Mashhad University of Medical Sciences

Hazard Identification and Evaluating Carcinogenic and Non-carcinogenic Risk Ratio in Exposure to Chemical Pollutants

Department of Health, Safety, and Environment Management, Mashhad University of Medical science

Dr Belin Tavakoli Sani

References

- U.S. EPA risk assessment documents including:
  - Risk Assessment Guidance for Superfund
  - Presenter's Manual for "Superfund Risk Assessment and How You Can Help"

Goals and Objectives

Mashhad University of Medical Sciences

- Review risk assessment process
- Discuss components of risk assessment
- Review types of data used in risk assessment

Types Of Risk Assessment

Mashhad University of Medical Sciences

- Human Health Risk Assessment

The characterization of the probability of potentially adverse health effects from human exposures to environmental hazards.

- Ecological Risk Assessment

A process that estimates the likelihood of undesirable ecological effects occurring as a result of human activities.

What is Risk Assessment?

Mashhad University of Medical Sciences

“ Risk Assessment is the process of determining, either **quantitatively or qualitatively**, the probability and magnitude of an undesired event.”

(Oklahoma Corporation Commission Risk Assessment Guidance Document, 1994)

EPA Definition of Health Risk Assessment

Mashhad University of Medical Sciences

- **Risk assessment:**

Qualitative and quantitative evaluation of the risk posed to human health and/or the environment by the actual or potential presence and/or use of specific pollutants

From EPA's "Terms of Environment" Glossary

Risk assessment:

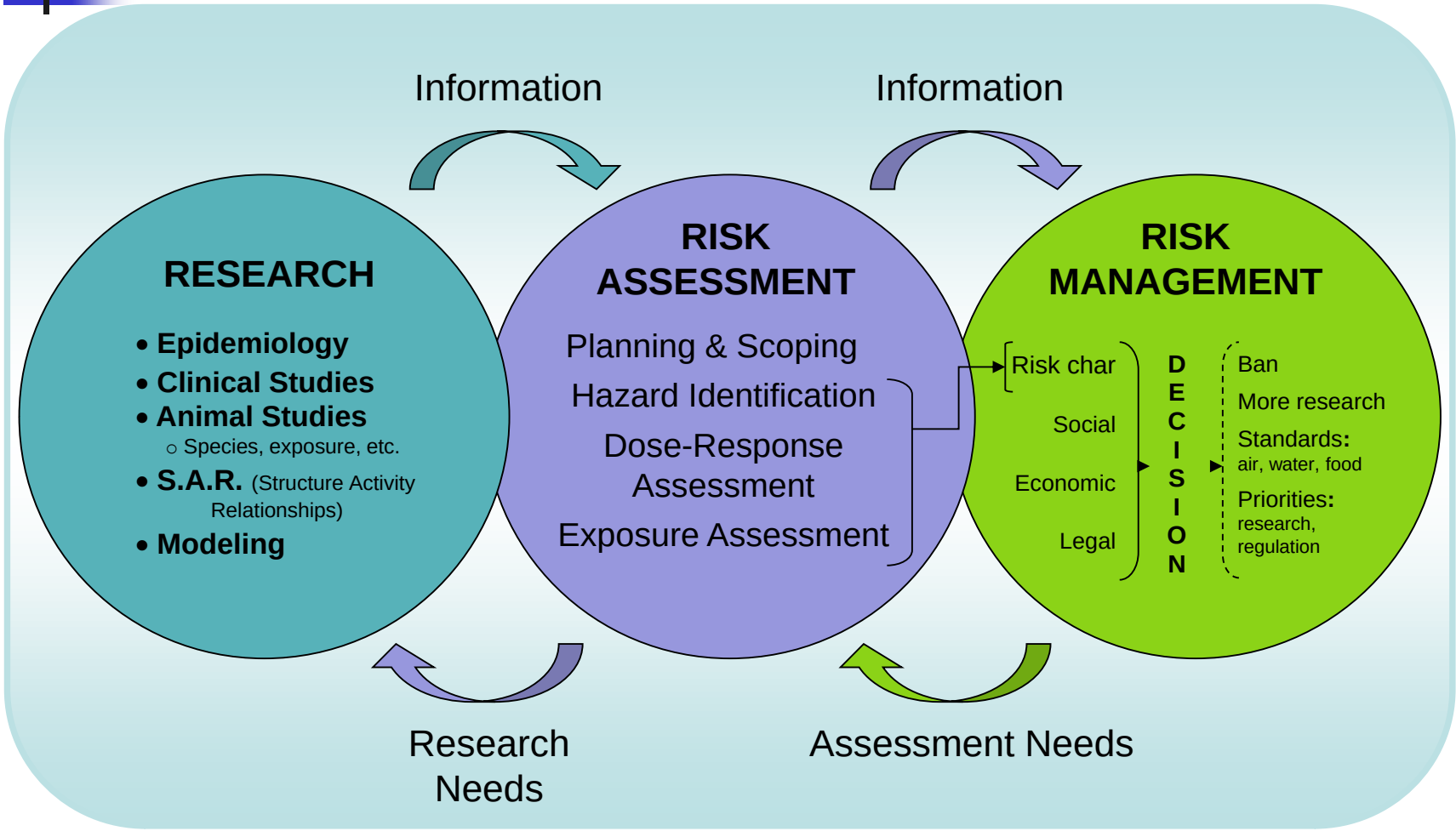
- An important concept to understand is that "risk" typically refers to the probability, or likelihood, that something might happen in the future.

- From the Terms of the Environment glossary, risk is "a measure of the probability that damage to life, health, property, and/or the environment will occur as a result of a given hazard."

•Hazard – is the potential to cause harm, by injury or ill health.

•Risk – is the likelihood of a hazard doing harm.

Overview of Human Health Risk Assessment



Planning and Scoping

Identify the Problem

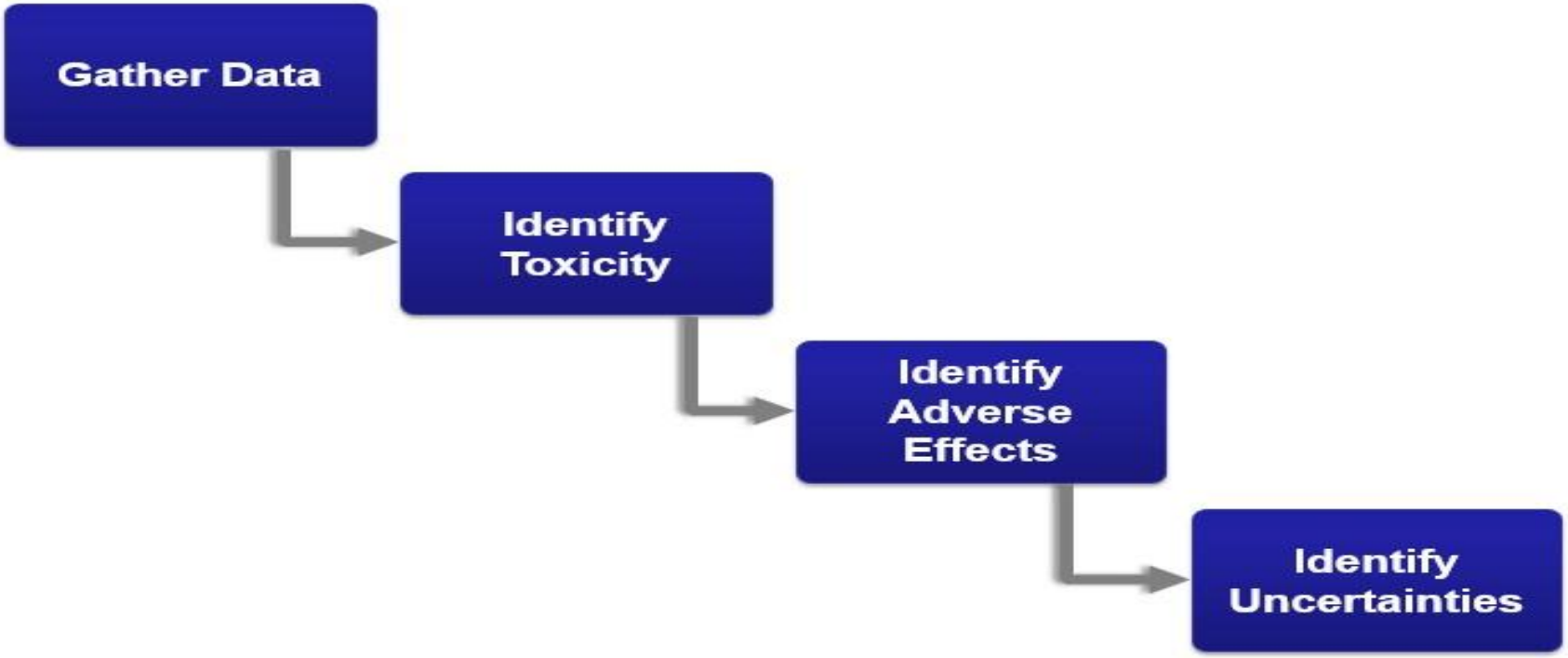
- What causal agents should be considered? *(chemical, bacteria…)*
- Who is affected? *(age, race, sensitive/susceptible, gender…)*
- Where does the problem/ gaps exist? *(sample size, sampling, missing data..)*
- What are risk management needs? *(uncertainties, legal, methods, technology, Financial, impact, employee, …)*
- What are stakeholder needs?

Four Steps to A Risk Assessment Document

1. Hazard Identification
2. Dose-Response Assessment
3. Exposure Assessment
4. Risk Characterization

1. Hazard Identification

Hazard identification involves gathering data and evaluating toxicity data on the types of health adverse effect (injury or disease) that may be produced by a chemical and the conditions of exposure under which injury or disease is produced.



Hazard Identification – Data

Gather Data

- What are the chemicals? *(Chemical and physical properties)*
- Which human populations might be affected?
- What toxicity data are available? *(Cancer, Non-Cancer….)*
  - ✓ Human Data (H.R.A.)
    - Epidemiology studies
    - Controlled human exposure studies
  - ✓ Animal Bioassay Data (E.R.A.)
  - ✓ Other Data
    - In Vitro Data
    - Structure-activity relationships
    - Metabolic data
    - Genomics

Hazard Identification – toxic

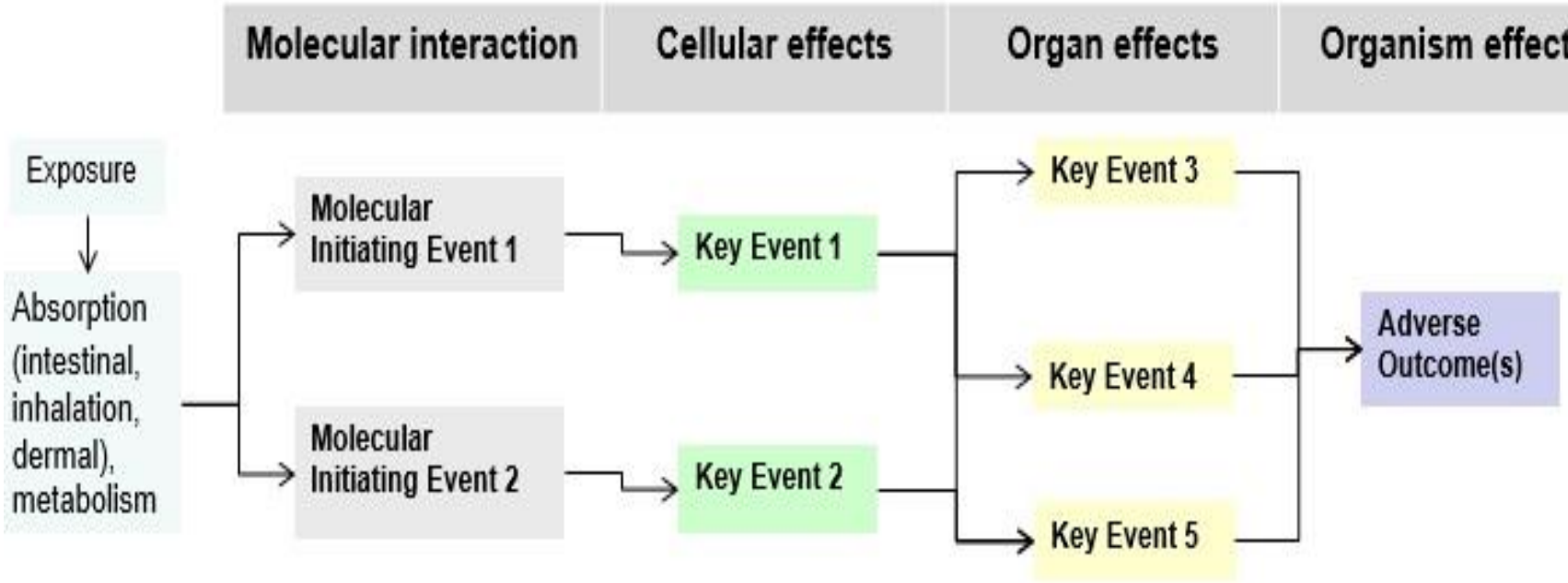
How toxic is the chemical?

