Occupational Cancer Risk: Exposure and Assessment

Basic Course In Occupational Medicine
Part III

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Disclosure 1

I am a consulting toxicologist, and I evaluate exposures to chemical agents and whether there is sufficient dose and exposure to cause an adverse effect.

In my practice, I evaluate the toxicity of metals to people, including the metals we discuss today.

I have been retained as an expert witness in cases involving chemical agents, including the metals we are discussing today.

My expert opinions are based on the foundational tenants of toxicology, including but not limited to exposure, dose, and threshold effect. I conduct my toxicological assessment following globally recognized guidelines.

I receive an honorarium for my presentations in this course.

Disclosure 2

We cover a lot of material in this one hour course. This course gives you an **introduction** to metal toxicology.

As a way to help you think about this, these are the items I consider for suspected toxicological issues. No singular piece is sufficient for determining causation.

1) Symptomatology
2) Occupational setting
3) Hobbies
4) Medications review
5) Objective testing (air, blood, urine, etc.)
6) Medical Hx
7) Review toxicological information

When in doubt, call a toxicologist.

What do we mean by conservative?

Toxicologist want to err on the side of protecting the public health:

Review the literature

Use higher air concentrations

Use higher doses

Use longer periods of exposure

Use acceptable exposure levels that are based on the most sensitive endpoint, then apply “safety factors” (uncertainty factors).

Learning Objectives

Reflect on exposures for carcinogens in the occupational setting

Learn how a toxicological risk assessment for carcinogens is conducted

Highlight applicable occupational standards

Discuss surveillance procedures for various metals

1. Introduction
2. General concepts of toxicology
3. Studies used in cancer toxicology
4. Cancer and occupational medicine

Cancer is a disease characterized by mutation, modified gene expression, cell proliferation, and aberrant cell growth.

Multiple causes of cancer have been established including infectious agents, radiation, and chemicals.

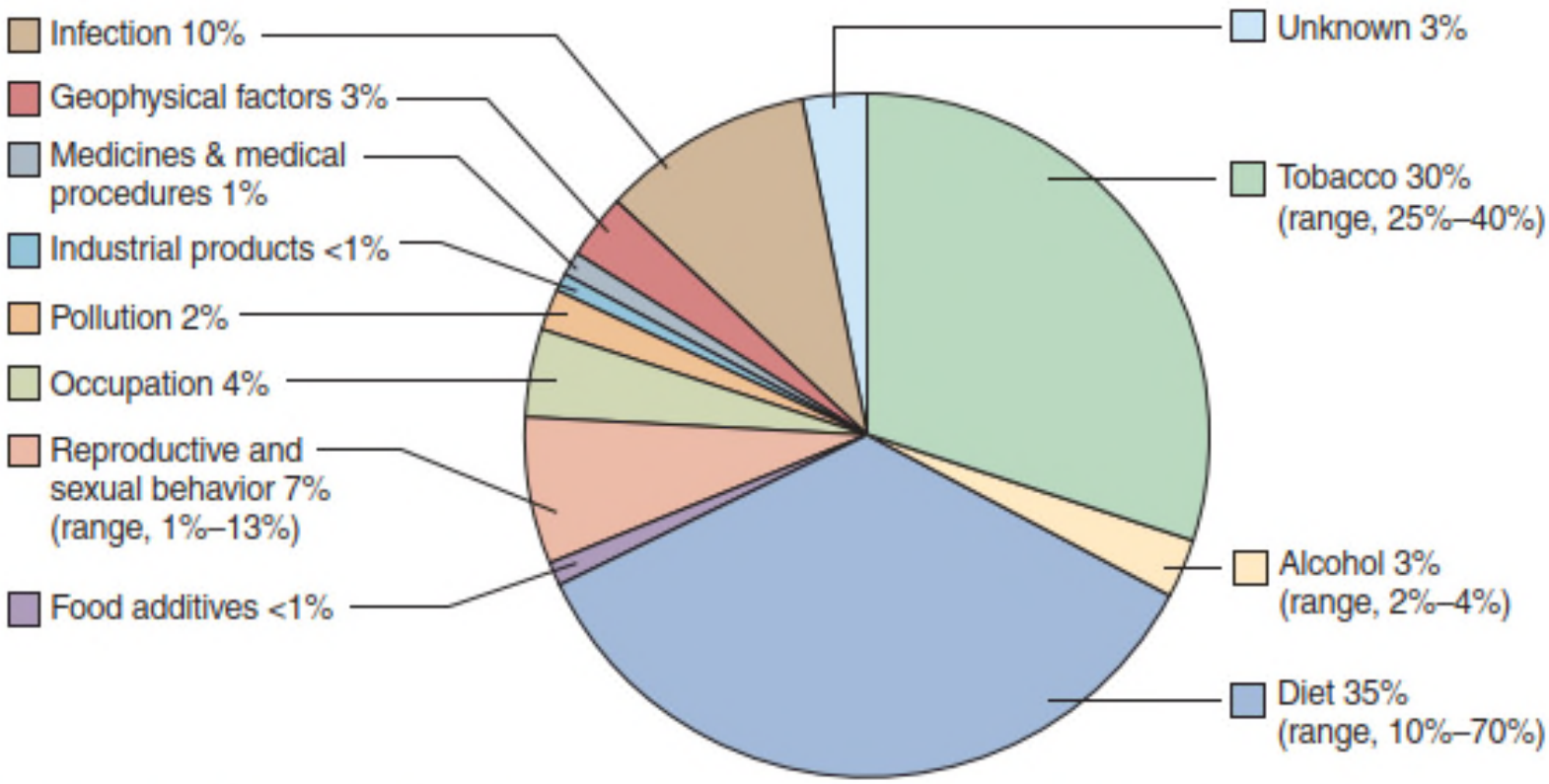


Figure 8-1. *Proportions of human cancer deaths attributed to various factors.* (Reproduced with permission from [no authors listed] Harvard reports on cancer prevention: causes of human cancer. Center for Cancer Prevention Harvard School of Public Health. *Cancer Causes and Control.* 1996;7 (Suppl 1):S3–S4, 1996.)

Casarett & Doull, 2013

Large Doses of Natural Chemicals Can Cause Cancer in Animals

Indole carbinol
Naturally found in:
Broccoli, cabbage

Caffeic acid
Naturally found in:
Coffee, Lettuce, Tomato, Apples, Potatoes

Psoralens
Naturally found in:
Celery, parsley

d-Limonene
Naturally found in:
Oranges, black pepper, nutmeg, mangos

Estragole
Naturally found in:
Basil

Aflatoxin
Naturally found in:
Peanut Butter

Hydrazines
Naturally found in:
Mushrooms

Allyl isothiocyanate
Naturally found in:
Mustard

Historical Events in Chemically Induced Cancer

DATE	INVESTIGATOR(S)	CAUSATIVE AGENT
1775	Pott	Soot and chimney sweeps
1822	Ayrton	Arsenic containing metal
1875	Thiersch	Sunlight
1876	Manourriez	Coal tar
1879	Harting and Hesse	Lung cancer and uranium
1892	Butlin	Soot and chimney sweeps
1895	Rehn	Manufacture of aniline dyes
1902	Frieben	X-rays
1915	Davis	Pipe smokers and betel nut chewers
1915	Yamagiwa, Ichikawa, and Tsusui	Induction of skin cancer in rabbits and mice by coal tar
1920	Leitch and Seguina	Radium radiation
1928	Delore and Bergamo	Benzene
1930	Kennaway and Hieger	Tumor induction by dibenz[*a*,*h*]anthracene
1932	Stephens	Nickel
1932	Alwens	Chromium compounds
1933	Cook, Hewett, and Hieger	Isolation of the carcinogen benzo[*a*]pyrene from coal tar
1936	Yoshida and Kinosita	Induction of liver cancer in rats by *o*-aminoazotoluene
1934	Wood and Gloyne	Arsenicals, beryllium, and asbestos
1934	Neitzel	Mineral oil mists and radiation
1936	Kawahata	Coal tar fumes
1938	Hueper, Wiley, and Wolfe	Induction of urinary cancer in dogs by 2-naphthylamine
1941	Berenblum, Rous, MacKenzie, and Kidd	Initiation and promotion stages in skin carcinogenesis with benzo[*a*]pyrene
1951	Miller and Miller	Carcinogen binding to cellular macromolecule
1956	Doll and Hill	Lung cancer and other causes of death in relation to smoking

Casarett & Doull, 2013

Terminology	
Neoplasia	New growth or autonomous growth of tissue
Neoplasm	The lesion resulting from the neoplasia
Benign	Lesions characterized by expansive growth, frequently exhibiting slow rates of proliferation that do not invade surrounding tissues
Malignant	Lesions demonstrating invasive growth, capable of metastases to other tissues and organs
Metastases	Secondary growths derived from a primary malignant neoplasm
Tumor	Lesion characterized by swelling or increase in size, may or may not be neoplastic
Cancer	Malignant neoplasm
Carcinogen	A physical or chemical agent that causes or induces neoplasia
Genotoxic	Carcinogens that interact with DNA resulting in mutation
Nongenotoxic	Carcinogens that modify gene expression but do not damage DNA

Casarett & Doull, 2013

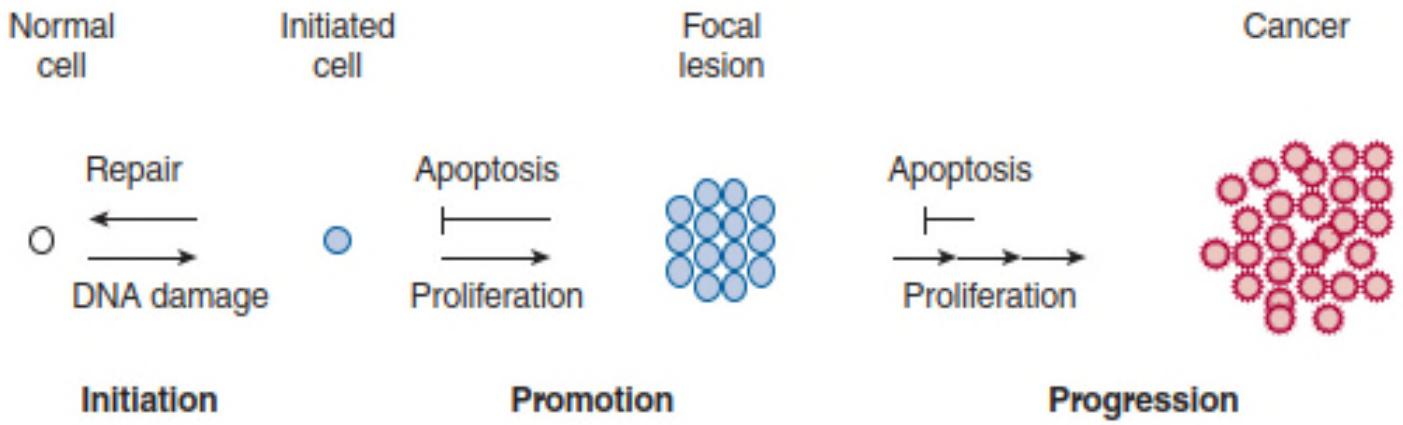


Figure 8-2. *Multistage model carcinogenesis.*

Casarett & Doull, 2013

Sources of tox information

- ACGIH Documentation of the TLVs and BEIs
- Hazardous Substances Databank (National Library of Medicine)
- Integrated Risk Information System (EPA)
- NIOSH Pocket Guide to Chemical Hazards
- Occupational Health Guidelines for Chemical Hazards (NIOSH/OSHA)
- Registry of Toxic Effects of Chemical Substances (MDL Information Systems)
- Toxicological Profiles (ATSDR)
- Disposition of Toxic Drugs and Chemicals in Man (12th Edition)
- Casarett & Doull Toxicology (9th Edition)

Health risk = Exposure x Hazard

Deer in Headlights. A deer caught in the headlights will freeze, much like an author or reader seeing a p-value < 0.05, and think there must be a real effect. Authors can exploit this phenomenon intentionally or fool both themselves and the reader. Illustration: Tom Boulton

-Young, S. S. & Karr, A. Deming, data and observational studies. Significance 8, 116–120 (2011).

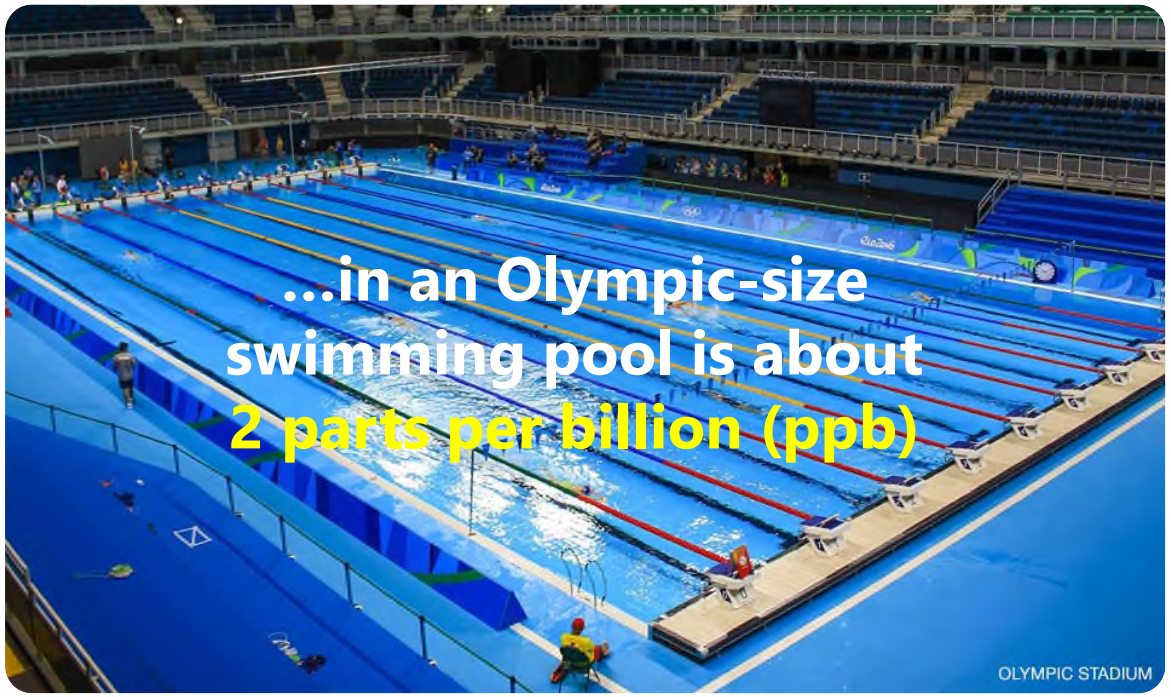
Publication bias

"There is general recognition that a paper has a much better chance of acceptance if something new is found. This means that, for publication, the claim in the paper has to be based on a p-value less than 0.05. From Deming's point of view, this is quality by inspection. The journals are placing heavy reliance on a statistical test rather than examination of the methods and steps that lead to a conclusion. As to having a p-value less than 0.05, some might be tempted to game the system through multiple testing, multiple modelling or unfair treatment of bias, or some combination of the three that leads to a small p-value. Researchers can be quite creative in devising a plausible story to fit the statistical finding."

