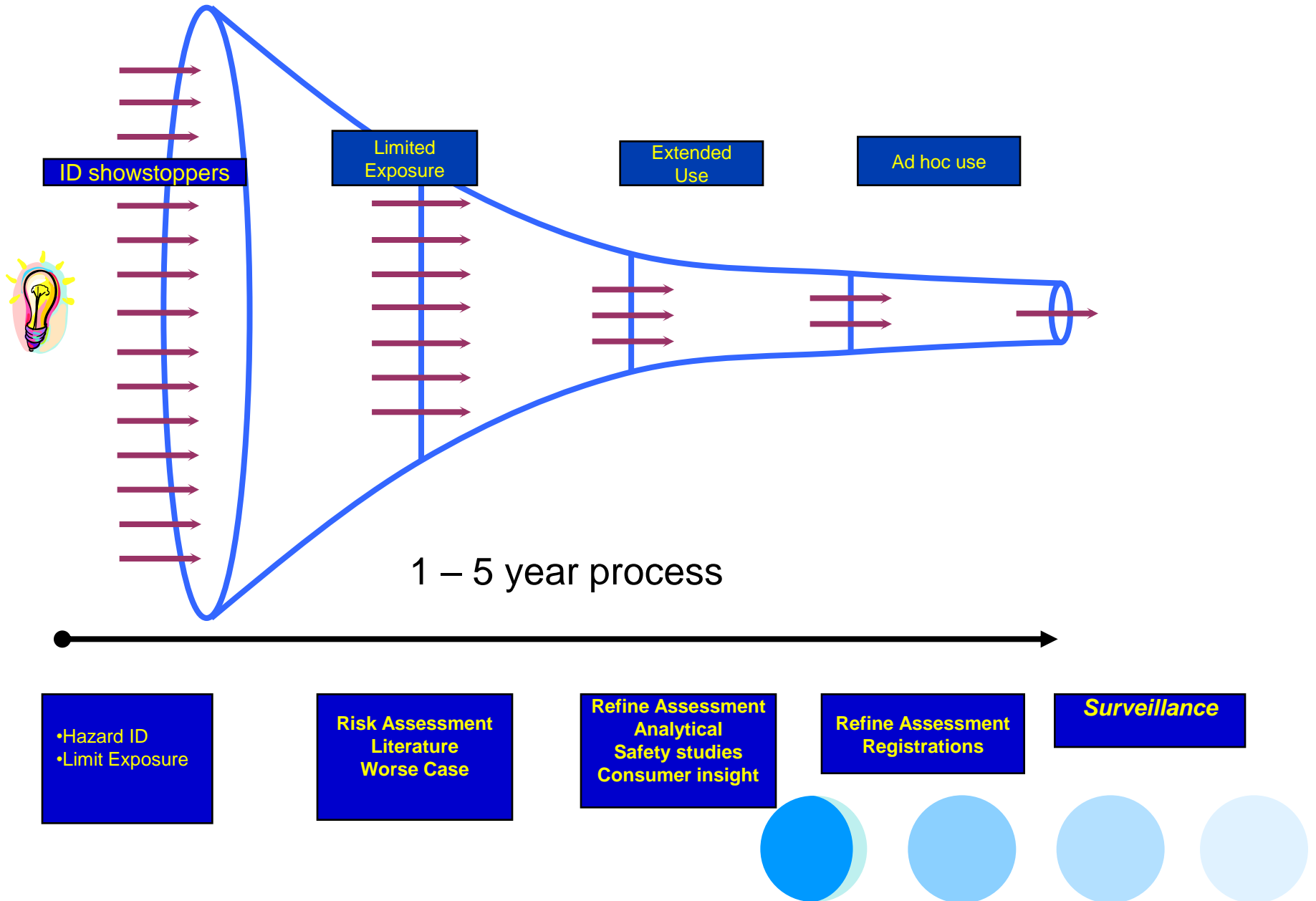
Example – Compact Liquid Laundry

Safety Assessment

MOS 165 - 2,500

20 Billion wash loads/year

176 Publications
56 Supplier studies
33 Internal studies

Formula Example: Premium Compact Liquid Laundry Detergent

Ingredient	%	Ingredient	%
Alcoholethoxy sulfate	20.1%	Diquaternium ethoxy sulfate	1.6%
Linear alkylbenzene sulfonate	2.7%	Polyethylene glycol-polyvinyl acetate	0.4%
Alkyl sulfate	6.5%	Polyethyleneimine propoxyethoxylate	1.0%
Laureth-9	0.8%	Diethylenetriamine pentaacetic acid	0.4%
Citric acid	3.8%	Disodium diaminostilbene disulfonate	0.01%
C12-18 fatty acids	2.0%	Ethanol	2.6%
Protease (stock)	1.5%	Propylene Glycol	4.6%
Amylase (stock)	0.3%	Diethylene Glycol	3.0%
Mannanase (stock)	0.1%	Polyethylene glycol	0.2%
Pectate Lyase (stock)	0.1%	Monoethanolamine	2.7%
Xyloglucanase (stock)	0.3%	Dye	0.01%
Borax	3.0%	Perfume	0.5%
Calcium formate	0.1%	NaOH	to pH 8.3
Sodium formate	0.1%	Water	to 100%