- **Effects** – What effects are observed from the data collected?
- **Toxicokinetics** – What does the body do to the chemical? **(ADME)**
- **Toxicodynamics** – What does the chemical do to the body?
- **Mode of action** – How does the chemical act to produce an effect?
- **Causality Framework** – A way to organize and evaluate toxicity information to assess causality given those data.
- **Weight of evidence** – How likely is this chemical to cause non-cancer effects or cancer and under what conditions?

نام فلز	اثرات
نقره	سمیت برای پوست و بافت سایر اندامها، مشکلات تنفسی،التهاب ریه و گلو، درد معده
آرسنیک	تاثیر بر فرآیندهای ضروری سلولی مانند فسفریلاسیون اکسایشی و سنتز ATP
باریوم	آریتمی قلبی، نارسایی تنفسی، اختلال گوارشی، جمع شدن مایعچه ای و فشار خون بالا
کادمیوم	سرطانزا،جهش زا،اختلالات غدد درون ریز، آسیب به ریه، شکننده شدن استخوانها،بهم زدن تعادل کلسیم در سیستمهای بیولوژیکی
کروم کل	ریزش مو، درماتیتهای آلرژیکی
مس	آسیب کلیوی- مغزی، در غلظتهای بالا منجر به سیروز کبدی و کم خونی مزمن، التهاب معده و روده
جیوه معدنی	بیماری های خود ایمنی، افسردگی، خواب آلودگی، خستگی، ریزش مو، بی خوابی، از دست دادن حافظه، بی قراری، اختلال در دید، لرزش، بد خلق و خونی، صدمه به مغز، نارسایی کلیوی و ریوی
نیکل	بیماری های آلرژیک پوستی مانند خارش، سرطانهای ریه، بینی، سینوسها و گلو در صورت استنشاق مداوم، ایمونوتوکسیک، نوروتوکسیک، ژنوتوکسیک، تاثیر بر باروری، ریزش مو
سرب	مواجهه ی بالای کودکان میتواند سبب اختلال در رشد، کاهش هوش، از دست دادن حافظه کوتاه مدت، ناتوانی در یادگیری و هماهنگی، ریسک بیماری قلبی عروقی شود.
سلنیوم	مواجهه حدود حدود ۳۰۰ میکروگرم در روز از طریق رژیم غذایی بر عملکرد غدد درون ریز، فعالیت سلول های ایمنی و دفاعی طبیعی تاثیر میگذارد. سمیت کبدی و اختلالات دستگاه گوارش

Frameworks used for evidence integration

- Adverse Outcome Pathways (AOPs) [OECD].
- Mode of Action Analysis [IPCS WHO].



Adapted from OECD 2013; Vinken et al 2013; Meek et al., 2013

Cancer Assessment Categories

TABLE 21.3. EPA Cancer Assessment Categories

Group A — human carcinogen	Sufficient human evidence for causal association between exposure and cancer
Group B1 — probably human carcinogen	Limited evidence in humans
Group B2 — probably human carcinogen	Inadequate evidence in humans, sufficient evidence in animals
Group C — possible human carcinogen	Limited evidence in animals
Group D — not classifiable as to human carcinogenicity	Inadequate evidence in animals
Group E — no evidence of carcinogenicity in humans	At least two adequate animal tests or both epidemiology and animal studies which are negative

Hazard Identification – Adverse Effect

What are the adverse effects?

Adverse effect: A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge *(U.S. EPA IRIS Glossary).*

- What are the affected organs or tissue systems?
- What is the severity of effects?
- *Who is more sensitive or susceptible?*
- *What factors affect susceptibility?*

Toxicity sources

- For more information:
  ToxCast:
  http://epa.gov/ncct/toxcast/
  ACToR:
  http://actor.epa.gov/actor
  ToxCast Data:
  http://epa.gov/ncct/toxcast/data.html
  CSS Dashboards:
  http://actor.epa.gov/actor/faces/

  CSSDashboardLaunch.jsp
- ECotox
  https://cfpub.epa.gov/ecotox/

Hazard Identification: Uncertainties

Uncertainty occurs because of a lack of knowledge. It is not the same as variability.

- Uncertainty can often be reduced by collecting more and better data.
- Variability is an inherent property of the population being evaluated. *(Adapted from U.S. EPA IRIS Glossary)*

Examples:

- Using animal data
- Variability within the human population
- Extrapolating the study duration *(sub-chronic/chronic..)*
- Strength of database/ Quality of data *(method, measurement, bias, sample size….)*

Exposure Contexts

- **Emergency Response**

  Example: EPA's Provisional Advisory Levels

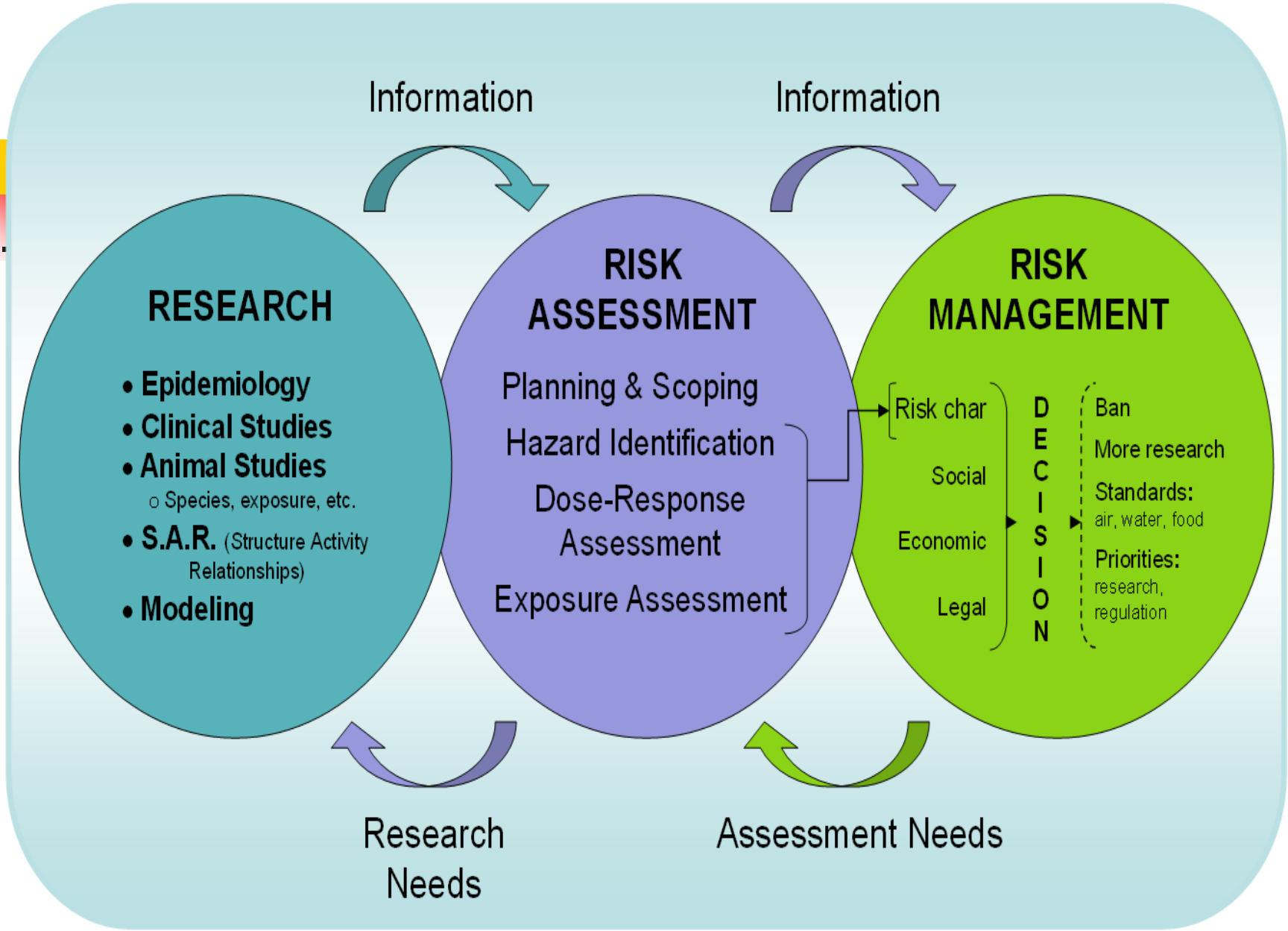
- **Occupational**

  Example: CDC-NIOSH Recommended Exposure Limits

- **Ambient or General Public**

  Example: CDC-ATSDR Minimal Risk Levels & EPA-IRIS Reference Dose/Concentrations

  https://www.epa.gov/iris
  https://cfpub.epa.gov/ncea/iris/search/index.cfm


Information
Information
RESEARCH
• Epidemiology
• Clinical Studies
• Animal Studies
o Species, exposure, etc.
• S.A.R. (Structure Activity Relationships)
• Modeling
RISK ASSESSMENT
Planning & Scoping
Hazard Identification
Dose-Response Assessment
Exposure Assessment
RISK MANAGEMENT
Risk char
Social
Economic
Legal
DECISION
Ban
More research
Standards: air, water, food
Priorities: research, regulation
Research Needs
Assessment Needs

2. Dose-Response Assessment

- The dose-response assessment involves describing the quantitative relationship between the amount of exposure to a chemical and the extent of toxic injury or disease.
  - The description is different for non-carcinogenic versus carcinogenic effects.

Terminology based *U.S. EPA IRIS Glossary*

- **Reference Value:** An estimate of an exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime.

- **Dose (mg/kg-day):** Milligram substance per kilogram body weight per day.

- **Concentration (mg/L, mg/kg, or mg/m^3):**

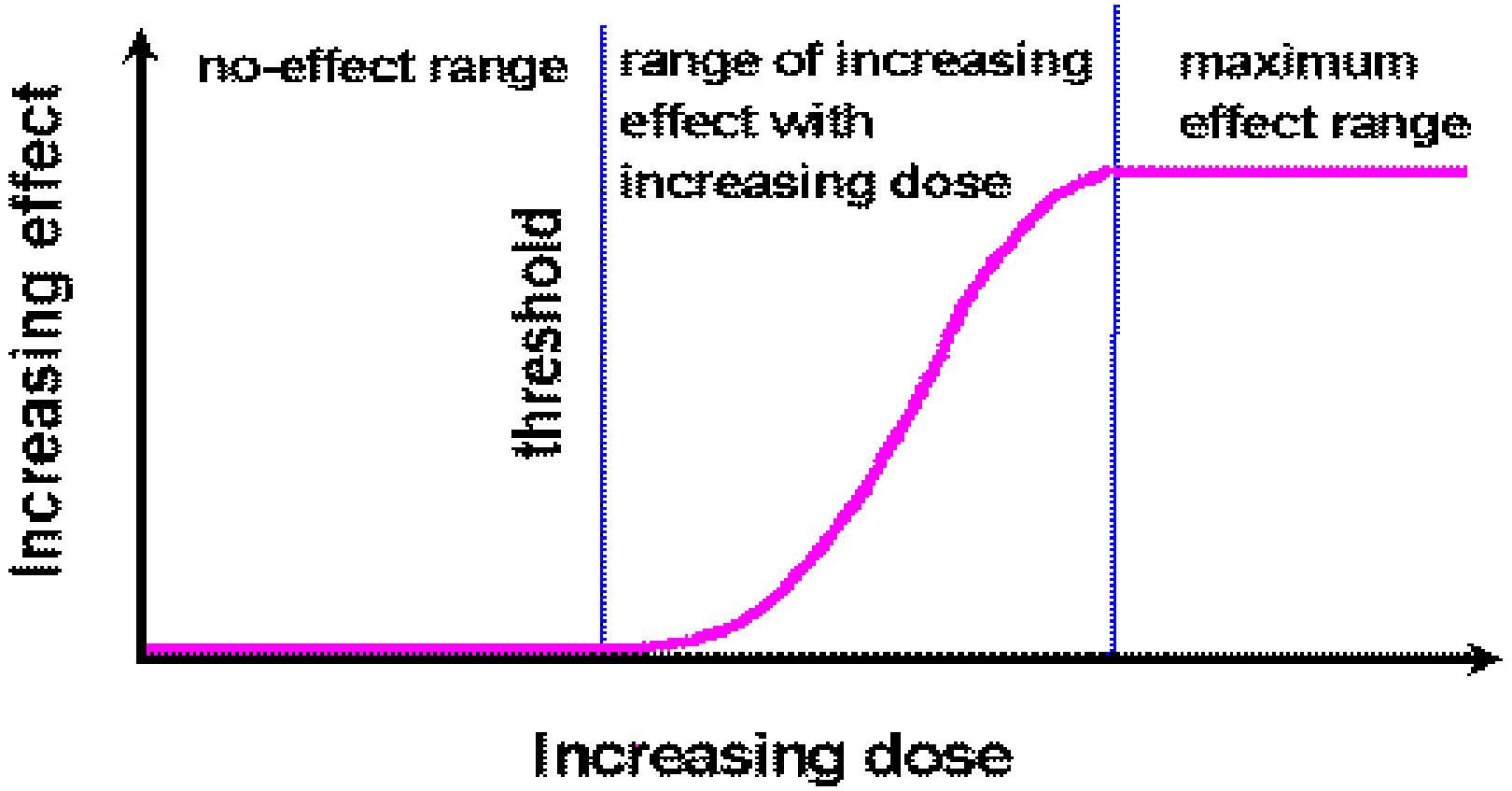
Milligram substance per liter water, kilogram soil or food, or cubic meter air.