-Young, S. S. & Karr, A. Deming, data and observational studies. Significance **8**, 116–120 (2011).

How Small is Small?

1 teaspoon of sugar…



One grain of sugar in an Olympic-size swimming pool is about **200 parts per quadrillion (ppq)**

Primary Routes of Exposure

Gastrointestinal (oral)

Pulmonary (inhalation)

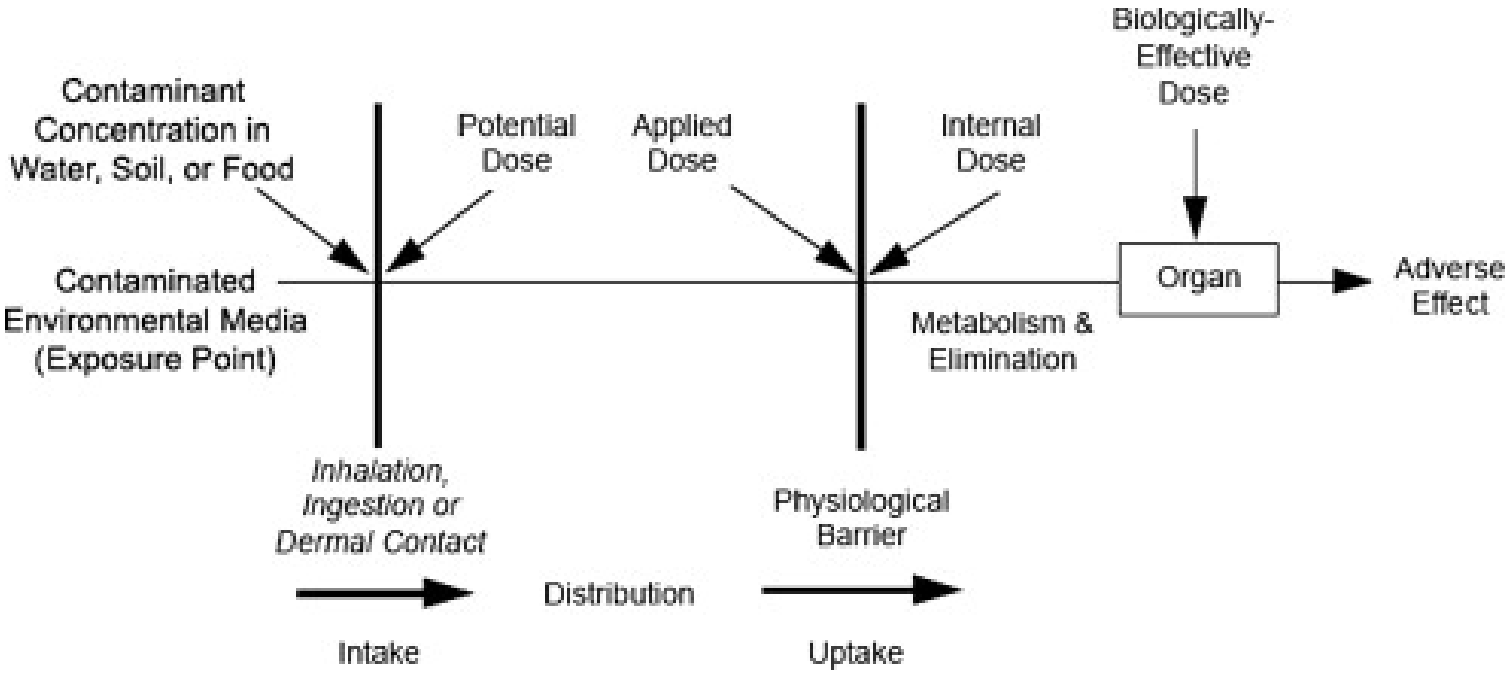
Dermal (skin application)

There are differences in the absorption of compounds depending on the route of exposure due to physiological differences between these organs.

There are accepted methodologies to extrapolate from one exposure route to another.

However, depending on the quality of the data, this leads to uncertainty.

The air concentration is just a distant step to arrive at the dose at the organ.



✓Presence ≠ Toxicity
✓Dose-response relationship

What is there that is not poison?

All things are poison and nothing (is) without poison.

Solely the dose determines that a thing is not a poison.

-Paracelsus (1493-1541)

Balance of Activation to Detoxification is Dose-Dependent

Toxicity Depends on Balance Of Activation to Detoxification

Phase I Enzymes
Activation or Protection

- cytochrome 450s
- lipoxygenases
- flavin-containing
- monooxygenases

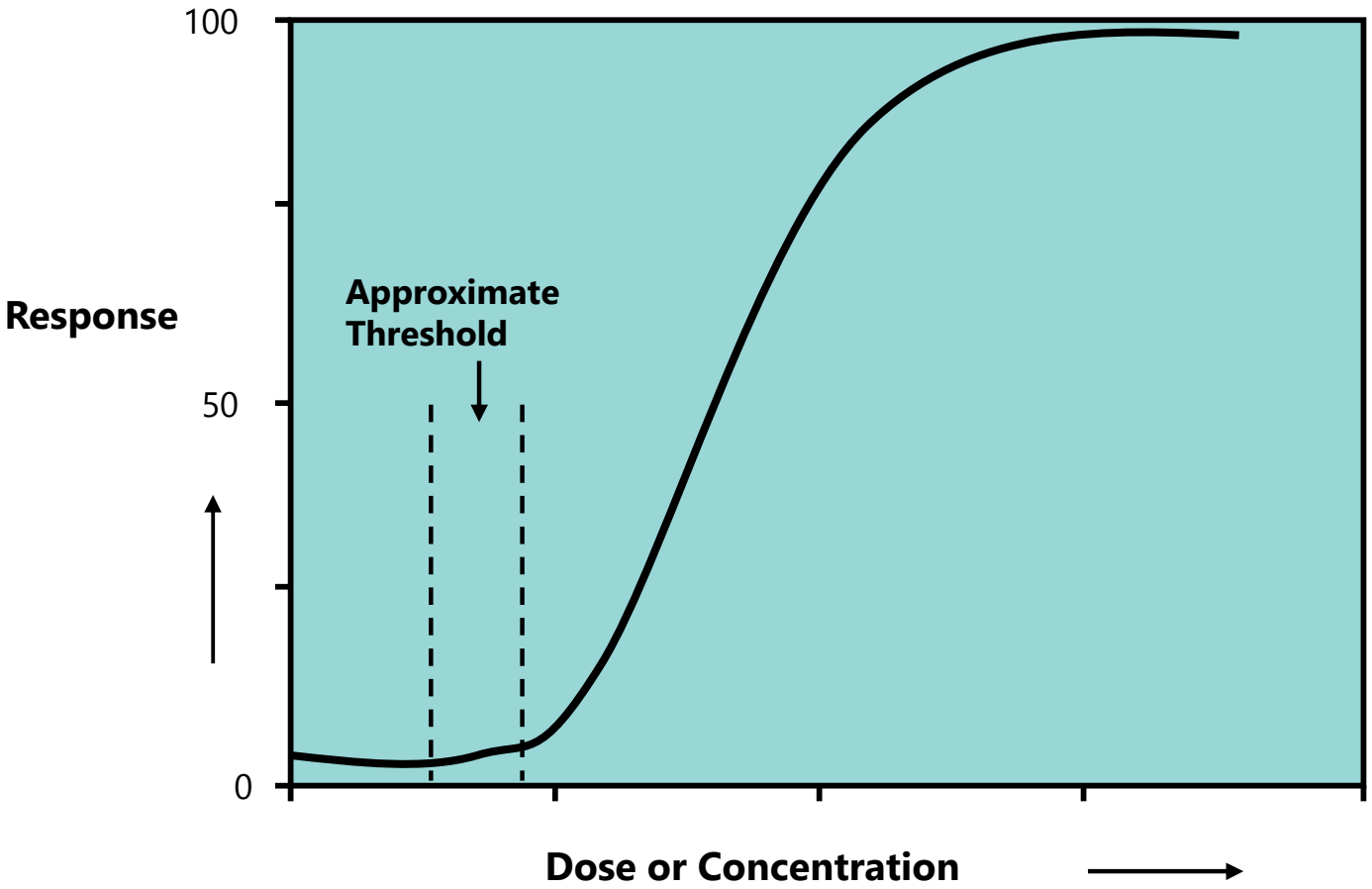
Phase II Enzymes
Protection Elimination

- Glutathione S-transferases
- Glucuronyltransferases
- Sulfotransferases
- N-Acetyltransferases
- Epoxide hydrolase
- Peroxidases
- Oxido-reductases

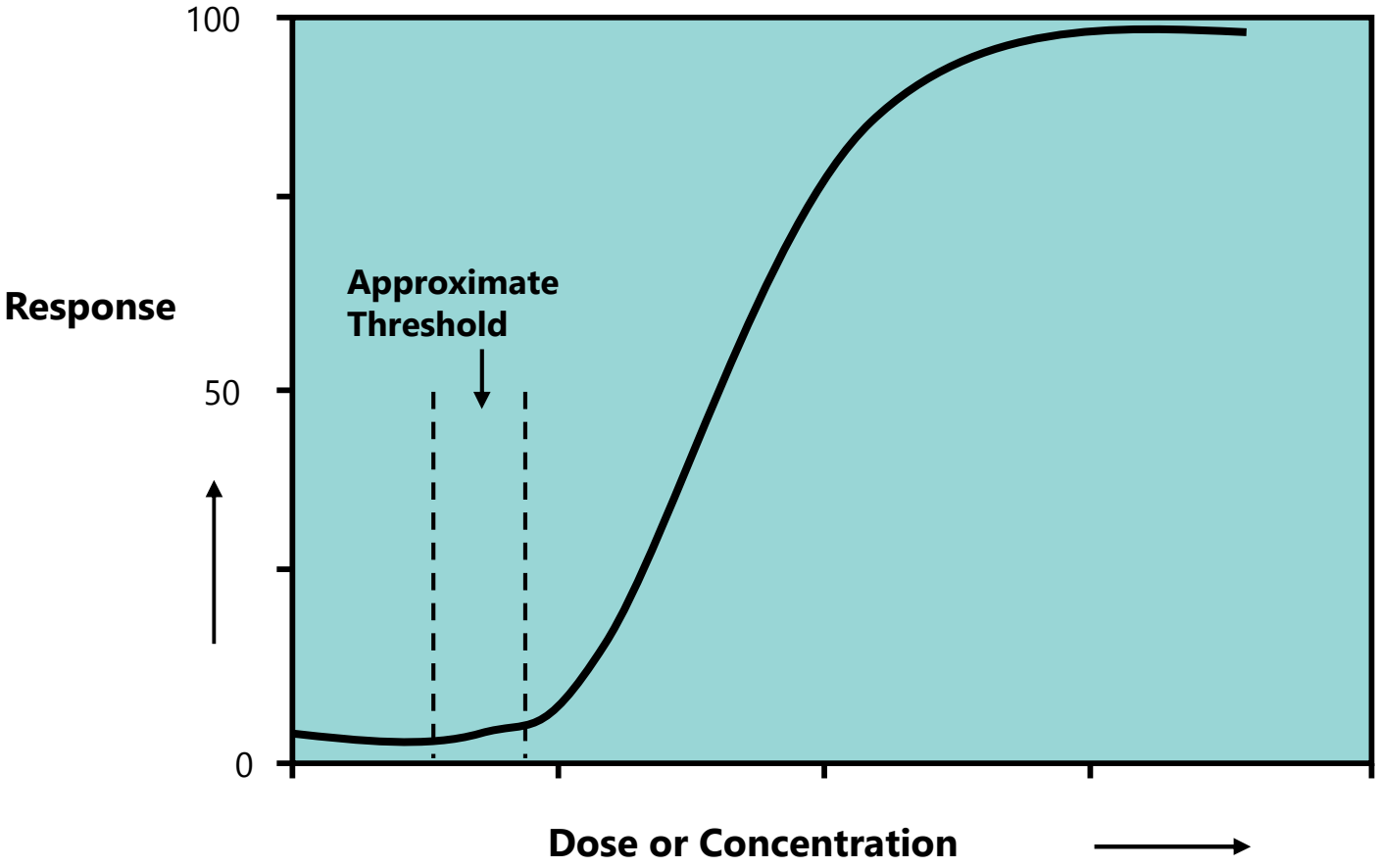
At low doses, protective pathways dominate