Alternatives decision

Profile	Surfactant	Protease
Performance	Good	Breakthrough
Biodegradation	Rapid	Rapid
Aquatic toxicity	Moderate	Mild
Bioaccumulation	Low	None
Renewable	Limited	Yes
Skin irritant	Mild	Mild
Eye Irritant	Moderate	Mild
Acute Tox	Mild	Mild
Pulmonary irritation	Moderate	Mild
Allergenicity	Negative	Type I
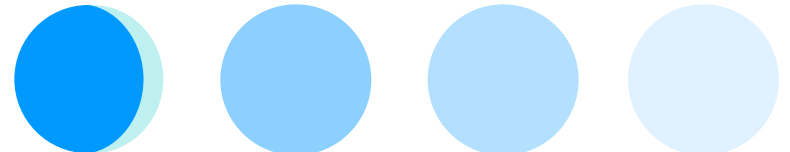
Decision to use proteases in laundry

ESTIMATED USE
PRODUCT LIMIT
STUDIES' SAFETY LIMIT

SAFE RANGE

ACTUAL USE

SAFETY MARGIN: TYPICALLY > 100x
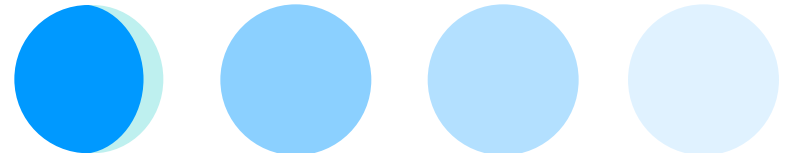
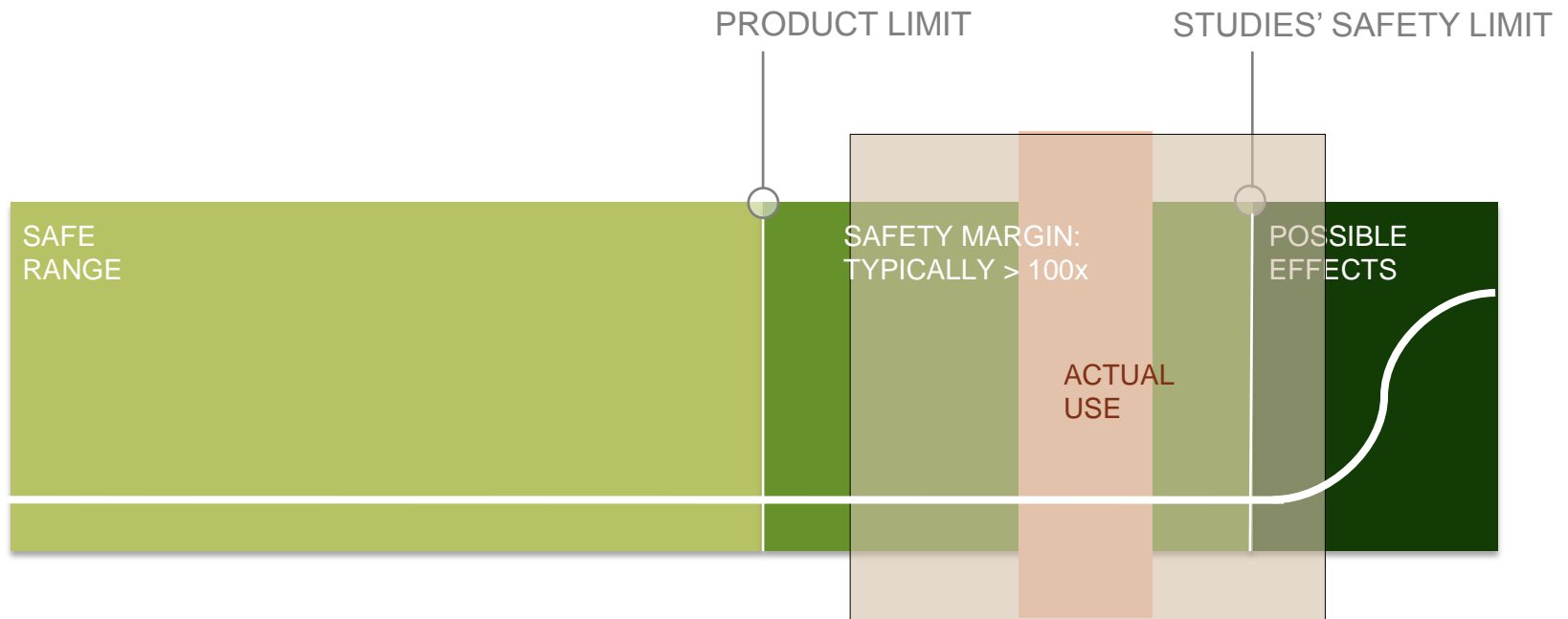POSSIBLE EFFECTS
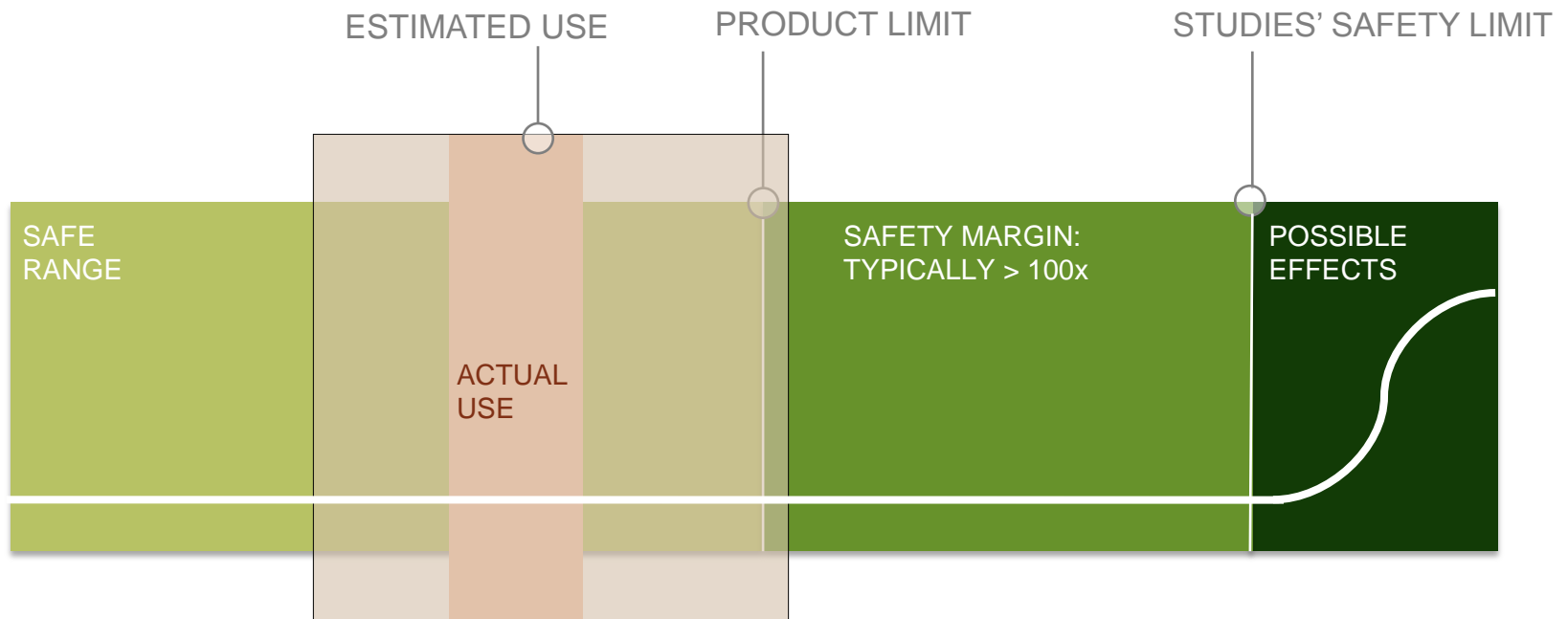
Concluded this use is safe

Decision on using proteases in body scrub

- Enhanced defoliation
- Milder to the skin
- More uniform effects

Decision to use proteases in body scrub

PRODUCT LIMIT

STUDIES' SAFETY LIMIT

SAFE
RANGE

SAFETY MARGIN:
TYPICALLY > 100x

POSSIBLE
EFFECTS

ACTUAL
USE

Concluded this use is not safe

Importance of "Informed Substitution"

Decision Elements

- Technological feasibility

- Does it improve health and environmental safety

- How does it impact cost, performance, economic/social considerations

- Is it sustainable

- What are the trade — offs

- Consumer preference

Touching lives, improving life. **P&G**™

Thanks for listening. Questions?

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