Reference values

Reference values are chemical doses or exposure concentrations **at or below** which adverse health effects in a population are not expected to occur. When these reference values are not purely health-based, in that other factors are also considered in the development of the value, effects might occur, but the frequency and severity of these effects is deemed "tolerable." This concept is often referred to as "acceptable risk."

- A chemical concentration in a specified environmental medium is commonly expressed as quantity of a substance per quantity of medium.
- Though these are two of the most common metrics for expressing reference values, some reference values are expressed as proportion of the population estimated to be affected at a specified concentration.

Dose-Response



Dose-Response Terminology

LOAEL
Lowest-Observed-Adverse-Effect Level. Lowest dose at which significant adverse effects are observed.

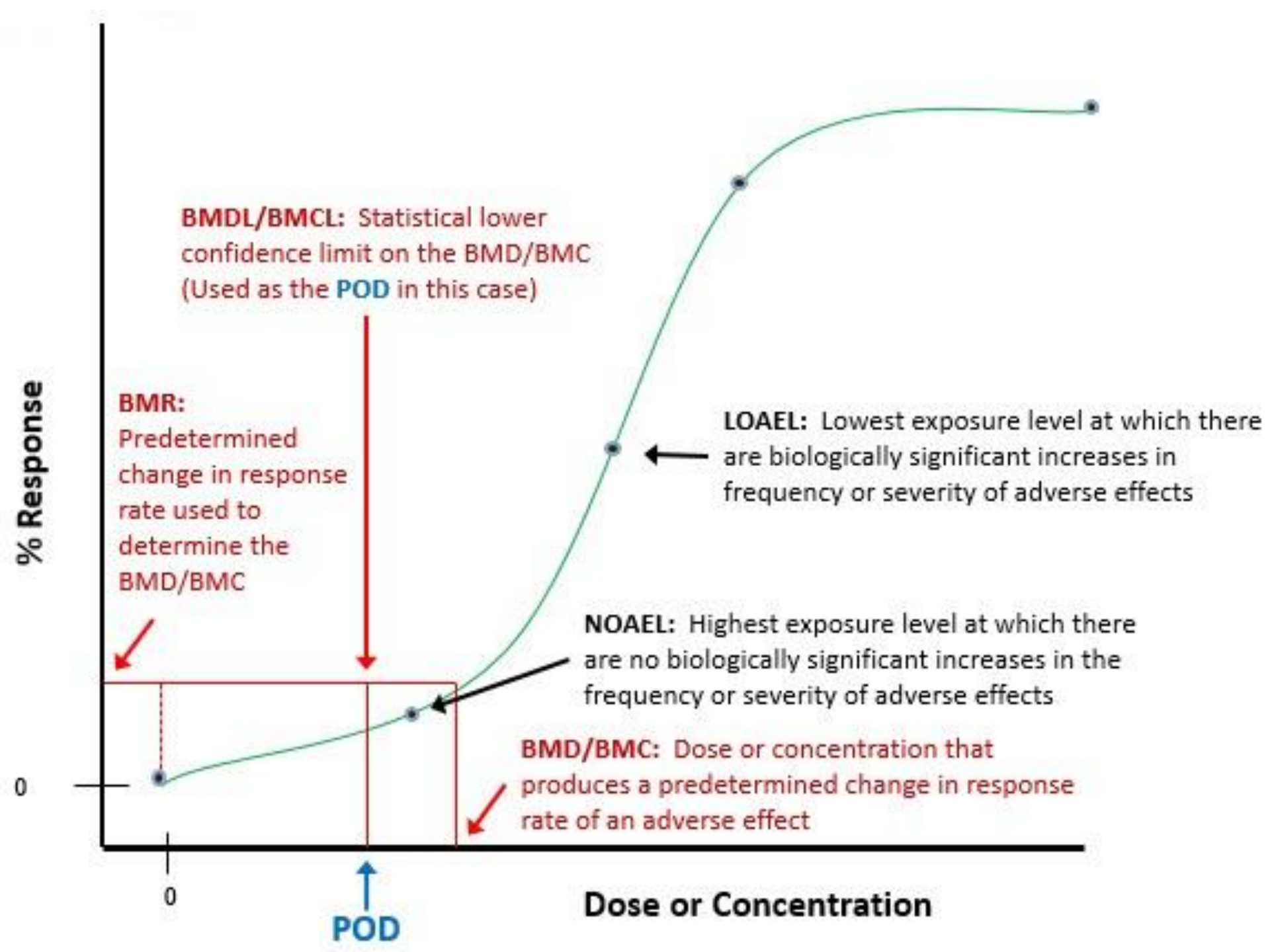
NOAEL
No-Observed-Adverse-Effect Level. Highest dose at which no significant adverse effects are observed.

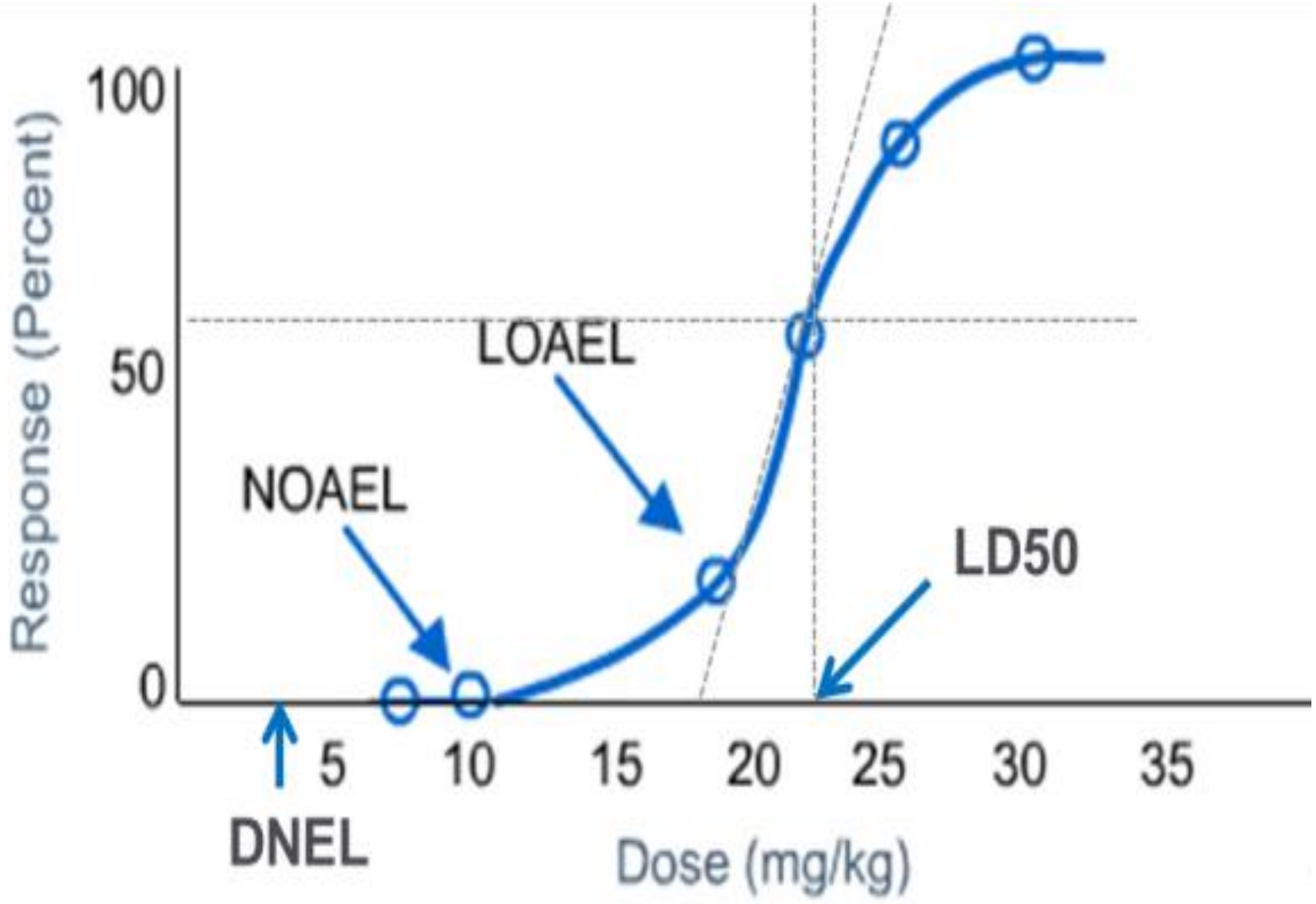
BMD
Benchmark Dose. An exposure to a low dose of a substance that is linked with a low (1-10%) risk of adverse health effects, or the dose associated with a specific biological effect.

BMDL
A lower, one-sided confidence limit on the BMD.

Critical effect
The first adverse effect or its known precursor that occurs to the most sensitive species as the dose rate of an agent increases.

Point of Departure
The dose-response point that marks the beginning of a low dose extrapolation.


BMDL/BMCL: Statistical lower confidence limit on the BMD/BMC (Used as the POD in this case)
BMR: Predetermined change in response rate used to determine the BMD/BMC
LOAEL: Lowest exposure level at which there are biologically significant increases in frequency or severity of adverse effects
NOAEL: Highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effects
BMD/BMC: Dose or concentration that produces a predetermined change in response rate of an adverse effect
% Response
0
0
POD
Dose or Concentration


100
50
0
Response (Percent)
LOAEL
NOAEL
LD50
5
10
15
20
25
30
35
DNEL
Dose (mg/kg)

Non-Carcinogenic Effects

- Allowable Daily Intake - The US Food and Drug Administration, the World Health Organization, and the Consumer Product Safety Commission use the **Allowable Daily Intake (ADI)** to calculate permissible chronic exposure levels.
  - The ADI is determined by applying safety factors to the highest dose in chronic human or animal studies that has been demonstrated not to cause toxicity.

Non-Carcinogenic Effects - Continued

- Reference Dose - The US Environmental Protection Agency has slightly modified the ADI. For the EPA, the acceptable safety level is known as the **Reference Dose (RfD)**
  - an estimate of a daily exposure level for human populations, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious health effects during a lifetime

Non-Carcinogenic Effects - Continued

- Minimum Risk Levels (MRLs), used by ATSDR, are similar to the EPA's Reference Dose (RfD) and Reference Concentration (RfC).
  - An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure.