At high doses, protective pathways overwhelmed

Threshold Response



Threshold Response



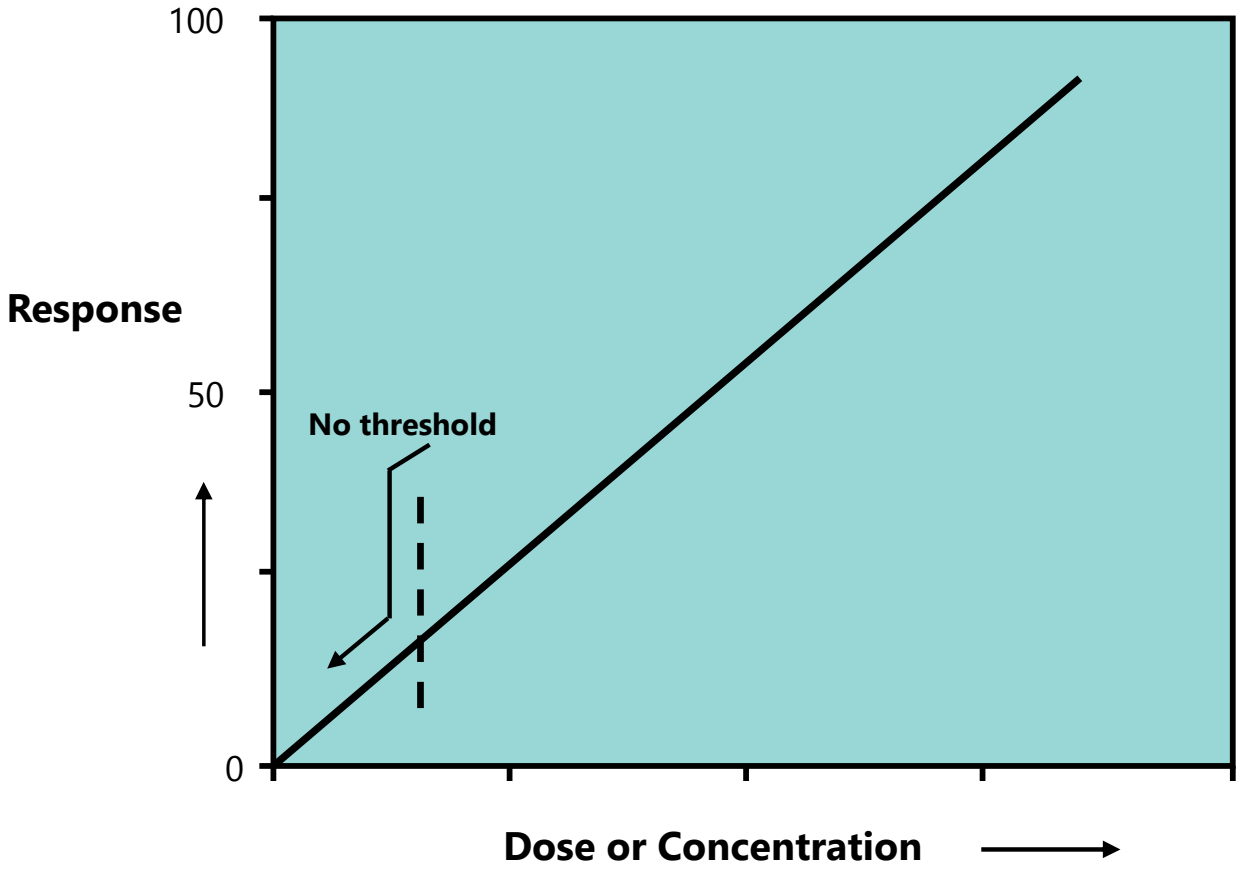
Seahawks Stadium

Toxicity occurs when a **dose is high enough** to occupy most available receptors

One person in the stadium does not make enough sound to impact the players on the field

68,740 cheering fans in the seats **activates** the "12th man"

Non-threshold Response



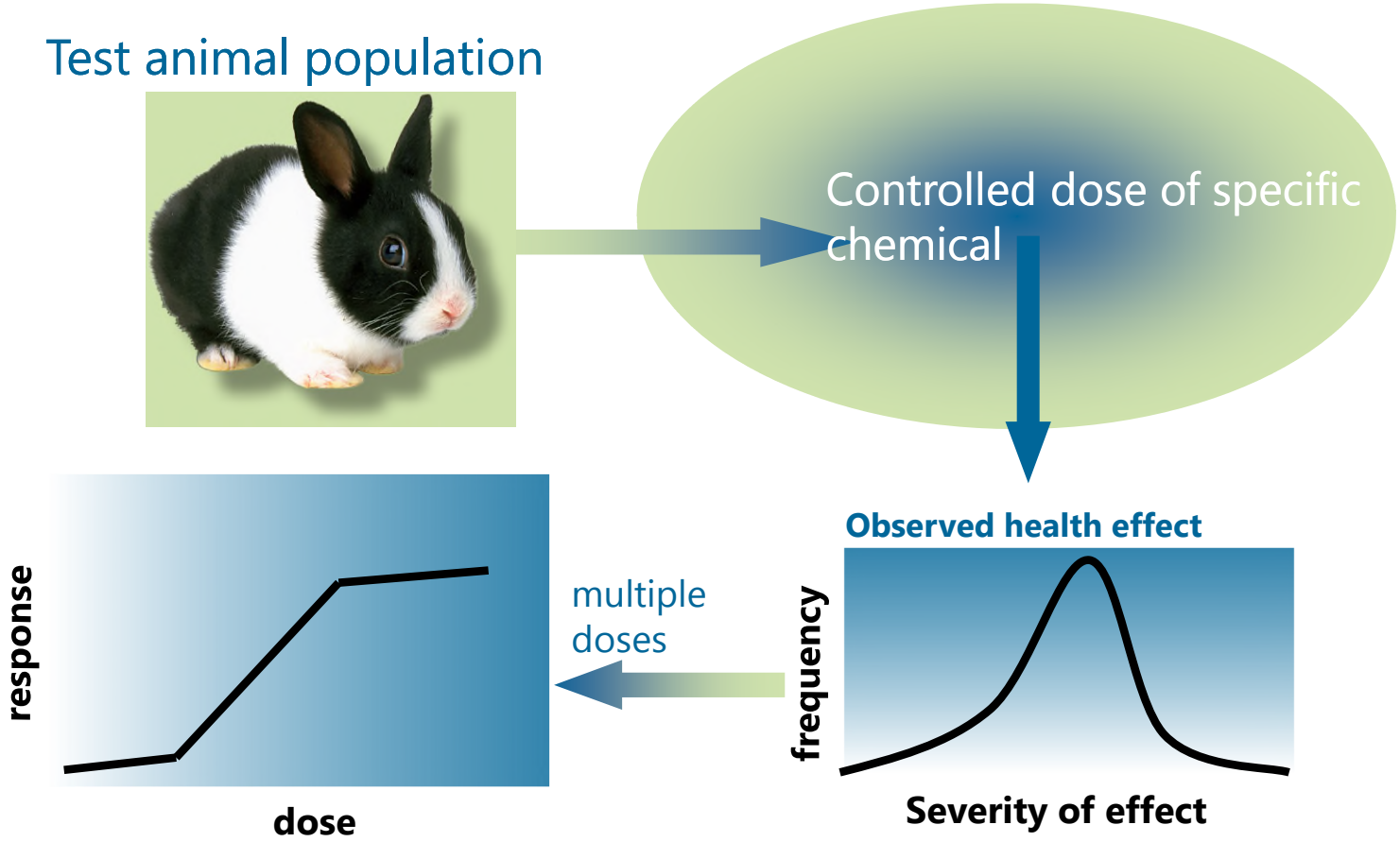
Cancer Slope Factor

Erroneously assumes an increased cancer risk at any dose.

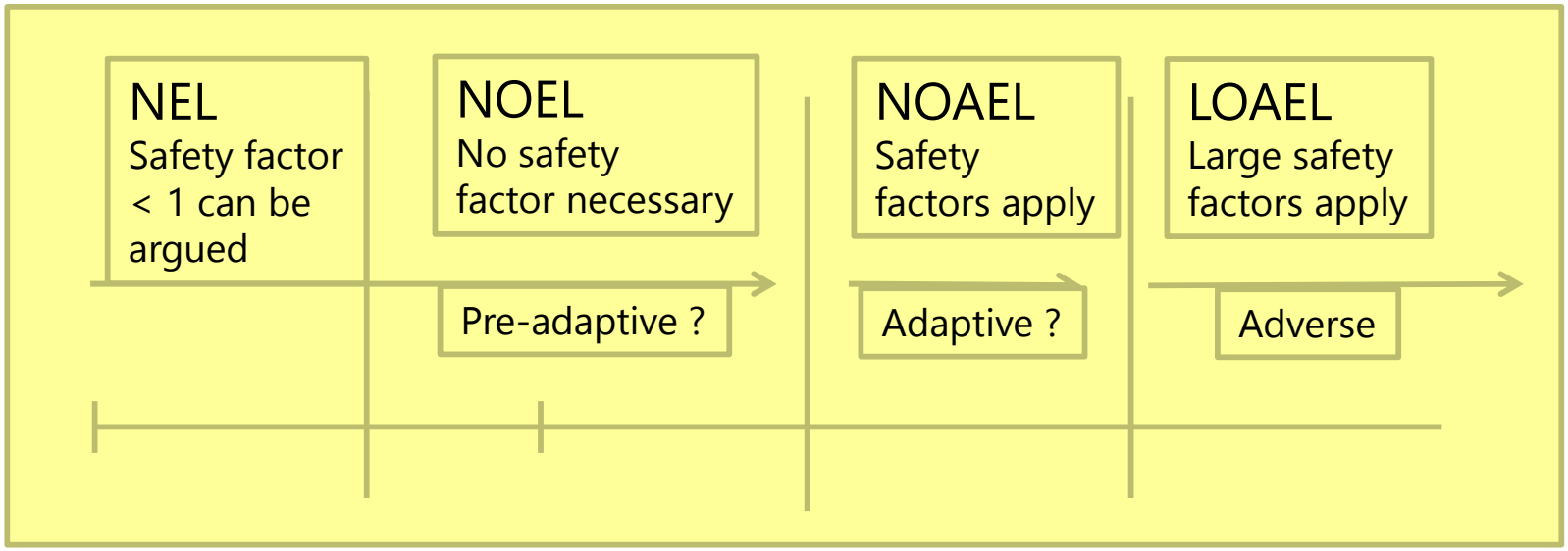
Acute *vs.* Chronic Exposures

Acute	Single dose with effects occurring for a short period of time (usually up to 96 hrs)
Subacute	Multiple doses administered for up to 14 days
Subchronic	Continuous dosing for up to 90 days
Chronic	Continuous dosing for up to 6 months to 2 years
Acute Toxicity Tests	$LD_{50,}$ Concentration of a chemical that causes 50% mortality of the test organism after a specified period of time (*e.g.* 96 hrs)

Animal Studies



Endpoints of Toxicology Studies and How Safety Factors Apply



Possible safety factors (uncertainty factors) are values of 1, 3, or 10

- **Extrapolation from animals to humans**
- **Extrapolation from LOAEL to NOAEL**
- **Database**
- **Extrapolation from healthy adults to sensitive populations**

Comparison of Animal Cancer Testing: Before and After 1970

Study Design Parameters	Pre-1970 Practices	Post-1970 Practices
Number of Dose Groups	Typically a single dose group	Minimum of three or more groups
Method of Administration (e.g., Dermal, Inhalation, Gavage, Dietary)	Dermal or inhalation exposure (assess occupational exposure)	Dietary or gavage to ensure dose
Length of Administration (How Long)	Variable	Established period of time: mouse 18 mos, rat 2 yrs
Animal Care	Not standardized	Rigidly controlled, standardized animal medicine practices
Tissue analysis	No uniform classification system	Established classifications
Pathology review	Single pathologist	Multiple pathologists
Statistical practices	None or non-standardized	Highly standardized
Group Size	Variable	Larger numbers of animals

Comparison of Animal Cancer Testing: Before and After 1970

Study Design Parameters	Pre-1970 Practices	Post-1970 Practices
Individual animal data	Not typically reported	Animals individually tracked and assessed
Species	Multiple species	Rats or mice
Strain	No consistent strain	Consistent strain or sensitive strain
Gender	Random gender selection	Both genders or most sensitive gender
Age	Varied	Studies begin at specific, young ages
Historical Controls (Summary of Control Animals)	Generally not available	An integral part of study design
Doses Administered (Total Dose and Variability Within Study Period)	May have relied on a minimum range finding study (dose could be adjusted during study)	Use of a subchronic study to set chronic dose levels (doses aren't typically adjusted)

Comparison of Animal Cancer Testing: Before and After 1970

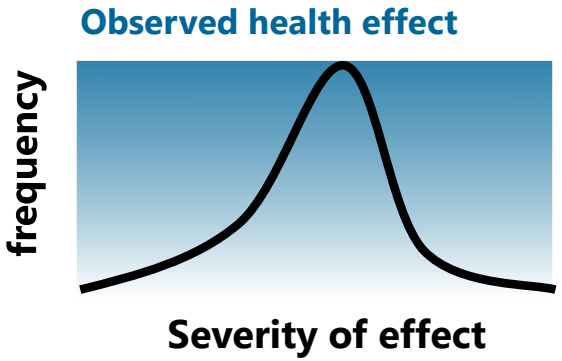
Study Design Parameters	Pre-1970 Practices	Post-1970 Practices
Observations	Limited	Comprehensive
Intervals of Administration (On/Off)	Variable intervals	Continuous
Test Substance	Purity impossible to determine	Purity confirmed, contaminants identified
Source of Test Compound	Not specified	Well documented
Record Keeping	No requirements	Good Laboratory Practice (GLP) regulations
Additional Analysis (e.g., Hematology, Urinalysis)	Limited	Comprehensive analyses
Laboratory Design	Not standardized	Clean/dirty corridor systems and Standard Operating Procedures
Study Segregation	Not standardized	One study per room

Human Studies

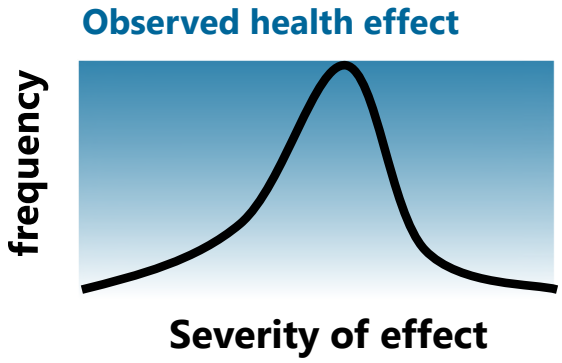
Test human population

Controlled dose of specific chemical

Mild, reversible effects only!