Carcinogenic Effects

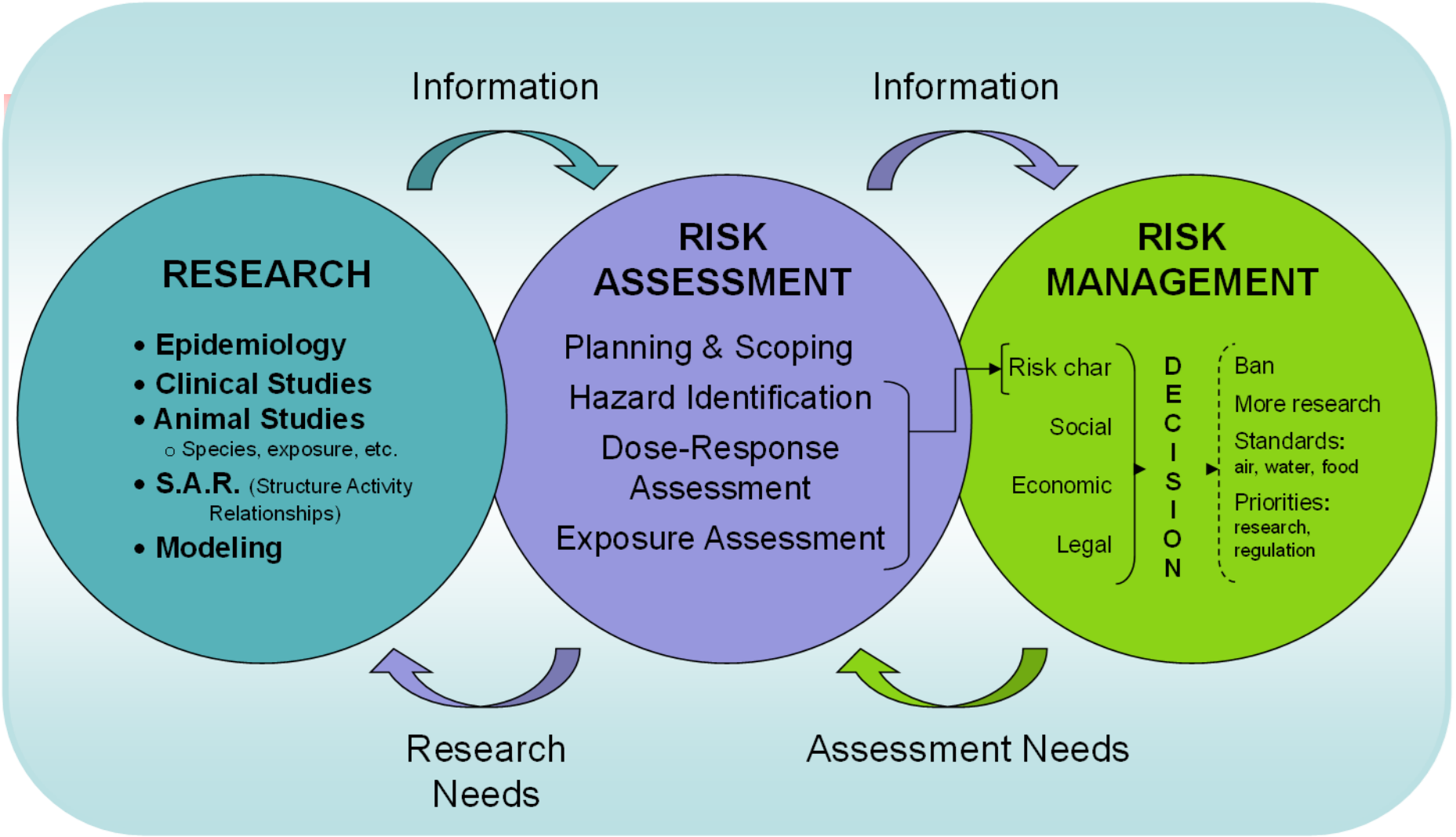
- Mathematical models are used to extrapolate from the high doses used in animal experiments to the low doses to which humans are normally exposed in a chronic setting.

Carcinogenic Effects - Continued

- The key risk assessment parameter derived from the carcinogen risk assessment process is the "slope factor". The slope factor is a toxicity value that quantitatively defines the relationship between dose and response.

Carcinogenic Effects - Continued

- Slope Factor = a plausible upper-bound estimate of the probability of a response per unit intake of chemical over a lifetime
  - Risk per unit dose
  - Units of Risk $(mg/kg\text{-}day)^{-1}$
  - Symbol for Slope Factor = q_1^*


Information
Information
RESEARCH
• Epidemiology
• Clinical Studies
• Animal Studies
o Species, exposure, etc.
• S.A.R. (Structure Activity Relationships)
• Modeling
RISK ASSESSMENT
Planning & Scoping
Hazard Identification
Dose-Response Assessment
Exposure Assessment
RISK MANAGEMENT
Risk char
Social
Economic
Legal
DECISION
Ban
More research
Standards: air, water, food
Priorities: research, regulation
Research Needs
Assessment Needs

3. Exposure Assessment

Exposure is contact made between an **agent** and **a target**

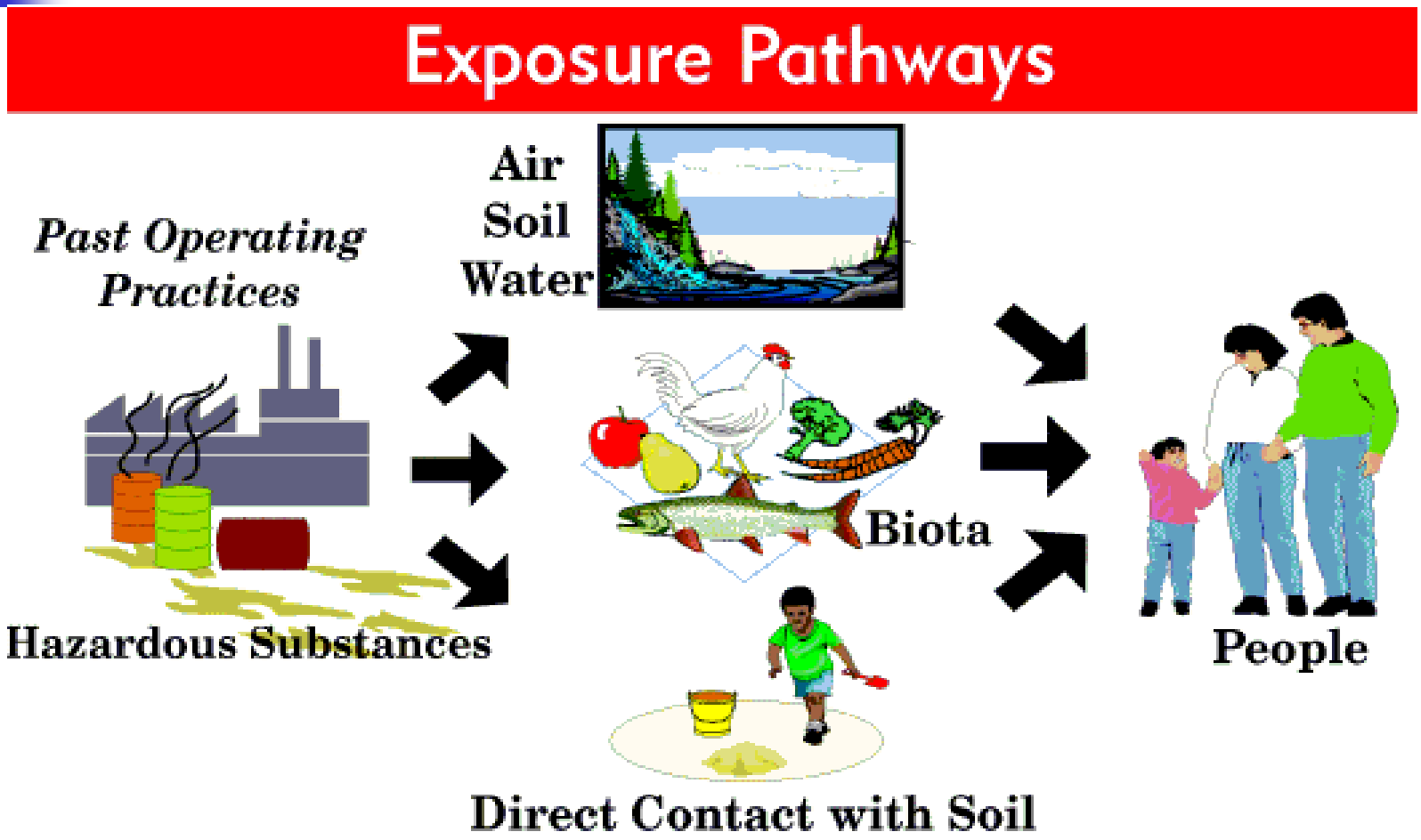
- **Exposure Assessment** The process of estimating or measuring the **magnitude, frequency, and duration** of exposure to an agent, along with the **number** and **characteristics of the population** exposed.

(U.S. EPA Exposure Factors Handbook)

Exposure Assessment

- **Who is Exposed?**
  - Adult, Child, Special Populations
- **How Are They Exposed?**
  - Ingestion, Inhalation, Skin Contact
- **What is the Concentration of Chemical to Which They are Exposed?**
  - ppm in Water or Soil, food
- **How Often Are They Exposed?**
  - Days per year, Number of years

Exposure Pathway Diagram

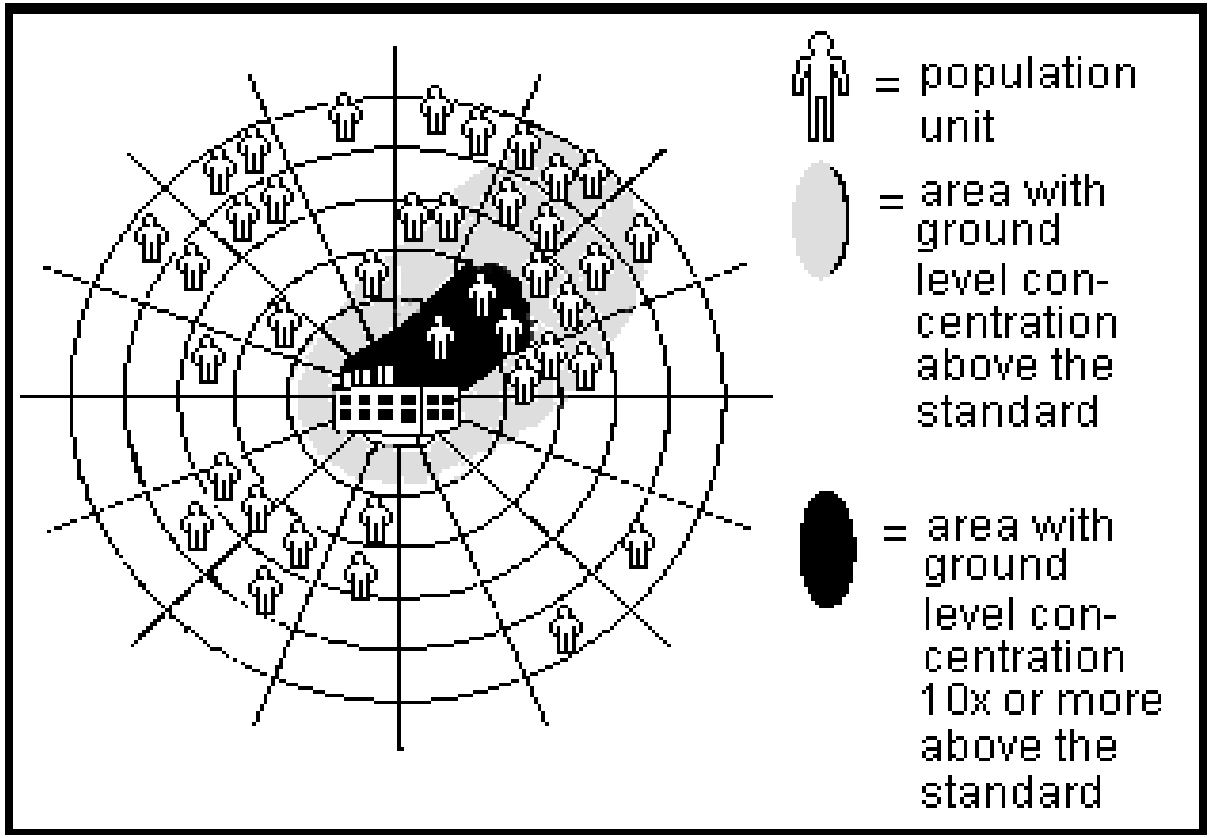


Identification of Exposure Pathways

- Contaminated groundwater – ingestion (drinking water), dermal contact (bathing), and inhalation of volatile organic compounds (showering)
- Surface water and sediments – incidental ingestion and dermal absorption of contaminants (people in bodies of water)
- Contaminated food – ingestion of contaminated fish tissue, vegetables and fruit grown in contaminated soil or covered with contaminated dust, meat, and dairy products

Range of Exposure

- "Central Tendency"
- "High End"

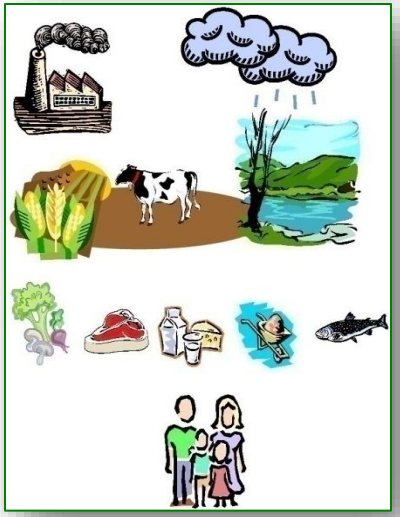


Quantify Exposure

Point of Contact Measurement

Reconstruction of Dose

Scenario Evaluation



Quantify Exposure

Point of Contact Measurement
(Field Measurements)

- Measure chemical concentrations over time
- At or near point of contact for exposure in question
- Various sampling methods

Examples of point of contact measurements: *Personal air sampler, Radiation dosimeter that an individual wears*

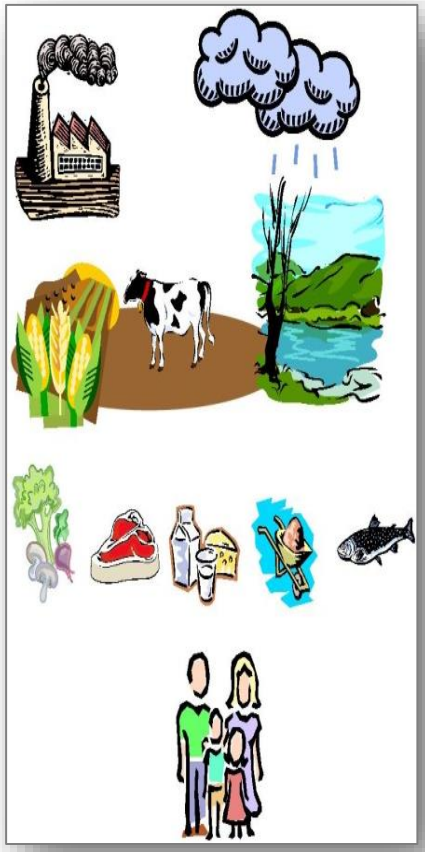
Quantify Exposure

Reconstruction of Dose
(Clinical Measurements)

E.g. *Cotinine is a metabolite of nicotine that can be used as a biomarker of exposure to tobacco products or environmental tobacco smoke.*

- Attempt to quantify internal dose based on physiological data
- Using measurements from the body, tissues
- Biomarkers of exposure, metabolites – involves extrapolation. Predictive estimate.

Quantify Exposure

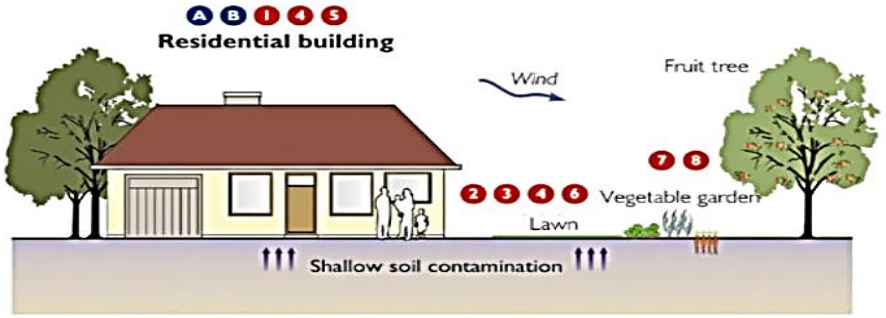


Scenario Evaluation

- Measure or estimate the amount of substance contacted at site
- Use equations and assumptions about behavior and exposure rates
- Mathematical estimation of exposure; predictive estimate

References that can be consulted for exposure factors:

- EPA's Exposure Factors Handbook.
- EPA's Superfund Risk Assessment Guidance.
- https://www.epa.gov/expobox

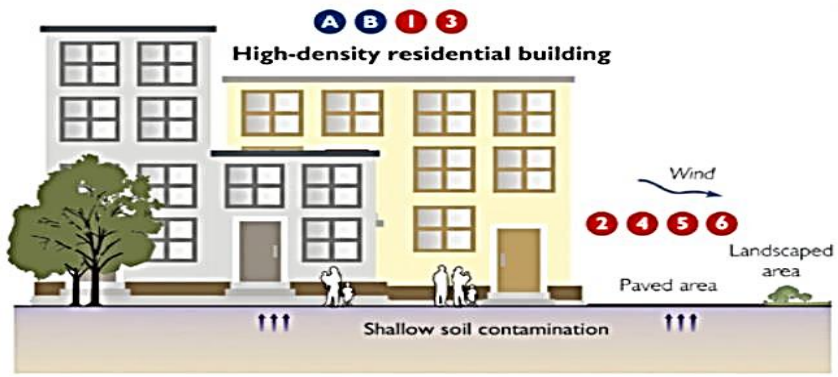


Exposure pathways

1. Indoor inhalation of vapours derived from shallow soil
2. Outdoor inhalation of vapours derived from shallow soil
3. Incidental ingestion of surface soil and dust particulates
4. Dermal contact with surface of soil and dust particulates
5. Indoor inhalation of dust particulates
6. Outdoor inhalation of dust particulates
7. Consumption of home-grown produce
8. Consumption of soil adhering to home-grown produce

Receptors

- A Adult residents
- B Child residents (0 - 6 years)



Exposure pathways

1. Indoor inhalation of vapours derived from shallow soil
2. Outdoor inhalation of vapours derived from shallow soil
3. Incidental ingestion of surface soil and dust particulates
4. Dermal contact with surface of soil and dust particulates
5. Indoor inhalation of dust particulates
6. Outdoor inhalation of dust particulates

Receptors

- A Adult residents
- B Child residents (0 - 6 years)

Exposure pathways

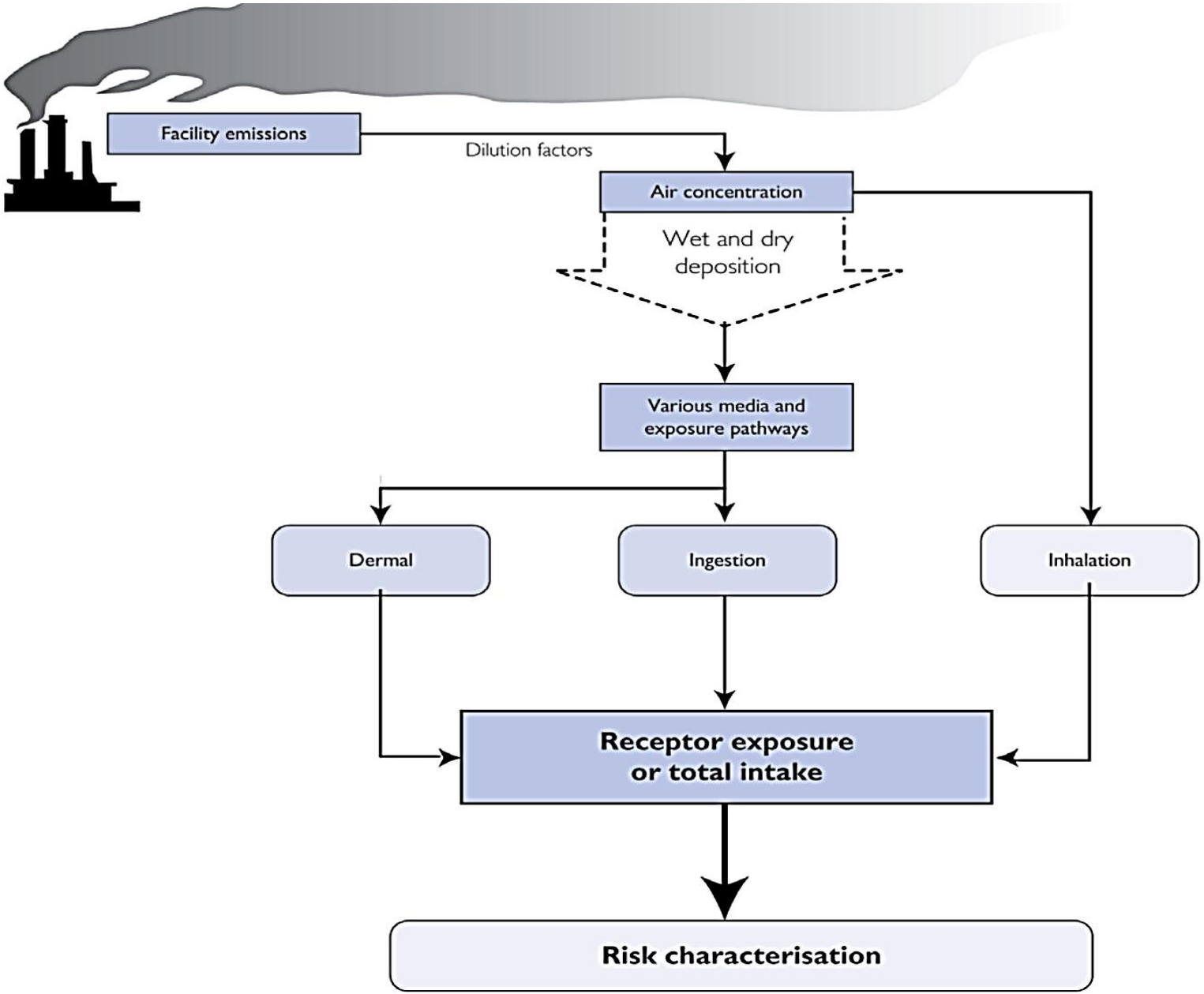
1. Indoor inhalation of vapours derived from soil contamination
2. Indoor inhalation of dust particulates
3. Outdoor inhalation of vapours derived from soil contamination
4. Outdoor inhalation of dust particulates
5. Dermal contact with dust particulates
6. Incidental ingestion of dust particulates

Receptors

- A Adult employees

1. Outdoor inhalation of vapours derived from soil contamination
2. Outdoor inhalation of dust particulates
3. Dermal contact with soil and dust particulates
4. Incidental ingestion of soil and dust particulates

- A Adult recreational users
- B Child recreational users (0–6 years)


Facility emissions
Dilution factors
Air concentration
Wet and dry deposition
Various media and exposure pathways
Dermal
Ingestion
Inhalation
Receptor exposure or total intake
Risk characterisation

Exposure Assessment Equation: Average Daily Dose (ADD) for non-cancer effects (Oral Pathway)