Epidemiology Study



Exposure to chemical(s)

IS THERE AN ASSOCIATION BETWEEN HEALTH EFFECT AND EXPOSURE?

Epidemiological Measures

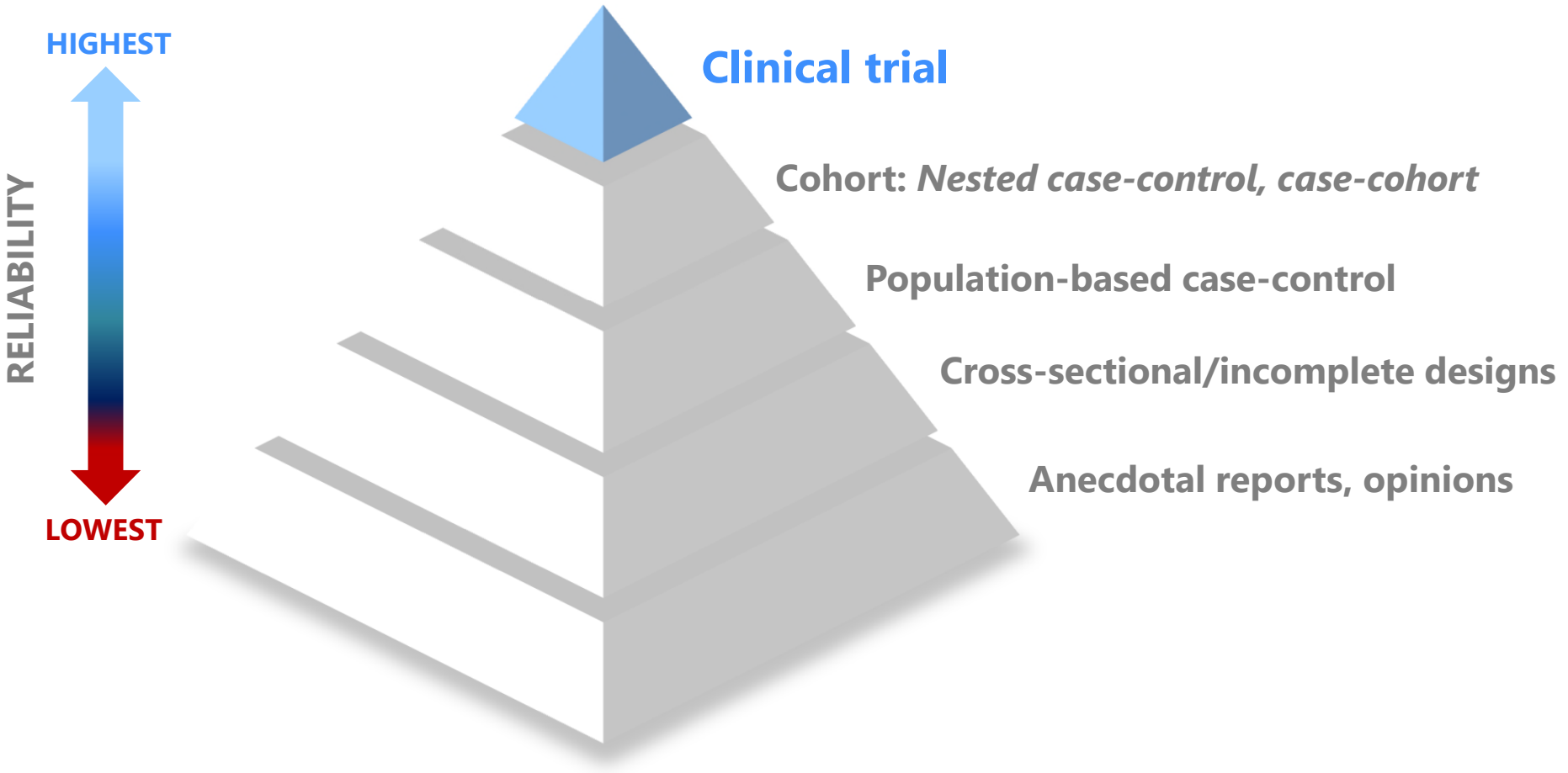
Measures of Comparison

- Absolute Measures
  - Risk Difference
  - Population Attributable Risk
- Relative Measures
  - Relative Risk