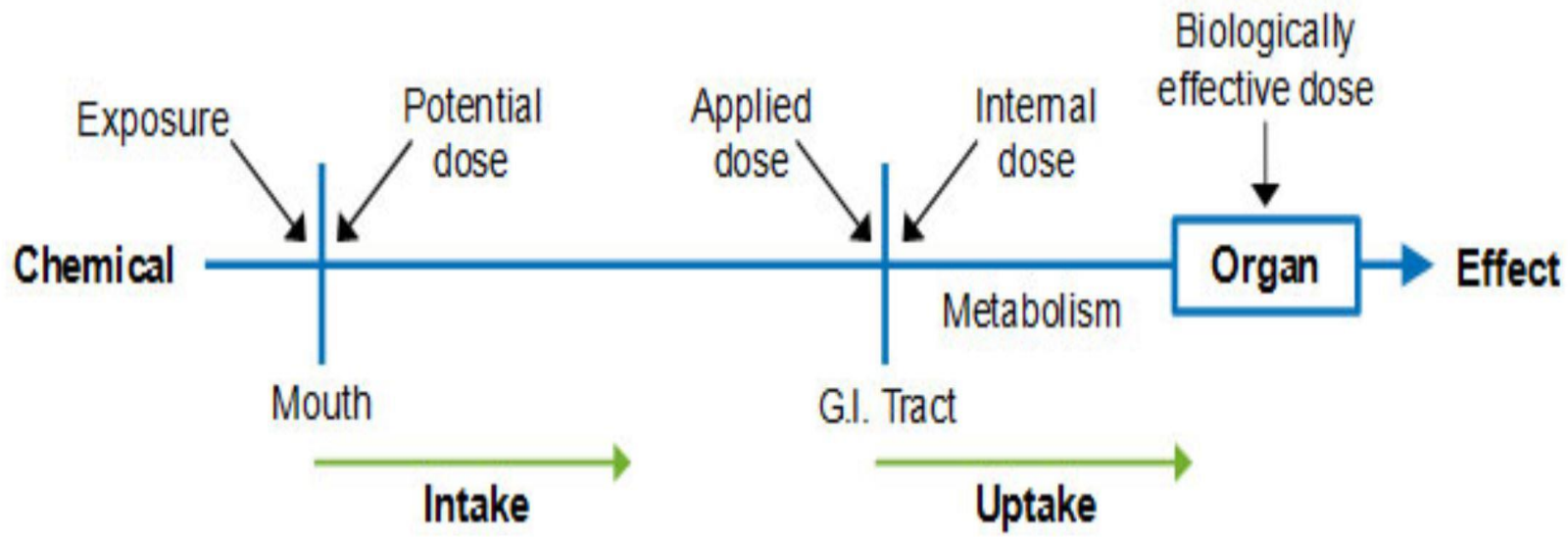


Illustration of Ingestion Route: Exposure and Dose (U.S. EPA, 1992)

https://www.epa.gov/expobox/exposure-assessment-tools-routes-ingestion

Exposure Assessment Equation: Average Daily Dose (ADD) for non-cancer effects (Oral Pathway)

$$Potential\ Dose = \frac{C \times CR \times EF \times ED}{AT \times BW}$$

C = Concentration of the contaminant within the media of interest (mg/kg; mg/L; mg/cm^2; mg/m^3)

CR = Contact rate of the media of interest (g/d; L/d; cm^2/d; m^3/d)

EF = Exposure frequency (365 day/year)

ED = Exposure duration (30 year)

BW = Body weight (70 kg)

AT = Averaging time (10950 day)

References that can be consulted for exposure factors: EPA's Child-Specific Exposure Scenarios Examples

- EPA's Exposure Factors Handbook.
- EPA's Superfund Risk Assessment Guidance.
- https://www.epa.gov/expobox

Exposure Assessment Equation: life Average Daily Dose (LADD) for Cancer effects

$$Potential\ Dose = \frac{C \times CR \times EF \times ED}{AT \times BW}$$

C = Concentration of the contaminant within the media of interest (**mg/kg; mg/L**; mg/cm^2; mg/m^3)

CR = Contact rate of the media of interest (K**g/d; L/d**; cm^2/d; m^3/d)

EF = Exposure frequency (365 day/year)

ED = Exposure duration (**70 years**)

BW = Body weight (70 kg)

AT = Averaging time (**25550 days**)

4. Risk Characterization

Risk characterization is the integration of information on hazard, exposure, and dose-response to provide an estimate of the likelihood that any of the identified adverse effects will occur in exposed people.
(IRIS Glossary Definition)

- Compares toxicity information to the exposure profiles developed for people we think might be exposed.
- Estimates likelihood that adverse effects will occur in people who are exposed.

- Includes assumptions and uncertainties associated with all steps in the risk assessment process.

Risk Characterization: Outcome

Noncancer Hazard Quotient (HQ): Ratio of estimated exposure to reference level at which no adverse health effects are expected.

Noncancer Hazard Index (HI): The sum of hazard quotients (HQs) for substances that affect the same target organ or organ system.

Cancer Risk: Incremental probability of developing cancer for an individual exposed to a given chemical over a lifetime.

Risk Characterization: Non-cancer Hazard Quotient

$$\textbf{Hazard Quotient (HQ)} = \frac{\textbf{ADD}\left(\frac{mg}{kg-day}\right)}{\textbf{RfD}\left(\frac{mg}{kg-day}\right)}$$

RfD: reference dose

ADD: average daily dose

If ADD is < RfD, then no problem- except when dealing with multiple chemicals

Risk Characterization: **Hazard Index**

- Rather than same mode-of-action (MOA), similarity is determined at the level of target organ
- For the HI approach, risks to humans are estimated under the implicit assumption that components are toxic in the same target (organ or system)

$$HI = HQ1 + HQ2 + HQ3$$

HI<1 is assumed, to denote safety over a lifetime
HI>1 is assumed risk management decision necessary

Risk Characterization: cancer Hazard Quotient

$$\text{Cancer Risk (Oral)} = \text{LADD}\left(\frac{mg}{kg-day}\right) \times \text{Oral Slope Factor}\left(\frac{mg}{kg-day}\right)^{-1}$$

- **CR ≤1 × 10^{-6}** **(Acceptable or safe food)**
- **1 × 10^{-6} ≤ CR ≤1 × 10^{-4}** ***(Borderline)**
- **CR ≥ 10^{-4}** ***(High risk)**

* risk management decision necessary

Further information:

Parameters	Values	Units
Exposure frequency (EF)	365	days/year
Exposure duration (ED)[b,c]	30 (non-carcinogenic); 70 (carcinogenic)	years
Body weight (BW)[a]	Adult: 70 Male: ? Female: ? Child: 16	kg
Average exposure time (AT)[c]	10950 (non-carcinogenic); 25550 (carcinogenic)	days
Reference dose (RfD)	0.004 for Cu, 0.3 for Zn, 0.3 for Ba, 0.14 for Mn, 0.0005 for Cd, 0.2 for B, 1.5 for Cr, 0.02 for Ni, 0.005 for Mo, 0.005 for Se, 0.0003 for Hg, 0.035 for artrazine, 0.02 for acetochlor, 0.0003 for hexachalorobenzene, 0.02 formalathion, 0.001 for chlorpyrifos	mg/kg/day
Slope factor (SF)	1.5 for As, 0.38 for Cd, 0.23 for artrazine, 1.6 for hexachalorobenzene, 0.34 for p,p-DDE, 0.24 for p,p-DDD	(kg·d)/mg

U.S. EPA, Risk Assessment Guidance for Superfund (RAGS), volume I: Human Health Evaluation Manual (HHEM) supplemental guidance. WashingtonDC: Office of emergency and remedial response; 1991 [EPA/540/R-92/003].
c. U.S. EPA. Exposure Factors Handbook: 2011 Edition. Washington, DC: Office of Research and Development; 2011 [EPA/600/R-090/052F].

https://iris.epa.gov/AtoZ/?list_type=alpha

Pollutants	Carcinogenic effects				Non-carcinogenic effects	
	U.S. EPA. IRIS	WHO.IARC	SF (kg·d/mg)	Source of the data	RfD (mg/kg-day)	Source of the data
Copper (Cu)	D (not classifiable as to human carcinogenicity)	Not listed	NA	NA	4.00E-03	Wang et al.,2014
Zinc (Zn)	NA	Not listed	NA	NA	3.00 E-01	IRIS
Cadmium (Cd)	B1 probable human carcinogen)	1(Carcinogenic to humans)	0.38	Wen et a.,2012	5.00E-04	IRIS
Chromium (Cr)	Not listed	3(Not classifiable as to its carcinogenicity to humans)	NA	NA	1.50E+00	IRIS
Nickel (Ni)	The U.S. EPA has not evaluated soluble salts of nickel.	2B(Possibly carcinogenic to humans)	NA	NA	2.00E-02	IRIS
Arsenic (As)	A (human carcinogen)	1(Carcinogenic to humans)	1.50	RAIS	3.00E-04	IRIS
Mercury (Hg)	D (not classifiable as to human carcinogenicity)	3(Not classifiable as to its carcinogenicity to humans)	NA	NA	3.00E-04	IRIS
Atrazine	NA	3(Not classifiable as to its carcinogenicity to humans)	0.23	RAIS	3.50E-02	IRIS
Acetochlor	NA	Not listed	NA	NA	2.00E-02	IRIS
Hexachloro-benzene	B2 (probable humancarcinogen)	2B(Possibly carcinogenic to humans)	1.60	IRIS	3.00E-04	IRIS
p,p'-DDE	B2 (probable humancarcinogen)	Not listed	0.34	RAIS	Not listed	IRIS
p,p'-DDD	B2 (probable humancarcinogen)	Not listed	0.24	RAIS	Not listed	IRIS

Example:

1. اگر میزان متوسط آرسنیک در آرد گندم توزیع شده در سطح شهر مشهد برابر با 0.2 mg/kg باشد و میزان متوسط مصرف روزانه افراد از محصولات غذایی ترکیب شده با آرد برابر با 0.6 kg/d نسبت خطر بهداشتی و سرطان زایی را محاسبه کنید.

1. ADD OR LADD

$$Potential\ Dose = \frac{C \times CR \times EF \times ED}{AT \times BW}$$

2.

$$\textbf{Hazard Quotient (HQ)} = \frac{\textbf{ADD}\left(\frac{mg}{kg-day}\right)}{\textbf{RfD}\left(\frac{mg}{kg-day}\right)}$$

3.

$$\textbf{Cancer Risk (Oral)} = \textbf{LADD}\left(\frac{mg}{kg-day}\right) \times \textbf{Oral Slope Factor}\left(\frac{mg}{kg-day}\right)^{-1}$$

Example:

1.اگر میزان متوسط آرسنیک در آرد گندم توزیع شده در سطح شهر مشهد برابر با 0.2 mg/kg باشد و میزان متوسط مصرف روزانه افراد از محصولات غذایی ترکیب شده با آرد برابر با 0.6 kg/d نسبت خطر بهداشتی و سرطان زایی را محاسبه کنید.

Variables	ADD (mg/kg.day)	LADD (mg/kg.day)
C	0.2 mg/kg	0.2 mg/kg
CR	0.6 kg/day	0.6 kg/day
EF	365 days	365 days
ED	30 years	70 years
BW	70 kg	70 kg
AT	10950	25550
RFD (As)		0.0003 mg/kg/d
OSF (As)		1.5 mg/kg/d

$$Potential\ Dose = \frac{C \times CR \times EF \times ED}{AT \times BW}$$

$$\text{Hazard Quotient (HQ)} = \frac{\text{ADD}\left(\frac{mg}{kg-day}\right)}{\text{RfD}\left(\frac{mg}{kg-day}\right)}$$

$$\text{Cancer Risk (Oral)} = \text{LADD}\left(\frac{mg}{kg-day}\right) \times \text{Oral Slope Factor}\left(\frac{mg}{kg-day}\right)^{-1}$$

1. ADD = 0.2*0.6*365*30/10950* 70= 0.00171

1. LADD = 0.2*0.6*365*70/25550* 70= 0.00171

2. HQ = ADD/RFD= 0.00171/0.0003= 5.71

3. CR = ADD * RFD= 0.00171 * 1.5= $0.00255 = 2 \times 10^{-3}$

Variables	ADD (mg/kg.day)	LADD (mg/kg.day)
C	0.2 mg/kg	0.2 mg/kg
CR	0.6 kg/day	0.6kg/day
EF	365 days	365 days
ED	30 years	70 years
BW	70 kg	70 kg
AT	10950	25550
RFD (As)		0.0003 mg/kg/d
OSF (As)		1.5 mg/kg/d

HQ = 5.71 > RFD> 1 (High)

$CR = 2 \times 10^{-3} > 1 \times 10^{-4}$ (High)

Risk management decision necessary

Dermal Pathway (Water Contact)