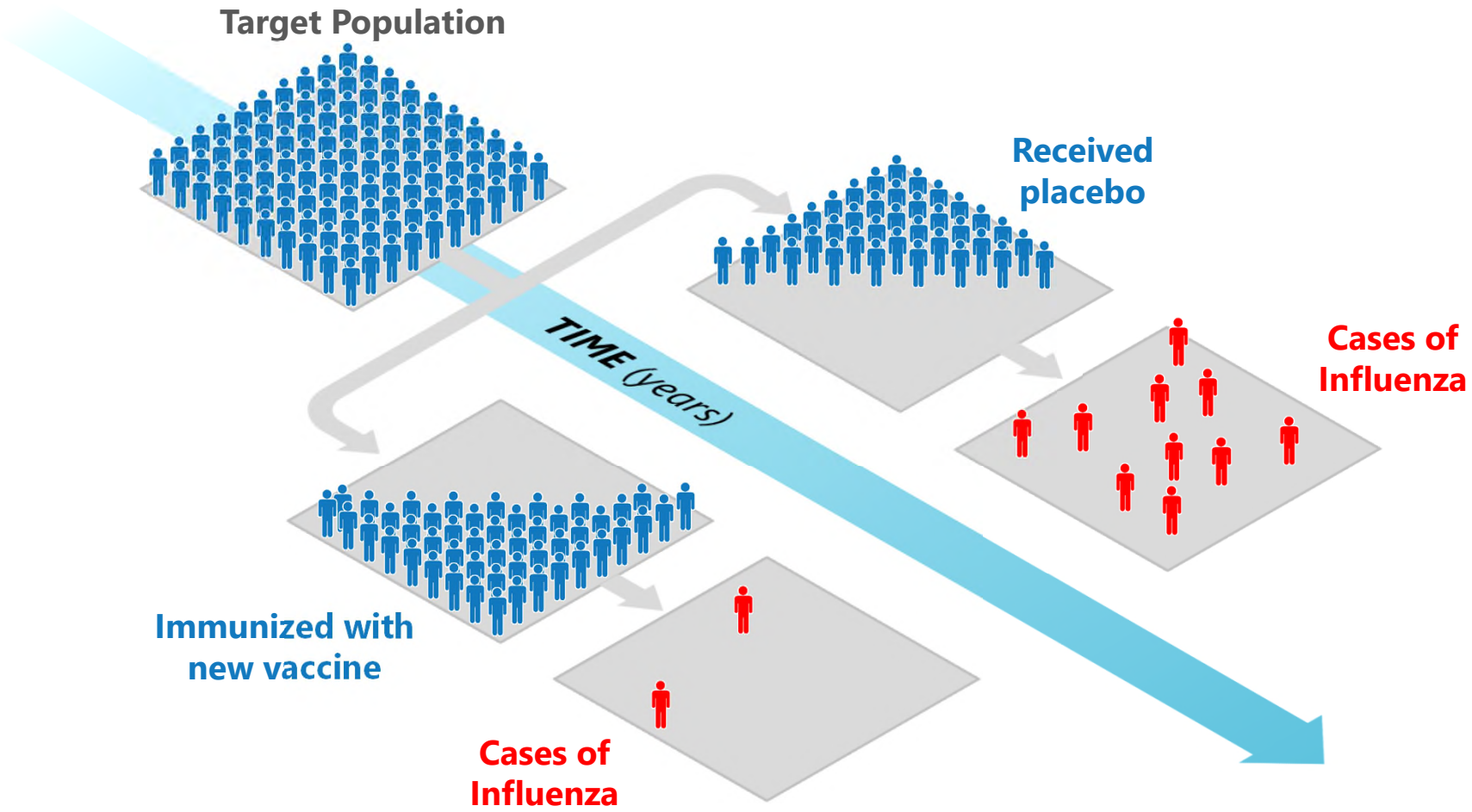
Estimates of Comparison

Odds Ratio

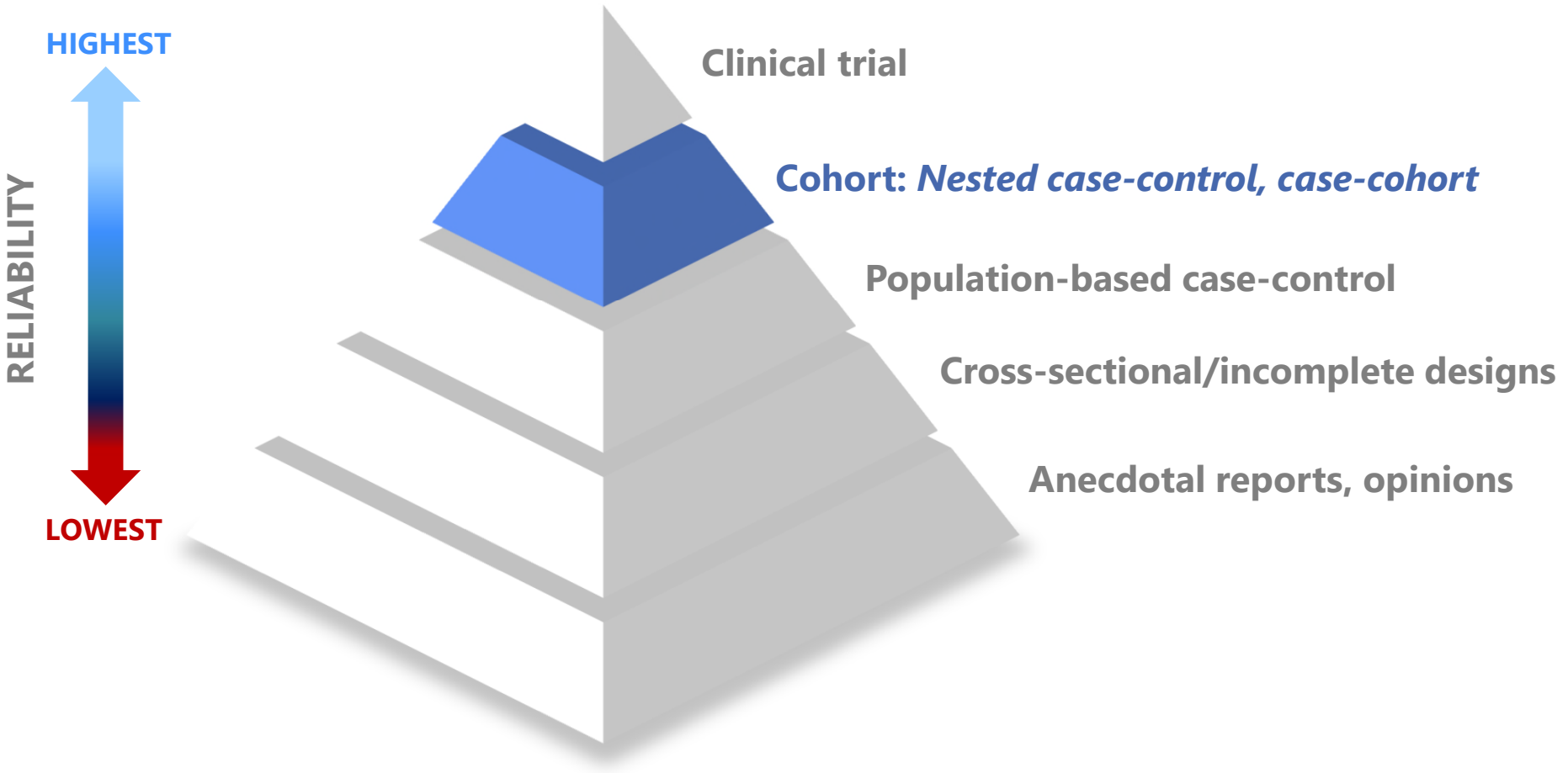
Hierarchy of Epidemiological Evidence



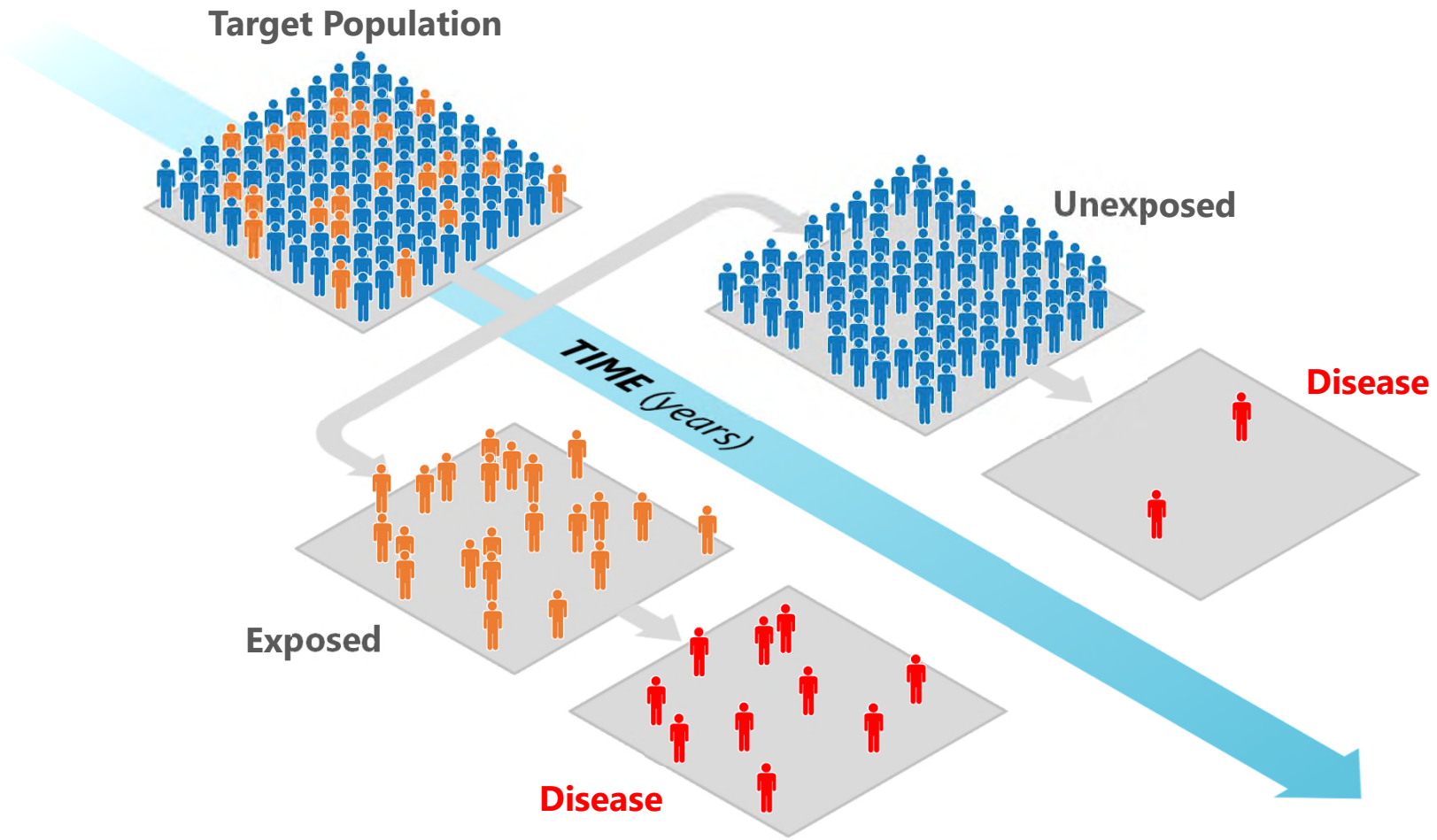
Example of Epidemiological Study: Clinical Trial