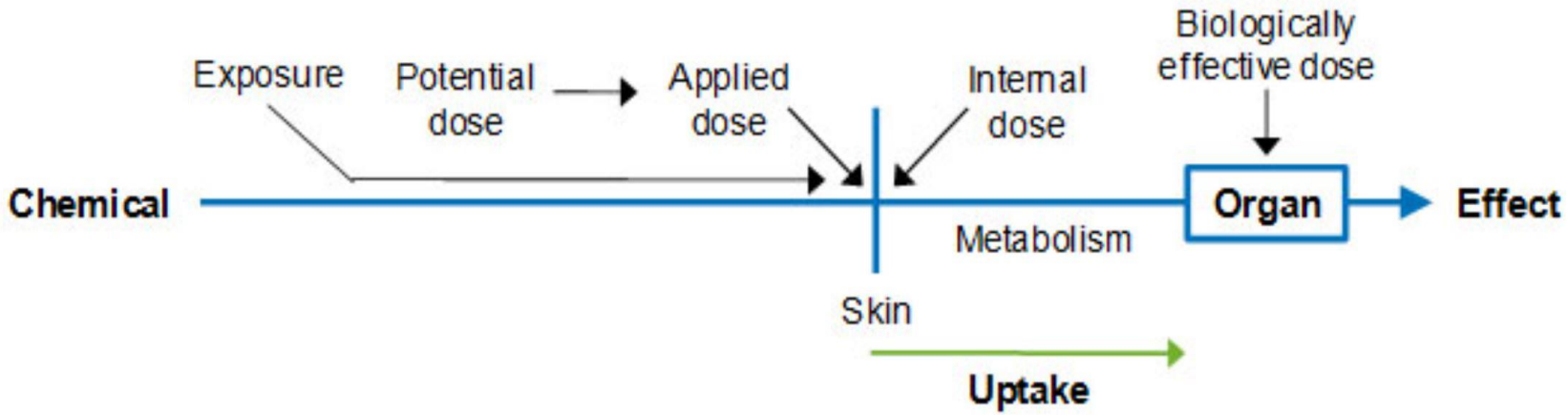


Illustration of Dermal Route: Exposure and Dose (U.S. EPA, 1992b)

https://www.epa.gov/expobox/exposure-assessment-tools-routes-dermal

Dermal Pathway (Water Contact)

Dermal Absorbed Dose – Water Contact

$$DAD = \frac{DA_{event} \times EV \times ED \times EF \times SA}{BW \times AT}$$

where:

Parameter		Definition (units)	Default Value
DAD	=	Dermally Absorbed Dose (mg/kg-day)	–
DA_{event}	=	Absorbed dose per event (mg/cm^2-event)	Chemical-specific, see Eq. 3.2, 3.3 and 3.4
SA	=	Skin surface area availablefor contact (cm^2)	See Exhibit 3-2
EV	=	Event frequency (events/day)	See Exhibit 3-2
EF	=	Exposure frequency (days/year)	See Exhibit 3-2
ED	=	Exposure duration (years)	See Exhibit 3-2
BW	=	Body weight (kg)	70 kg (adult) 15 kg (child)
AT	=	Averaging time (days)	noncarcinogenic effects AT = ED x 365 d/yr carcinogenic effects AT = 70 yr x 365 d/yr

Dermal Absorbed Dose Per Event

DA_{event} (mg/cm^2-event) is calculated for inorganics or highly ionized organic chemicals as follows:

$$DA_{event} = K_p \times C_w \times t_{event}$$

where:

Parameter		Definition (units)	Default Value
DA_{event}	=	Absorbed dose per event (mg/cm^2-event)	–
K_p	=	Dermal permeability coefficient of compound in water (cm/hr)	Chemical-specific, see Exhibit A-6 and Appendix B
C_w	=	Chemical concentration in water (mg/cm^3)	Site-specific, non-ionized fraction, see Appendix A for more discussion
t_{event}	=	Event duration (hr/event)	See Exhibit 3-2

Dermal Permeability Coefficient of Compound in Water (Kp)

EXHIBIT 3-1

PERMEABILITY COEFFICIENTS FOR INORGANICS

Compound	Permeability Coefficient K_p (cm/hr)
Cadmium	1×10^{-3}
Chromium (+6)	2×10^{-3}
Chromium (+3)	1×10^{-3}
Cobalt	4×10^{-4}
Lead	1×10^{-4}
Mercury (+2)	1×10^{-3}
Methyl mercury	1×10^{-3}
Mercury vapor	0.24
Nickel	2×10^{-4}
Potassium	2×10^{-3}
Silver	6×10^{-4}
Zinc	6×10^{-4}
All other inorganics	1×10^{-3}

EXHIBIT 3-2

RECOMMENDED DERMAL EXPOSURE VALUES FOR CENTRAL TENDENCY AND RME RESIDENTIAL SCENARIOS – WATER CONTACT

Exposure Parameters	Central Tendency Scenario				RME Scenario			
	Showering/ Bathing		Swimming		Showering/ Bathing		Swimming	
Concentration- C_w (mg/cm^3)	Site-specific		Site-specific		Site-specific		Site-specific	
Event frequency- EV (events/day)	1		Site-specific		1		Site-specific	
Exposure frequency- EF (days/yr)	350		Site-specific		350		Site-specific	
Event duration- t_{event} (hr/event)	**Adult[1]**	**Child[2]**	**Adult**	**Child**	**Adult[1]**	**Child[2]**	**Adult**	**Child**
	0.25	0.33	Site-specific		0.58	1.0	Site-specific	
Exposure duration- ED (yr)	9	6	9	6	30	6	30	6
Skin surface area- SA (cm^2)	18,000	6,600	18,000	6,600	18,000	6,600	18,000	6,600
Dermal permeability coefficient-K_p (cm/hr)	Chemical-specific values Exhibits B-3 and B-4							

[1] Adult showering scenario used as the basis for the chemical screening for the dermal pathway, as shown in Appendix B, Exhibits B-3 and B-4. Event duration for adult exposure is based on showering data from the EFH (U.S. EPA, 1997a).

[2] Event duration for child exposure is based on bathing data from the EFH (U.S. EPA, 1997a).

EXHIBIT C-1

BODY PART-SPECIFIC SURFACE AREA CALCULATIONS (CHILDREN)

CHILDREN	Fraction of Total SA (unitless)[1]								Total Body SA (m^2 50th %tile)[2]			
Age (y)	Head	Face[3]	Arms	Forearms[4]	Hands	Legs	Lower legs[4]	Feet	Age (y)	Male Child	Female Child	
<1[5]	0.182	0.0607	0.137	0.0617	0.053	0.206	0.082	0.0654	<1[5]	0.603	0.579	
1<2	0.165	0.0550	0.13	0.0585	0.0568	0.231	0.092	0.0627	1<2[5]	0.603	0.579	
2<3	0.142	0.0473	0.118	0.0531	0.053	0.232	0.093	0.0707	2<3	0.603	0.579	
3<4	0.136	0.0453	0.144	0.0648	0.0607	0.268	0.107	0.0721	3<4	0.664	0.649	
4<5	0.138	0.0460	0.14	0.0630	0.057	0.278	0.111	0.0729	4<5	0.731	0.706	
5<6[6]	0.131	0.0437	0.131	0.0590	0.0471	0.271	0.108	0.069	5<6[6]	0.793	0.779	
6<7	0.131	0.0437	0.131	0.0590	0.0471	0.271	0.108	0.069	6<7	0.866	0.843	
7<8[6]	0.12	0.0400	0.123	0.0554	0.053	0.287	0.115	0.0758	7<8[6]	0.936	0.917	
8<9[6]	0.12	0.0400	0.123	0.0554	0.053	0.287	0.115	0.0758	8<9[6]	1	1	
9<10	0.12	0.0400	0.123	0.0554	0.053	0.287	0.115	0.0758	9<10	1.07	1.06	
10<11[6]	0.0874	0.0291	0.137	0.0617	0.0539	0.305	0.122	0.0703	10<11[6]	1.18	1.17	
11<12[6]	0.0874	0.0291	0.137	0.0617	0.0539	0.305	0.122	0.0703	11<12[6]	1.23	1.3	
12<13	0.0874	0.0291	0.137	0.0617	0.0539	0.305	0.122	0.0703	12<13	1.34	1.4	
13<14	0.0997	0.0332	0.121	0.0545	0.0511	0.32	0.128	0.0802	13<14	1.47	1.48	
14<15[6]	0.0796	0.0265	0.131	0.0590	0.0568	0.336	0.134	0.0693	14<15[6]	1.61	1.55	
15<16[6]	0.0796	0.0265	0.131	0.0590	0.0568	0.336	0.134	0.0693	15<16[6]	1.7	1.57	
16<17	0.0796	0.0265	0.131	0.0590	0.0568	0.336	0.134	0.0693	16<17	1.76	1.6	Total avg SA for
17<18	0.0758	0.0253	0.175	0.0788	0.0513	0.308	0.123	0.0728	17<18	1.8	1.63	male/female (m^2)
	Fraction of Total SA: Age-Weighted Body Part-Specific Average											
<1 to <6	0.149	0.050	0.133	0.060	0.055	0.248	0.099	0.069	Total SA (<1to<6yr):	0.666	0.645	**0.656**
<7 to <18	0.097	0.032	0.133	0.060	0.053	0.307	0.123	0.072	Total SA (<7to<18yr):	1.330	1.293	**1.312**
	Surface Area by Body Part (cm^2)[7]											
<1 to <6	977	326	874	393	358	1624	650	451				
<7 to <18	1276	425	1749	787	700	4026	1610	949				

1. Taken from *Exposure Factors Handbook* 1997, Table 6-8.
2. Taken from *Exposure Factors Handbook* 1997, Table 6-6 (male) and Table 6-7 (female).
3. Face SA was assumed to be 1/3 of head SA.
4. Assumed forearm-to-arm ratio (0.45) and lowerleg-to-leg ratio (0.4) equivalent to an adult.
5. Due to lack of data for indicated ages, it was assumed that children <1 and 1<2 yr old had the same total SA as children 2<3 yr old.
6. Due to lack of data for indicated ages, it was assumed that body-part-specific fraction of total SA was equal to that of the next oldest age with data.
7. Body-part-weighted SA for children was calculated by multiplying body-part-specific fraction of
8. Taken from *Exposure Factors Handbook* 1997, Tables 6-2 (male) and 6-3 (female).

EXHIBIT C-1

BODY PART-SPECIFIC SURFACE AREA CALCULATIONS (ADULTS)

ADULT			
	Surface Area of Adults (50th percentile[8]) (cm^2)		
Body Part	Male	Female	Average
Total	19400	16900	18150
Face[3]	433	370	402
Forearms[4]	1310	1035	1173
Hands	990	817	904
Lower legs[4]	2560	2180	2370
Feet	1310	1140	1225

Dermal Pathway (Soil Contact)

Dermal Absorbed Dose – Soil Contact

$$DAD = \frac{DA_{event} \times EF \times ED \times EV \times SA}{BW \times AT} \qquad (3.11)$$

where:

Parameter		Definition (units)	Default Value
DAD	=	Dermal Absorbed Dose (mg/kg-day)	–
DA_{event}	=	Absorbed dose per event (mg/cm^2-event)	Chemical-specific, see Equation 3.12
SA	=	Skin surface area available for contact (cm^2)	See Appendix C and Equations 3.13 to 3.16
EV	=	Event frequency (events/day)	See Exhibit 3-5
EF	=	Exposure frequency (days/year)	See Exhibit 3-5
ED	=	Exposure duration (years)	See Exhibit 3-5
BW	=	Body weight (kg)	70 kg (adult), 15 kg (child)
AT	=	Averaging time (days)	noncarcinogenic effects AT = ED x 365 d/yr carcinogenic effects AT = 70 yr x 365 d/yr

Absorbed Per Event (Soil)

Dermal Absorbed Dose Per Event – Soil Contact

DA_{event} (mg/cm^2-event) is calculated as follows:

$$DA_{event} = C_{soil} \times CF \times AF \times ABS_d \qquad (3.12)$$

where:

Parameter		Definition (units)	Default Value
DA_{event}	=	Absorbed dose per event (mg/cm^2-event)	–
C_{soil}	=	Chemical concentration in soil (mg/kg)	Site-specific
CF	=	Conversion factor (10^{-6} kg/mg)	10^{-6} kg/mg
AF	=	Adherence factor of soil to skin (mg/cm^2-event) (Referred to as contact rate in RAGS, Part A)	See Section 3.2.2.3 and Appendix C
ABS_d	=	Dermal absorption fraction	See Exhibit 3-4

EXHIBIT C-2

ACTIVITY BODY PART-SPECIFIC SOIL ADHERENCE FACTORS (continued)