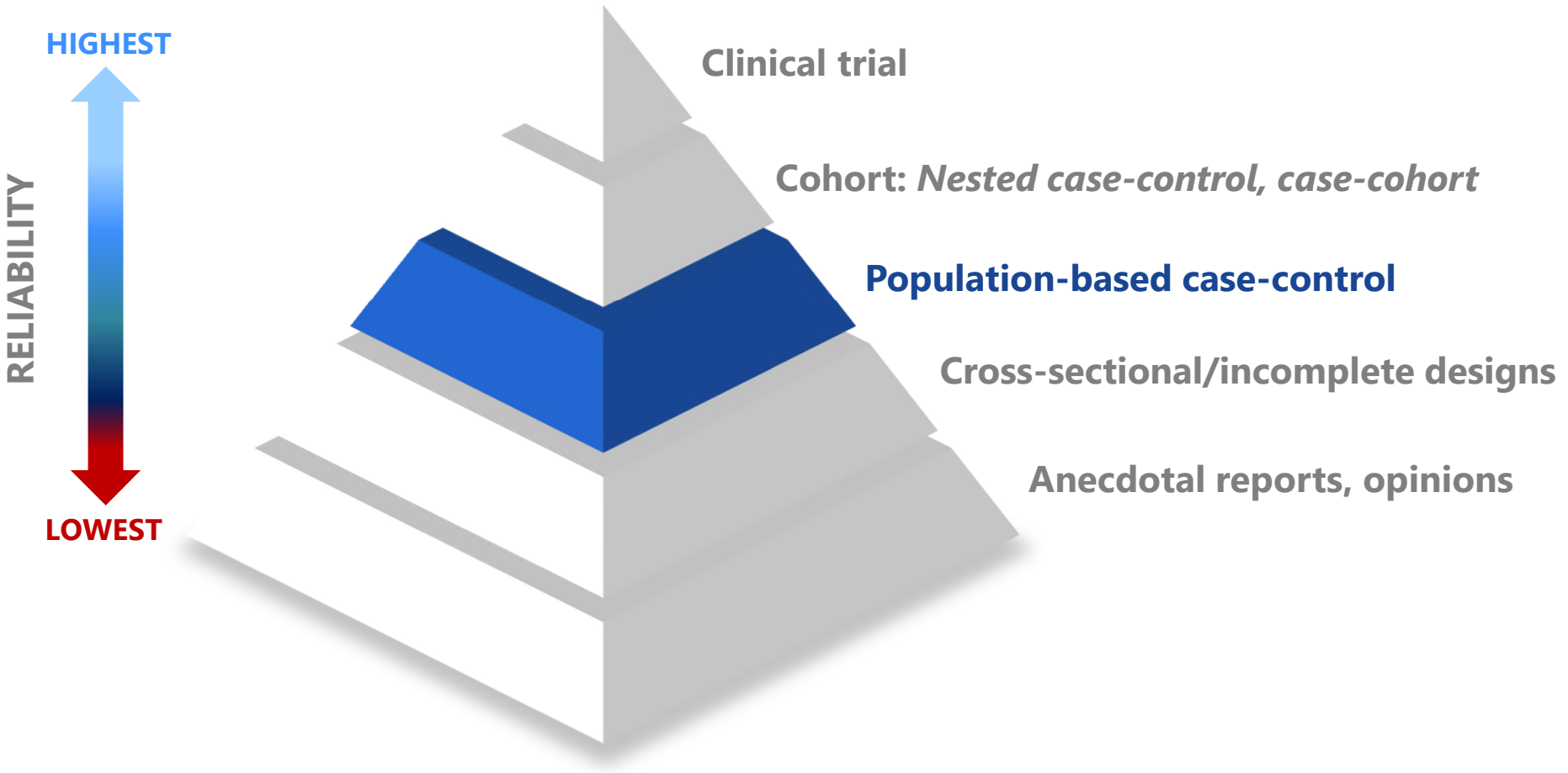
Hierarchy of Epidemiological Evidence



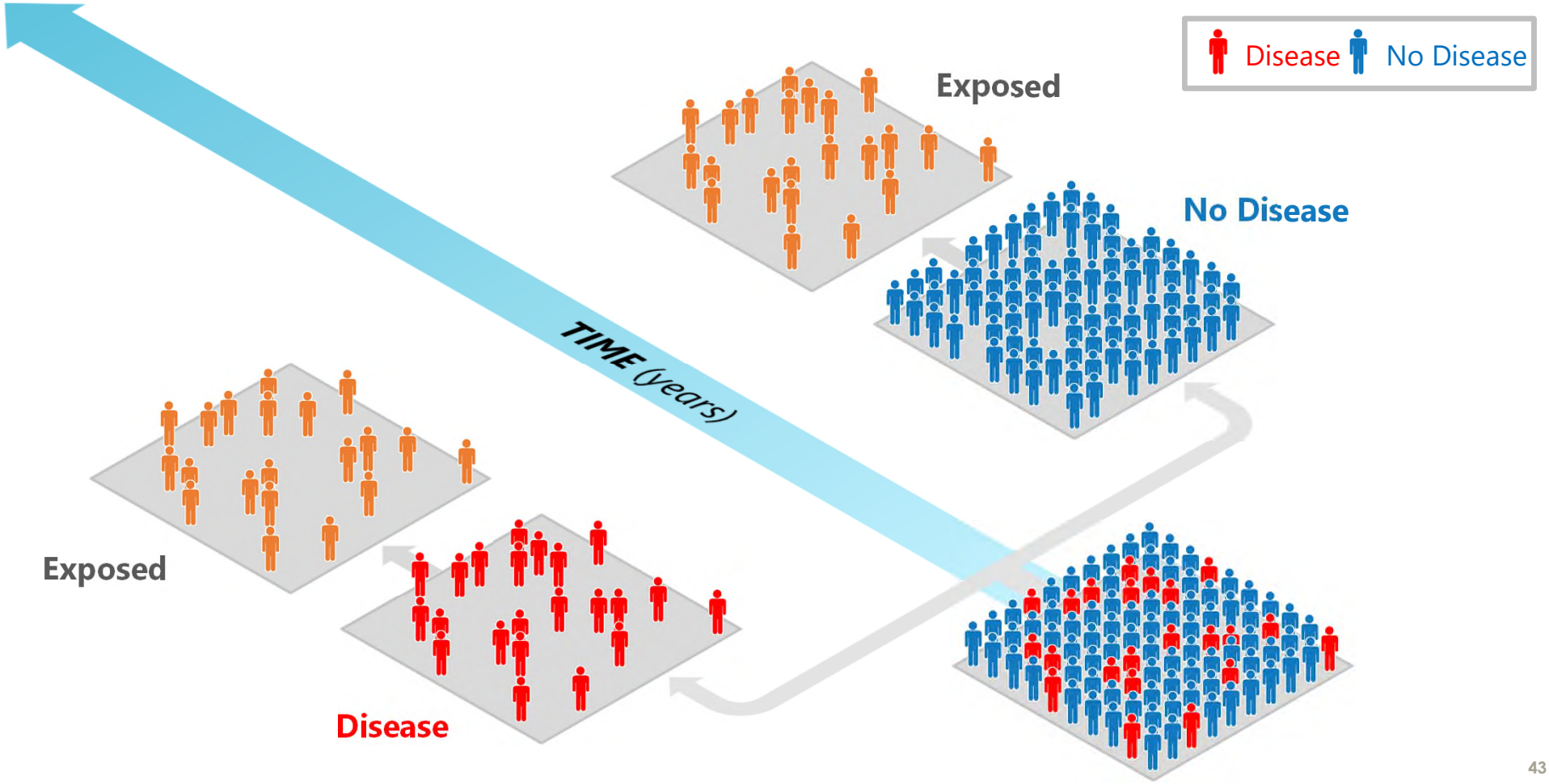
Cohort Study



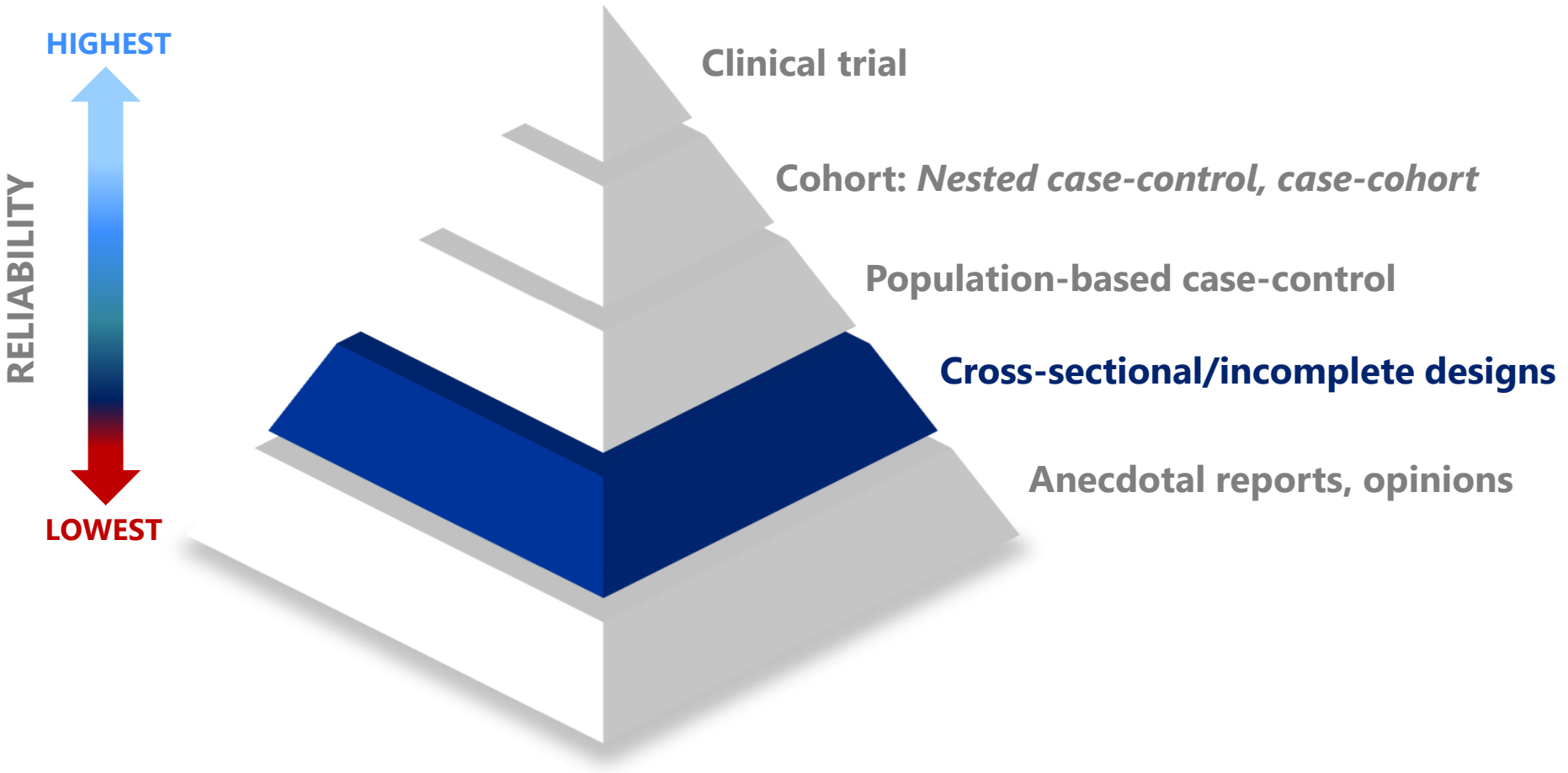
Hierarchy of Epidemiological Evidence



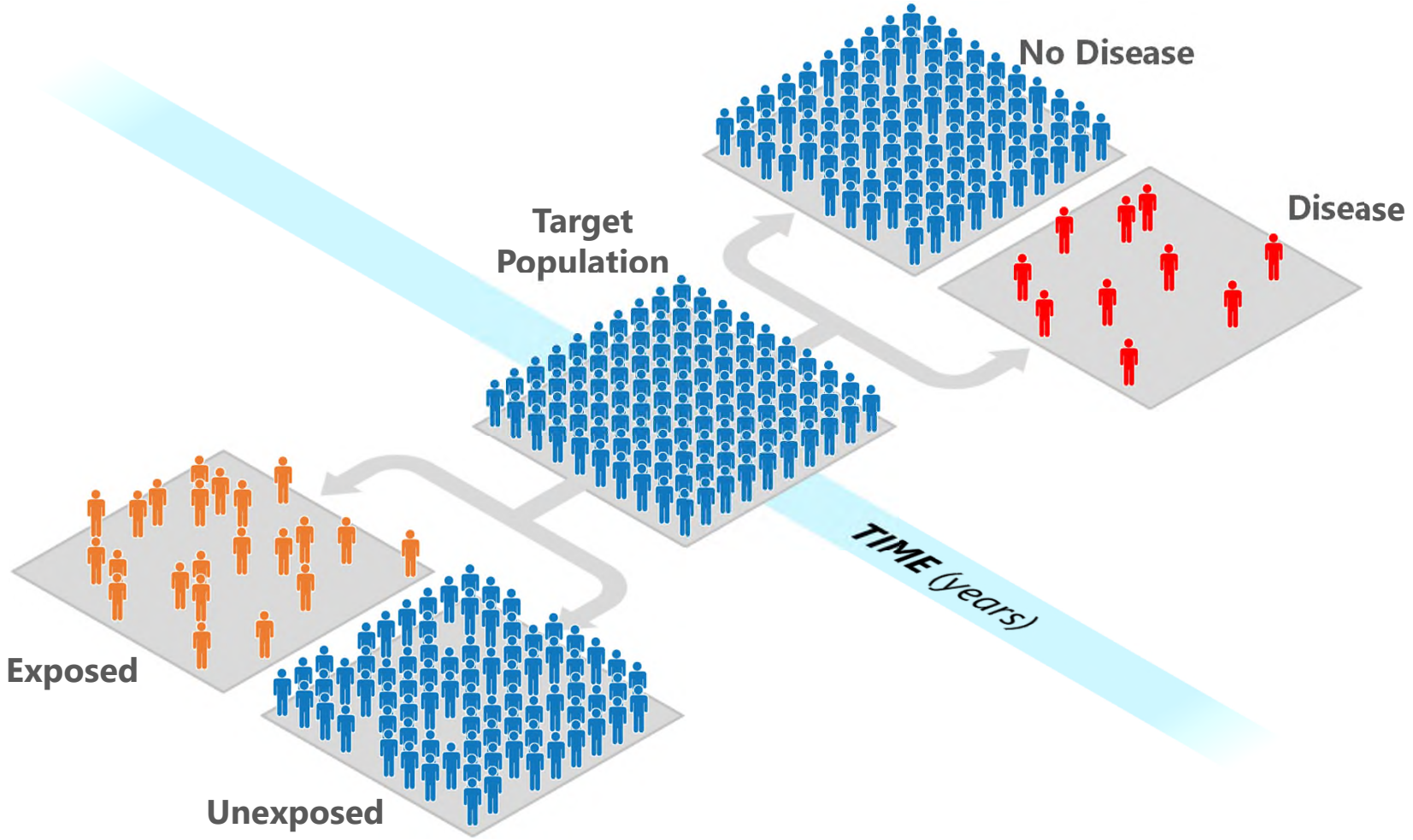
Case-Control Study



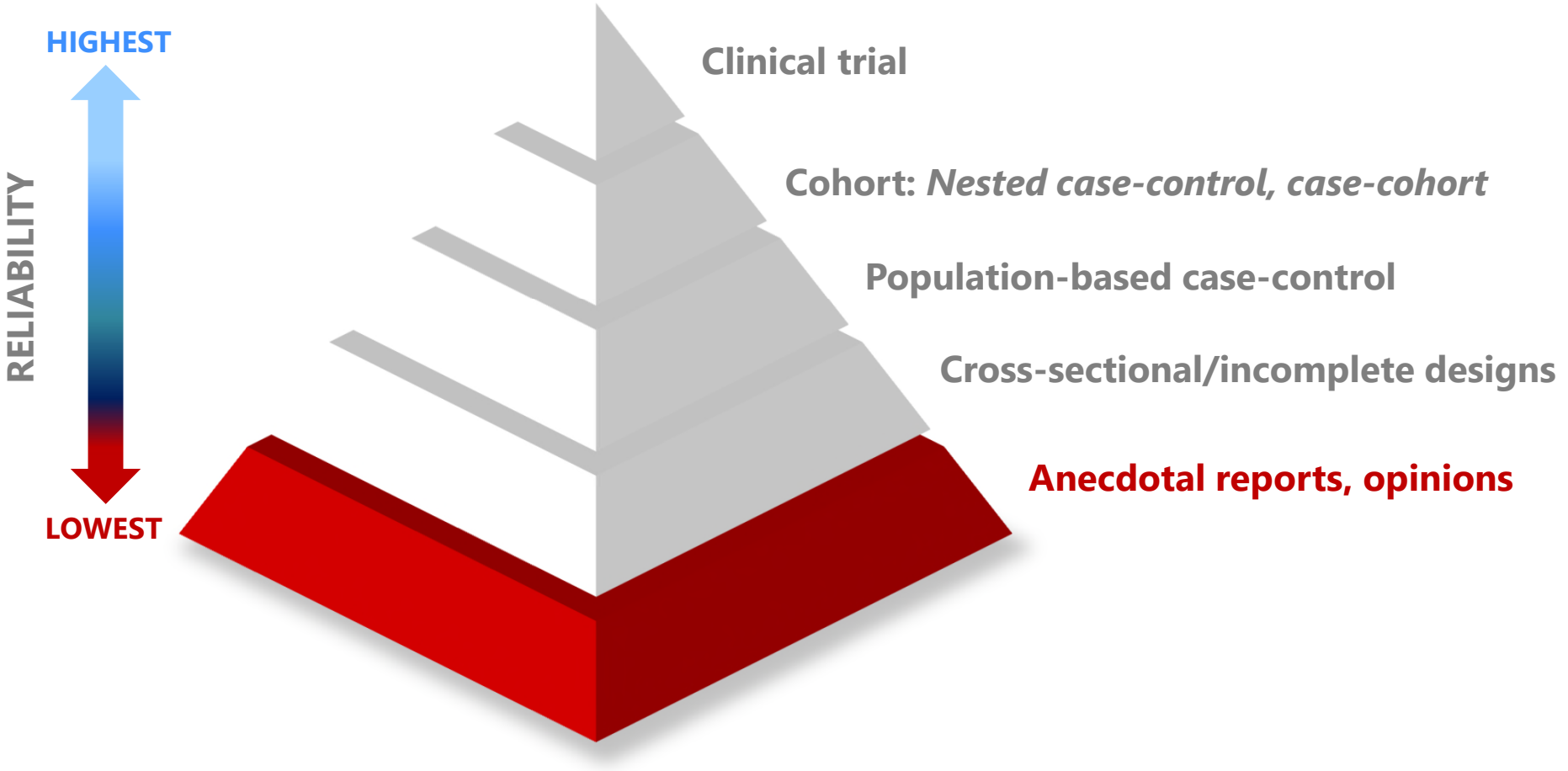
Hierarchy of Epidemiological Evidence



Cross-Sectional Study

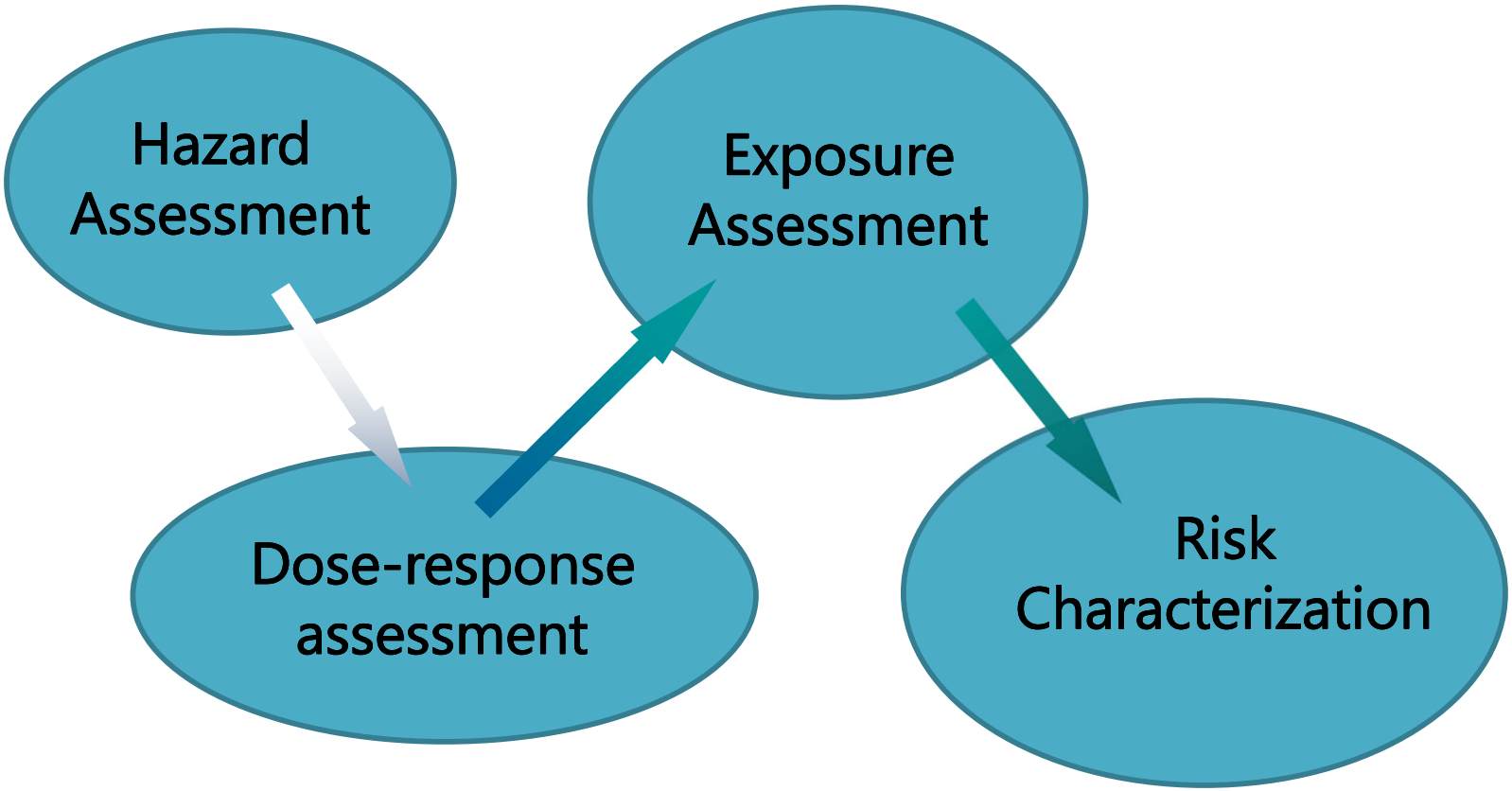


Hierarchy of Epidemiological Evidence



Human health risk assessment

Globally Accepted Toxicological Risk Assessment



Examples of guidelines to conduct toxicology risk assessments (there are more)

Cancer – 1986, 1996, 1999, 2003 (draft)

Chemical Mixtures – 1986, 2000 (sup)

Developmental Toxicity – 1991

Ecological Risk Assessment – 1998

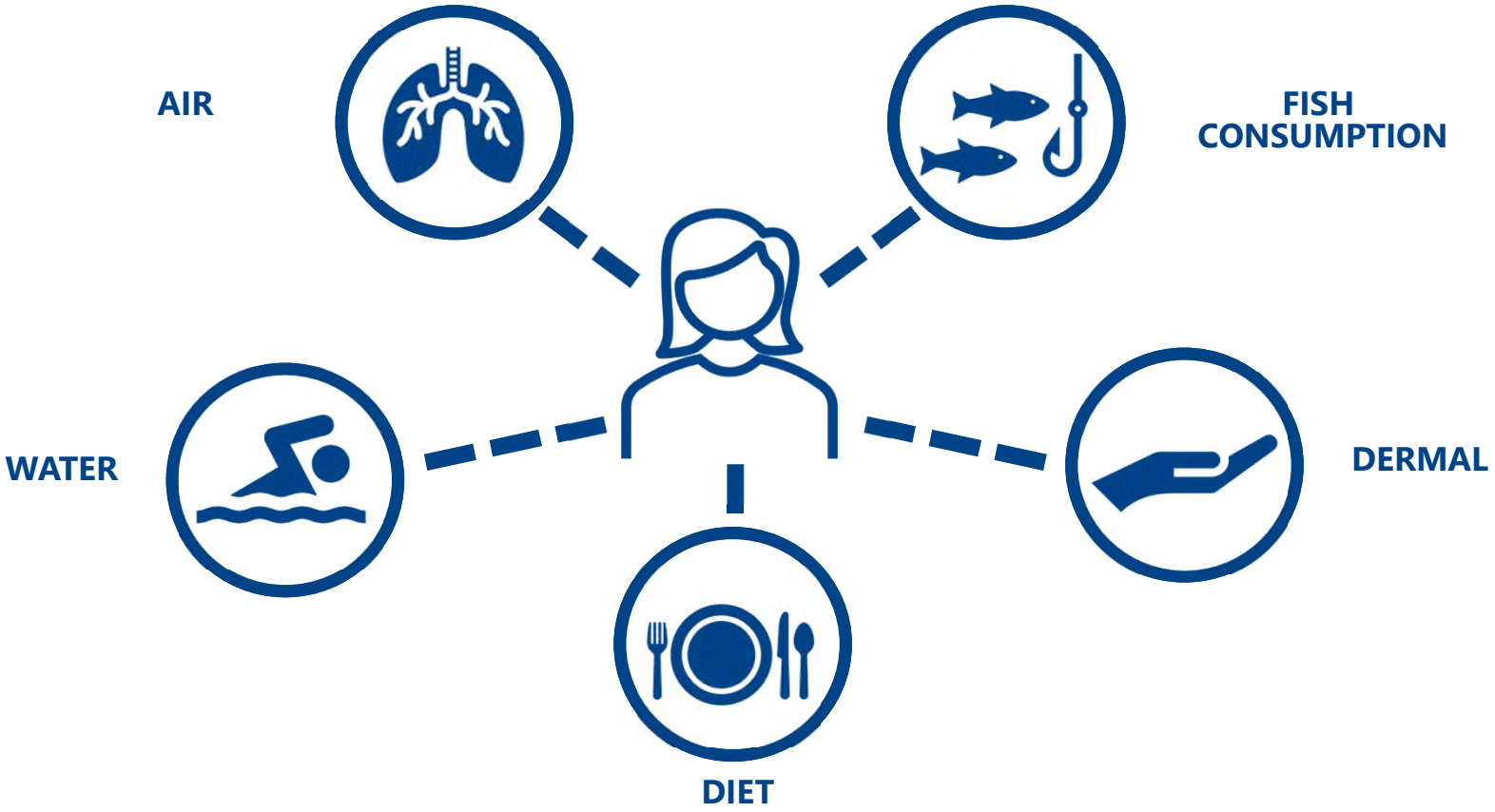
Exposure Assessment – 1992

Mutagenicity – 1998

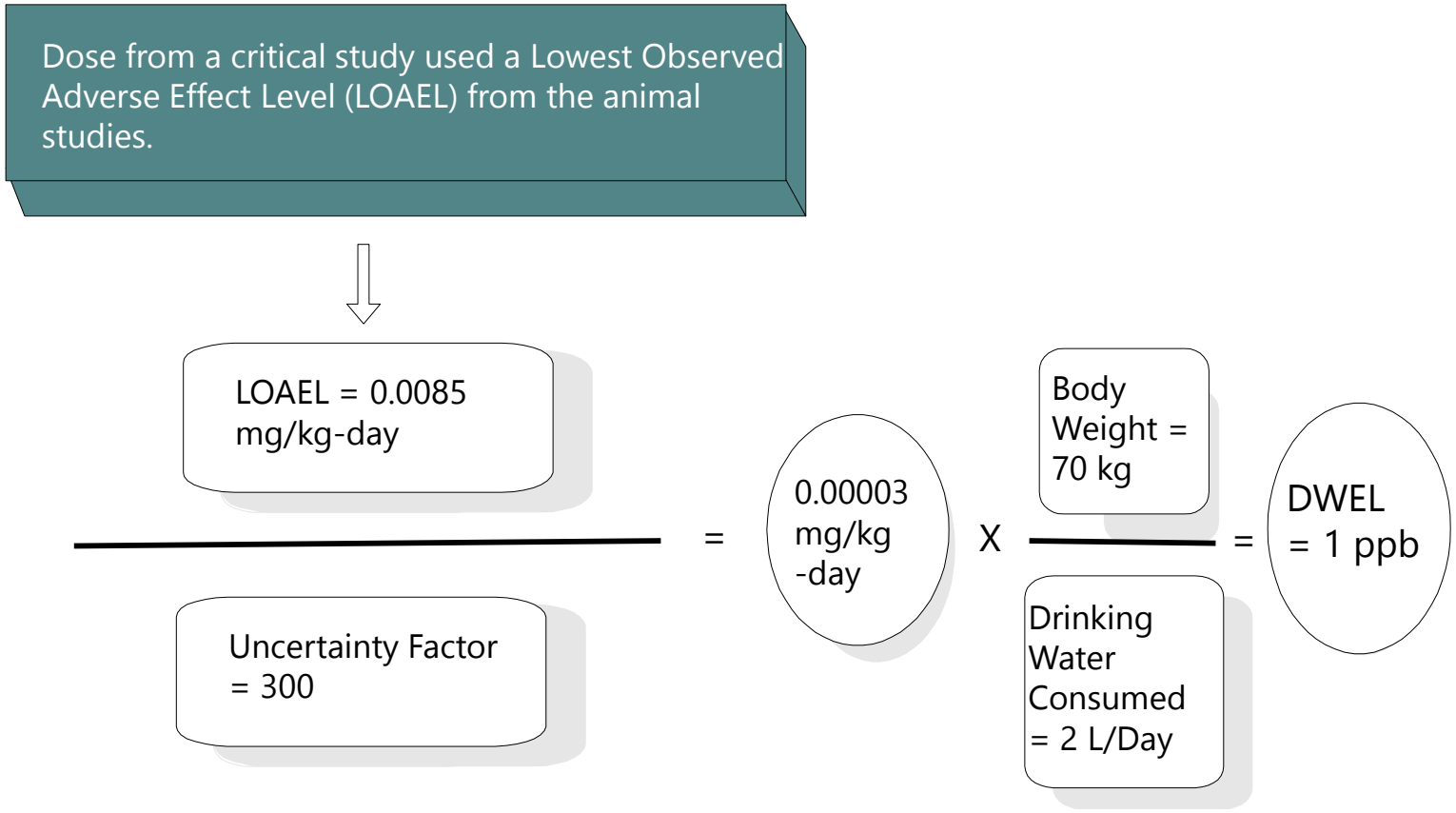
Neurotoxicity – 1998

Reproductive Toxicity - 1996

Risk Assessment: Exposure Parameters



Derivation of Reference Dose (RfD)



EPA Uncertainty Factors: Example

LOAEL: 5000 ng/kg-day

1700 ng/kg-day

÷3

Potential **inter**species **sensitivity differences** between humans and monkeys

170 ng/kg-day

÷10

Potential **intra**species **sensitivity differences** among humans

60 ng/kg-day

÷3

Potential **difference** between the **LOAEL** and the corresponding No Observed Adverse Effect Level **(NOAEL)**

20 ng/kg-day

EPA health protective level

÷3

Extrapolation from sub-chronic **(55 months)** exposure to a chronic reference dose (RfD) were utilized

Cancer risk equation

Basic Risk Equation - Cancer

Risk = (I) * (CSF)

I = Intake (mg/kg/day)

CSF = Cancer Slope Factor $(g/kg/day)^{-1}$)

What are acceptable levels of exposure?

US EPA Guidelines

1×10^{-4}

1×10^{-6} *Deminimis*

Example

Chemical X risk = 2×10^{-6}

Average risk to develop cancer in the US is 1/3 or 0.33

Incremental risk due to exposure to Chemical X

.000002 + 0.333333 = 0.333335

How to develop an acceptable risk guideline

Health Criterion

Rearrange to "solve for" Intake

Intake = Risk * CSF

How to develop an acceptable exposure?

Chemical X Criteria for Acceptable Exposures

$$\text{Criterion} = \frac{\textbf{Risk Level} * \textbf{BW}}{\textbf{CSF} * \textbf{ECR}}$$

Risk Level = 1 X 10^{-6} (One in a million)

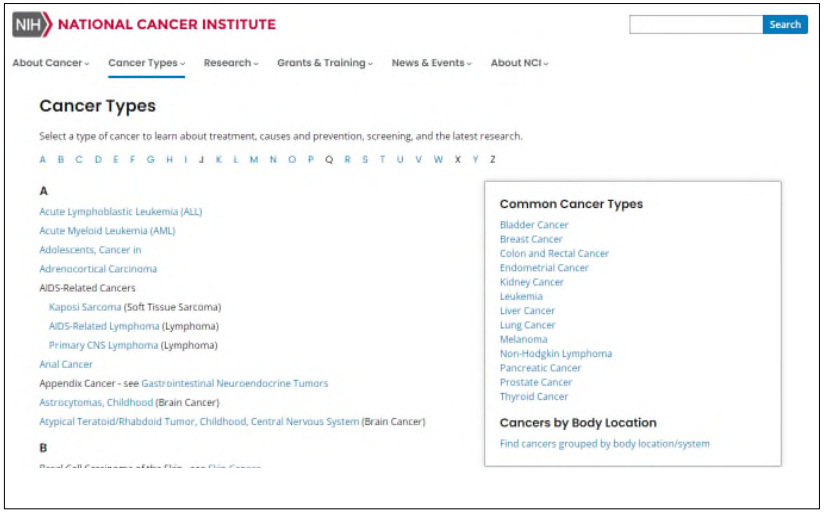
BW = Body Weight = 70 kg

CSF = Cancer Slope Factor = 2.0 $(mg/kg\text{-}day)^{-1}$

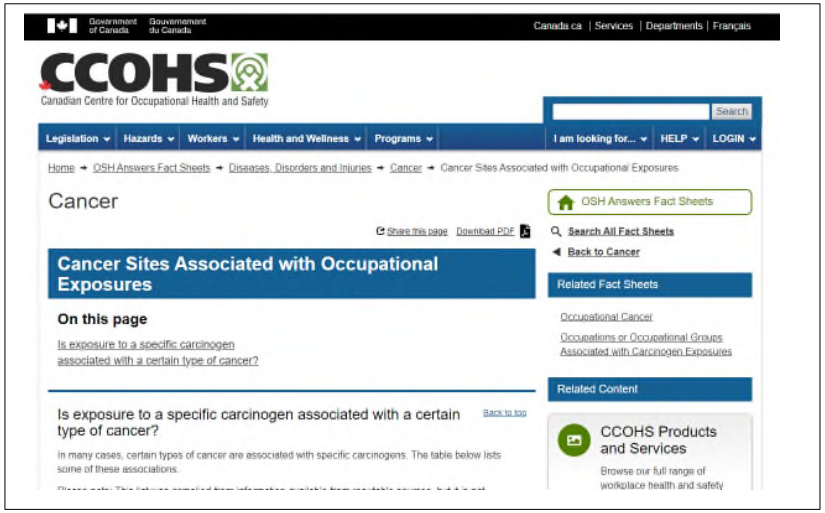
ECR = Exposure Rate = 6.5 g/day

Uncertainty, what does that mean?

Lists of cancers and associations with agents



https://www.cancer.gov/types



https://www.ccohs.ca/oshanswers/diseases/carcinogen_site.html

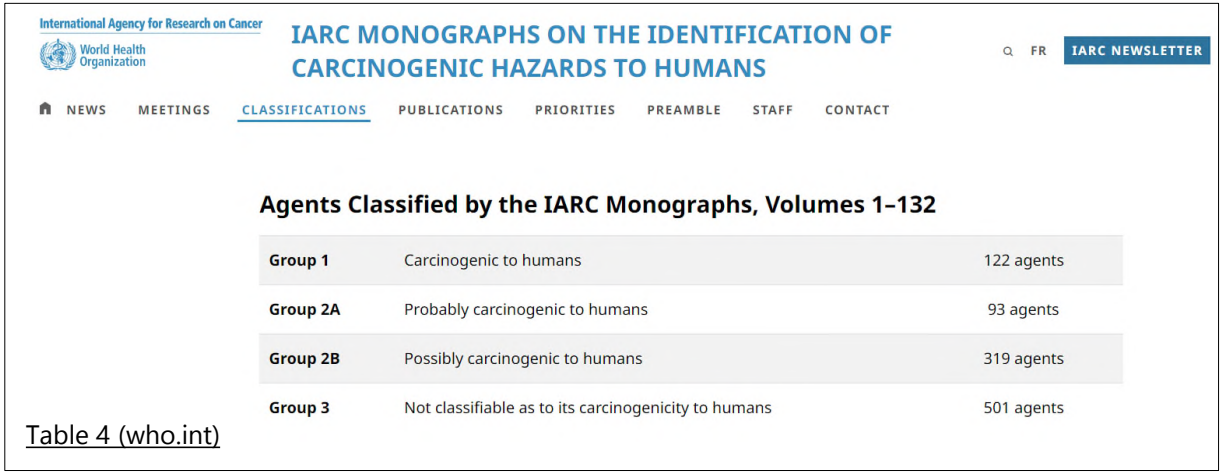


Table 4 (who.int)

OSHA: 29 CFR 1990

Category	Definition
I	substance meets the definition of a potential occupational carcinogen in (1) humans, or (2) in a single mammalian species in a long-term bioassay where the results are in concordance with some other scientifically evaluated evidence of a potential carcinogenic hazard, or (3) in a single mammalian species in an adequately conducted long-term bioassay, in appropriate circumstances where the Secretary determines the requirement for concordance is not necessary.
II	The substance meets the criteria set forth in 1990.112(a), but the evidence is found by the Secretary to be only "suggestive"; or the substance meets the criteria set forth in 1990.112(a) in a single mammalian species without evidence of concordance.