Activity	ID	Age	Gender	Post-activity Loading (mg/cm^2)					Weighted AFs (mg/cm^2)	
				Hands	Arms	Legs	Faces	Feet	Geometric Mean	95th Percentile
Heavy Equipment Operators No. 1	E1a	54	M	0.115	0.053	x	0.064	x		
	E1b	34	M	0.281	0.080	x	0.104	x		
	E1c	51	M	0.155	0.091	x	0.152	x		
	E1d	21	M	0.940	0.161	x	0.109	x		
Heavy Equipment Operators No. 2	E2a	54	M	0.206	0.192	x	0.146	x		
	E2b	34	M	0.430	0.339	x	0.194	x		
	E2c	51	M	0.227	0.223	x	0.499	x		
	E2d	21	M	0.500	0.358	x	0.200	x		
			Avg(ln x)	-1.245	-1.867	x	-1.874	x		
			Stdev(ln x)	0.682	0.692	x	0.605	x		
			GeoMean	0.288	0.155	x	0.154	x		
			1-tailed t-dist. value	1.895	1.895	x	1.895	x		
			95th Percentile	1.049	0.573	x	0.483	x		
							(face, forearms, hands)		0.203	0.732
Utility Workers No. 1	U1a	45	M	0.149	0.052	x	0.095	x		
	U1b	27	M	0.243	0.131	x	0.079	x		
	U1c	24	M	0.561	0.184	x	0.084	x		
	U1d	35	M	0.364	0.783	x	0.215	x		
	U1e	24	M	0.437	0.311	x	0.082	x		
Utility Workers No. 2	U2a	23	M	0.269	0.189	x	0.062	x		
	U2b	28	M	0.906	0.835	x	0.197	x		
	U2c	24	M	0.187	0.179	x	0.074	x		
	U2d	34	M	0.109	0.298	x	0.113	x		
	U2e	24	M	0.221	0.219	x	0.092	x		
	U2f	36	M	0.390	0.426	x	0.119	x		
			Avg(ln x)	-1.226	-1.385	x	-2.283	x		
			Stdev(ln x)	0.611	0.793	x	0.393	x		
			GeoMean	0.293	0.250	x	0.102	x		
			1-tailed t-dist. value	1.812	1.812	x	1.812	x		
			95th Percentile	0.889	1.053	x	0.208	x		
							(face,forearms,hands)		0.242	0.856

EXHIBIT 3-4

RECOMMENDED DERMAL ABSORPTION FRACTION FROM SOIL

Compound	Dermal Absorption Fraction (ABS_d)[1]	Reference
Arsenic	0.03	Wester, et al. (1993a)
Cadmium	0.001	Wester, et al. (1992a) U.S. EPA (1992a)
Chlordane	0.04	Wester, et al. (1992b)
2,4-Dichlorophenoxyacetic acid	0.05	Wester, et al. (1996)
DDT	0.03	Wester, et al. (1990)
TCDD and other dioxins -if soil organic content is >10%	0.03 0.001	U.S. EPA (1992a)
Lindane	0.04	Duff and Kissel (1996)
Benzo(a)pyrene and other PAHs	0.13	Wester, et al. (1990)
Aroclors 1254/1242 and other PCBs	0.14	Wester, et al.(1993b)
Pentachlorophenol	0.25	Wester, et al. (1993c)
Semivolatile organic compounds	0.1	—

[1] The values presented are experimental mean values.

EXHIBIT 3-5

RECOMMENDED DERMAL EXPOSURE VALUES FOR CENTRAL TENDENCY AND RME RESIDENTIAL AND INDUSTRIAL SCENARIOS – SOIL CONTACT

Exposure Parameters		Central Tendency		RME Scenario	
		Residential	Industrial	Residential	Industrial
Concentration- C_{soil} (mg/kg)		site-specific values			
Event frequency (events/day)		1	1	1	1
Exposure frequency (days/yr)		site-specific	219	350	250
Exposure duration (yr)		9	9	30	25
Skin surface area (cm^2)	Adult	5,700	3,300	5,700	3,300
	Child	2,800	NA	2,800	NA
Soil adherence factor (mg/cm^2)	Adult	0.01	0.02	0.07	0.2
	Child	0.04	NA	0.2	NA
Dermal absorption fraction		chemical-specific values (Exhibit 3-4)			

NA: not applicable

Parameter	Definition	Default - Child	Default - Adult
TRL	Target Risk Level (unitless)	10^{-6}	10^{-6}
BW	Body Weight (kg)	15	70
AT	Averaging Time (yr)	70	70
SF_{ABS}	Absorbed Cancer Slope Factor $(mg/kg\text{-}day)^{-1}$	chemical-specific	chemical-specific
ED	Exposure Duration (yr)	6	30
EV	Event Frequency (events/day)	1	1
EF	Exposure Frequency (days/yr)	350	350
FA	Fraction Absorbed (unitless)	chemical-specific	chemical-specific
$t_{event\text{-}RME}$	Event Duration (hr)	1 (bathing)	0.58 (showering)
SA	Surface Area (cm^2)	6,600	18,000
K_p	Permeability coefficient (cm/hr)	chemical-specific	chemical-specific
ABS_{GI}	Absorption Fraction (unitless)	chemical-specific	chemical-specific
event	Lag time per event (hr)	chemical-specific	chemical-specific
SF_o	Oral Cancer Slope Factor (mg/kg-day)	chemical-specific	chemical-specific
t*	Time to Reach Steady-State (hr)	chemical-specific	chemical-specific
DAD	Dermal Absorbed Dose (mg/kg-day)	site-specific	site-specific
DAD_{event}	Absorbed Dose per Event (mg/cm^2-event)	site-specific	site-specific

Inhalation Pathway

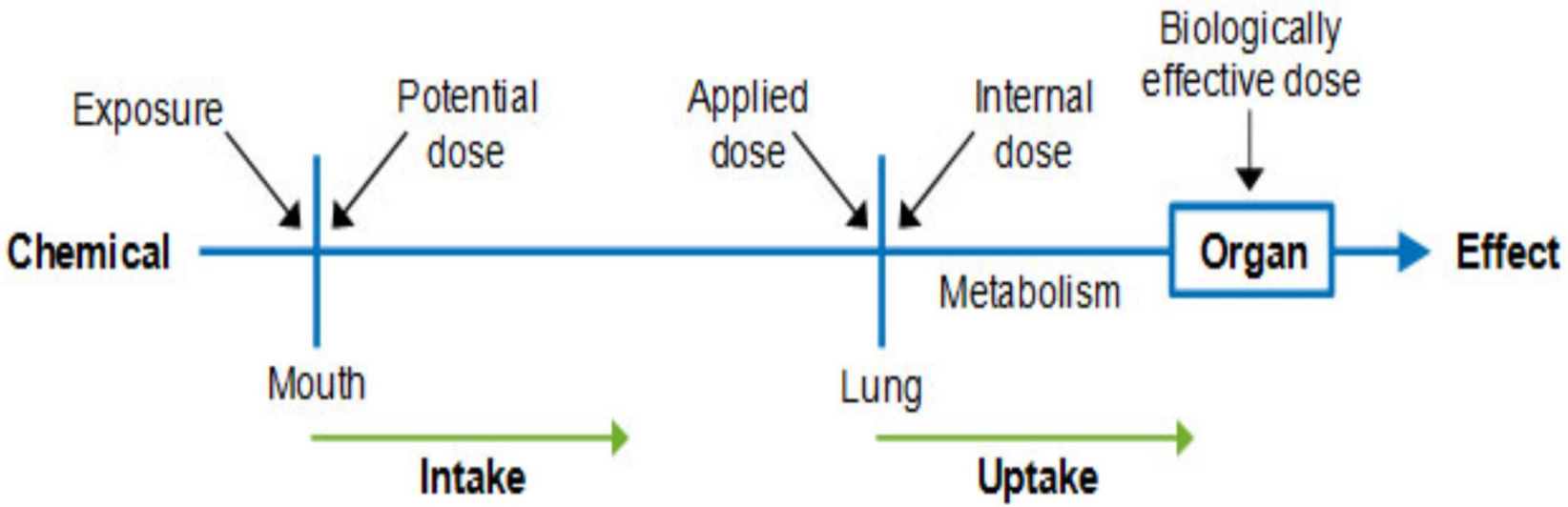


Illustration of Inhalation Route: Exposure and Dose (U.S. EPA, 1992)

Inhalation Pathway

ADD = Cair x InhR x ET x EF x ED/BW x AT

Where:

ADD = Average daily dose (mg/kg-day)

$\mathbf{C_{air}}$ = Concentration of contaminant in air (mg/m^3)

InhR = Inhalation rate (m^3/hour)

ET = Exposure time (hours/day)

EF = Exposure frequency (days/year)

ED = Exposure duration (years)

BW = Body weight (kg)

AT = Averaging time (days)

$$HI = LADD_c / RfC \times 1000 \mu g/g$$

$$ILCR = IUR \times LADD_a$$

Table 6-27. Selected Inhalation Rate Values During Different Activity Levels Obtained From Various Literature Sources

Subject	BW (kg)	Resting			Light Activity			Heavy Work			Maximal Work During Exercise		
		f	VT	V*	f	VT	V*	f	VT	V*	f	VT	V*
Adolescent													
Male, 14–16 years		16	330	5.2							53	2,520	113
Male, 14–15 years	59.4												
Female, 14–16 years		15	300	4.5									
Female, 14–15 years; 164.9 cm L	56										52	1,870	88
Children													
10 year; 140 cm L		16	300	4.8	24	600	14						
Males, 10–11 years	36.5										58	1,330	71
Males, 10–11 years; 140.6 cm L	32.5										61	1,050	61
Females, 4–6 years	20.8										70	600	40
Females, 4–6 years; 111.6 cm L	18.4										66	520	34
Infant, 1 year		30	48	1.4[a]									
Newborn	2.5	34	15	0.5									
20 hours–13 weeks	2.5–5.3										68[b]	51[a,b]	3.5[b]
9.6 hours	3.6	25	21	0.5									
6.6 days	3.7	29	21	0.6									
Adult													
Man	68.5	12	750	7.4	17	1,670	29	21	2,030	43			
1.7 m^2 SA		12	500	6									
30 years; 170 cm L		15	500	7.5	16	1,250	20						
20–33 years	70.4										40	3,050	111
Woman	54	12	340	4.5	19	860	16	30	880	25			
30 years; 160 cm L		15	400	6	20	940	19						
20–25 years; 165.8 cm L	60.3										46	2,100	90
Pregnant (8^{th} month)		16	650	10									

[a] Calculated from $V^* = f \times VT$.
[b] Crying.

BW = body weights.
f = frequency (breaths/minute).
VT = tidal volume (mL).
V* = minute volume (L/minute).
cm L = length/height.

Table 6-26. Time Weighted Average of Daily Inhalation Rates (DIRs) Estimated From Daily Activities[a]

Subject	Inhalation Rate (m^3/hour)		DIR[b] (m^3/day)
	Resting	Light Activity	
Adult Man	0.45	1.2	22.8
Adult Woman	0.36	1.14	21.1
Child (10 years)	0.29	0.78	14.8
Infant (1 year)	0.09	0.25	3.76
Newborn	0.03	0.09	0.78

[a] Assumptions made were based on 8 hr resting and 16 hr light activity for adults and children (10 years); 14 hr resting and 10 hr light activity for infants (1 year); 23 hr resting and 1 hr light activity for newborns.

[b]

$$DIR = \frac{1}{T}\sum_{i=1}^{K} IR_i t_i$$

DIR = Daily Inhalation Rate,
IR_i = Corresponding inhalation rate at i^{th} activity,
t_i = Hours spent during the i^{th} activity,
k = Number of activity periods, and
T = Total time of the exposure period (i.e., a day).

Table 6-30. Activity Pattern Data Aggregated for Three Microenvironments by Activity Level for All Age Groups

Microenvironment	Activity Level	Average Hours Per Day in Each Microenvironment at Each Activity Level
Indoors	Resting	9.82
	Light	9.82
	Moderate	0.71
	Heavy	0.10
	TOTAL	20.4
Outdoors	Resting	0.51
	Light	0.51
	Moderate	0.65
	Heavy	0.12
	TOTAL	1.77
In Transportation Vehicle	Resting	0.86
	Light	0.86
	Moderate	0.05
	Heavy	0.0012
	TOTAL	1.77

Source: Adapted from U.S. EPA (1985).

Additional Resources

- EPA Benchmark Dose Software
  http://www.epa.gov/ncea/bmds/
- EPA-Expo-Box (A Toolbox for Exposure Assessors)
  https://www.epa.gov/expobox
- EPA Risk Assessment Guidelines:
  http://www.epa.gov/riskassessment/guidance.htm
- Human Health Risk Assessment Program

  https://www.epa.gov/aboutepa/about-human-health-risk-assessment-program

Contact Information

Dr Belin Tavakoli
tavakkolisanib@mums.ac.ir

Crystal Ball Programs