Group	Description	Definition	Number of agents
Group 1	Carcinogenic to humans	• Sufficient evidence of carcinogenicity OR • Evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity	121
Group 2A	Probably carcinogenic to humans*	•Limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals OR •Inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans OR •Limited evidence of carcinogenicity in humans, but belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A	89
Group 2B	Possibly carcinogenic to humans*	• Limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals OR • Inadequate evidence of carcinogenicity in humans but sufficient evidence of carcinogenicity in experimental animals OR • Inadequate evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals, but with supporting evidence from mechanistic and other relevant data	318
Group 3	Not classifiable as to its carcinogenicity to humans	• Evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals OR • Evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals, but strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans OR • Agents that do not fall into any other group • Agents in Group 3 are not determined to be non-carcinogenic or safe overall, but often means that further research is needed.	499
Group 4	Probably not carcinogenic to humans	• Evidence suggesting lack of carcinogenicity in humans and in experimental animals OR • Inadequate evidence of carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data	1

Update: 3/26/2021

Environmental Protection Agency

The US Environmental Protection Agency (EPA) maintains the Integrated Risk Information System (IRIS), an electronic database that contains information on human health effects from exposure to certain substances in the environment.

The EPA uses a rating system similar to that of IARC when describing the cancer-causing potential of a substance:

Group A: Carcinogenic to humans

Group B: Likely to be carcinogenic to humans

Group C: Suggestive evidence of carcinogenic potential

Group D: Inadequate information to assess carcinogenic potential

Group E: Not likely to be carcinogenic to humans

OSHA Regulated Carcinogens

- asbestos
- 4-Nitrobiphenyl
- alpha-Naphthylamine
- Methyl chloromethyl ether
- 3,3'-Dichlorobenzidine (and its salts)
- bis-Chloromethyl ether
- beta-Naphthylamine
- Benzidine
- 4-Aminodiphenyl
- Ethyleneimine
- beta-Propiolactone
- 2-Acetylaminofluorene
- 4-Dimethylaminoazobenzene
- N-Nitrosodimethylamine
- Vinyl chloride
- Inorganic arsenic
- Cadmium
- Benzene
- Coke oven emissions
- 1,2-dibromo-3-chloropropane
- Acrylonitrile
- Ethylene oxide
- Formaldehyde
- Methylenedianiline
- 1,3-Butadiene
- Methylene Chloride

List of Classifications by cancer sites with *sufficient* or *limited evidence* in humans, Volumes 1 to 125[a]

Cancer site	Carcinogenic agents with *sufficient evidence* in humans	Agents with *limited evidence* in humans
Lip, oral cavity, and pharynx		
Lip		Hydrochlorothiazide Solar radiation
Oral cavity	Alcoholic beverages Betel quid with tobacco Betel quid without tobacco Human papillomavirus type 16 Tobacco, smokeless Tobacco smoking	Human papillomavirus type 18
Salivary gland	X-radiation, gamma-radiation	Radioiodines, including Iodine-131
Tonsil	Human papillomavirus type 16	
Pharynx	Alcoholic beverages Betel quid with tobacco Human papillomavirus type 16 Tobacco smoking	Asbestos (all forms) Printing processes Tobacco smoke, secondhand
Nasopharynx	Epstein-Barr virus Formaldehyde Salted fish, Chinese-style Tobacco smoking Wood dust	
Digestive tract, upper	Acetaldehyde associated with consumption of alcoholic beverages	
Digestive organs		
Oesophagus	Acetaldehyde associated with consumption of alcoholic beverages Alcoholic beverages Betel quid with tobacco Betel quid without tobacco Tobacco, smokeless Tobacco smoking X-radiation, gamma-radiation	Dry cleaning Pickled vegetables (traditional Asian) Rubber production industry Very hot beverages (squamous cell carcinoma)

List of Classifications by cancer sites with *sufficient* or *limited evidence* in humans, Volumes 1 to 125[a]

Cancer site	Carcinogenic agents with *sufficient evidence* in humans	Agents with *limited evidence* in humans
Stomach	*Helicobacter pylori* Rubber production industry Tobacco smoking X-radiation, gamma-radiation	Asbestos (all forms) Epstein-Barr virus Lead compounds, inorganic Nitrate or nitrite (ingested) under conditions that result in endogenous nitrosation Pickled vegetables (traditional Asian) Processed meat (consumption of) Salted fish, Chinese-style
Colon and rectum	Alcoholic beverages Processed meat (consumption of) Tobacco smoking X-radiation, gamma-radiation	Asbestos (all forms) Night shift work Red meat (consumption of) *Schistosoma japonicum*
Anus	Human immunodeficiency virus type 1 Human papillomavirus type 16	Human papillomavirus types 18, 33
Liver and bile duct	Aflatoxins Alcoholic beverages *Clonorchis sinensis* 1,2-Dichloropropane Estrogen-progestogen contraceptives Hepatitis B virus Hepatitis C virus *Opisthorchis viverrini* Plutonium Thorium-232 and its decay products Tobacco smoking (in smokers and in smokers' children) Vinyl chloride	Androgenic (anabolic) steroids Arsenic and inorganic arsenic compounds Betel quid without tobacco DDT Dichloromethane (Methylene chloride) Human immunodeficiency virus type 1 *Schistosoma japonicum* Trichloroethylene X-radiation, gamma-radiation
Gall bladder	Thorium-232 and its decay products	
Pancreas	Tobacco, smokeless Tobacco smoking	Alcoholic beverages Red meat (consumption of) Thorium-232 and its decay products X-radiation, gamma-radiation

List of Classifications by cancer sites with *sufficient* or *limited evidence* in humans, Volumes 1 to 125[a]

Cancer site	Carcinogenic agents with *sufficient evidence* in humans	Agents with *limited evidence* in humans
Digestive tract, unspecified		Radioiodines, including Iodine-131
Respiratory organs		
Nasal cavity and paranasal sinus	Isopropyl alcohol manufacture using strong acids Leather dust Nickel compounds Radium-226 and its decay products Radium-228 and its decay products Tobacco smoking Wood dust	Carpentry and joinery Chromium(VI) compounds Formaldehyde Textile manufacturing
Larynx	Acid mists, strong inorganic Alcoholic beverages Asbestos (all forms) Tobacco smoking	Human papillomavirus type 16 Rubber production industry Sulfur mustard Tobacco smoke, secondhand
Lung	Acheson process, occupational exposures associated with Aluminium production Arsenic and inorganic arsenic compounds Asbestos (all forms) Beryllium and beryllium compounds Bis(chloromethyl)ether; chloromethyl methyl ether (technical grade) Cadmium and cadmium compounds Chromium(VI) compounds Coal, indoor emissions from household combustion Coal gasification Coal-tar pitch Coke production Engine exhaust, diesel Hematite mining (underground) Iron and steel founding MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture) Nickel compounds	Acid mists, strong inorganic Art glass, glass containers and pressed ware (manufacture of) Benzene Biomass fuel (primarily wood), indoor emissions from household combustion of Bitumens, occupational exposure to oxidized bitumens and their emissions during roofing Bitumens, occupational exposure to hard bitumens and their emissions during mastic asphalt work Carbon electrode manufacture *alpha*-Chlorinated toluenes and benzoyl chloride (combined exposures) Cobalt metal with tungsten carbide Creosotes

List of Classifications by cancer sites with *sufficient* or *limited evidence* in humans, Volumes 1 to 125[a]

Cancer site	Carcinogenic agents with *sufficient evidence* in humans	Agents with *limited evidence* in humans
	Outdoor air pollution Painting Particulate matter in outdoor air pollution Plutonium Radon-222 and its decay products Rubber production industry Silica dust, crystalline Soot Sulfur mustard Tobacco smoke, secondhand Tobacco smoking Welding fumes X-radiation, gamma-radiation	Diazinon Fibrous silicon carbide Frying, emissions from high-temperature Hydrazine Insecticides, non-arsenical, occupational exposures in spraying and application Printing processes 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin
Bone, skin, and mesothelium, endothelium, and soft tissue		
Bone	Plutonium Radium-224 and its decay products Radium-226 and its decay products Radium-228 and its decay products X-radiation, gamma-radiation	Radioiodines, including Iodine-131
Skin (melanoma)	Polychlorinated biphenyls Solar radiation Ultraviolet-emitting tanning devices	
Skin (other malignant neoplasms)	Arsenic and inorganic arsenic compounds Azathioprine Coal-tar distillation Coal-tar pitch Cyclosporine Methoxsalen plus ultraviolet A Mineral oils, untreated or mildly treated Shale oils Solar radiation Soot X-radiation, gamma-radiation	Creosotes Human immunodeficiency virus type 1 Human papillomavirus types 5 and 8 (in patients with *epidermodysplasia verruciformis*) Hydrochlorothiazide Merkel cell polyomavirus (MCV) Nitrogen mustard Petroleum refining, occupational exposures

List of Classifications by cancer sites with *sufficient* or *limited evidence* in humans, Volumes 1 to 125[a]

Cancer site	Carcinogenic agents with *sufficient evidence* in humans	Agents with *limited evidence* in humans
		Ultraviolet-emitting tanning devices
Mesothelium (pleura and peritoneum)	Asbestos (all forms) Erionite Fluoro-edenite Painting	
Endothelium (Kaposi sarcoma)	Human immunodeficiency virus type 1 Kaposi sarcoma herpesvirus	
Soft tissue		Polychlorophenols or their sodium salts (combined exposures) Radioiodines, including iodine-131 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin
Breast and female genital organs		
Breast	Alcoholic beverages Diethylstilbestrol Estrogen-progestogen contraceptives Estrogen-progestogen menopausal therapy X-radiation, gamma-radiation	Dieldrin Digoxin Estrogen menopausal therapy Ethylene oxide Night shift work Polychlorinated biphenyls Tobacco smoking
Vulva	Human papillomavirus type 16	Human immunodeficiency virus type 1 Human papillomavirus types 18, 33
Vagina	Diethylstilbestrol (exposure in utero) Human papillomavirus type 16	Human immunodeficiency virus type 1

List of Classifications by cancer sites with *sufficient* or *limited evidence* in humans, Volumes 1 to 125[a]

Cancer site	Carcinogenic agents with *sufficient evidence* in humans	Agents with *limited evidence* in humans
Uterine cervix	Diethylstilbestrol (exposure in utero) Estrogen-progestogen contraceptives Human immunodeficiency virus type 1 Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 Tobacco smoking	Human papillomavirus types 26, 53, 66, 67, 68, 70, 73, 82
Endometrium	Estrogen menopausal therapy Estrogen-progestogen menopausal therapy Tamoxifen	Diethylstilbestrol
Ovary	Asbestos (all forms) Estrogen menopausal therapy Tobacco smoking	Talc-based body powder (perineal use) X-radiation, gamma-radiation
Male genital organs		
Penis	Human papillomavirus type 16	Human immunodeficiency virus type 1 Human papillomavirus type 18
Prostate		Androgenic (anabolic) steroids Arsenic and inorganic arsenic compounds Cadmium and cadmium compounds Firefighters, occupational exposure Malathion Night shift work Red meat (consumption of) Rubber production industry Thorium-232 and its decay products X-radiation, gamma-radiation
Testis		DDT Diethylstilbestrol (exposure in utero)

List of Classifications by cancer sites with *sufficient* or *limited evidence* in humans, Volumes 1 to 125[a]

Cancer site	Carcinogenic agents with *sufficient evidence* in humans	Agents with *limited evidence* in humans
		N,*N*-Dimethylformamide Firefighters, occupational exposure Perfluorooctanoic acid
Urinary tract		
Kidney	Tobacco smoking Trichloroethylene X-radiation, gamma-radiation	Arsenic and inorganic arsenic compounds Cadmium and cadmium compounds Perfluorooctanoic acid Printing processes Welding fumes
Renal pelvis and ureter	Aristolochic acid, plants containing Phenacetin Phenacetin, analgesic mixtures containing Tobacco smoking	Aristolochic acid
Urinary bladder	Aluminium production 4-Aminobiphenyl Arsenic and inorganic arsenic compounds Auramine production Benzidine Chlornaphazine Cyclophosphamide Magenta production 2-Naphthylamine Painting Rubber production industry *Schistosoma haematobium* Tobacco smoking *ortho*-Toluidine X-radiation, gamma-radiation	4-Chloro-*ortho*-toluidine Coal-tar pitch Dry cleaning Engine exhaust, diesel Hairdressers and barbers, occupational exposure 2-Mercaptobenzothiazole Pioglitazone Printing processes Soot Tetrachloroethylene Textile manufacturing

List of Classifications by cancer sites with *sufficient* or *limited evidence* in humans, Volumes 1 to 125[a]

Cancer site	Carcinogenic agents with *sufficient evidence* in humans	Agents with *limited evidence* in humans
Eye, brain, and central nervous system		
Eye	Human immunodeficiency virus type 1 Ultraviolet radiation from welding Ultraviolet-emitting tanning devices	Solar radiation
Brain and central nervous system	X-radiation, gamma-radiation	Radiofrequency electromagnetic fields (including from wireless phones)
Endocrine glands		
Thyroid	Radioiodines, including Iodine-131 X-radiation, gamma-radiation	
Lymphoid, hematopoietic, and related tissue		
Leukaemia and/or lymphoma	Azathioprine Benzene[b] Busulfan 1,3-Butadiene Chlorambucil Cyclophosphamide Cyclosporine Epstein-Barr virus Etoposide with cisplatin and bleomycin Fission products, including Strontium-90 Formaldehyde *Helicobacter pylori* Hepatitis C virus Human immunodeficiency virus type 1 Human T-cell lymphotropic virus type 1 Kaposi sarcoma herpesvirus Lindane Melphalan MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture) Pentachlorophenol Phosphorus-32 Rubber production industry	Benzene[b] Bischloroethyl nitrosourea (BCNU) Chloramphenicol DDT Diazinon Dichloromethane (Methylene chloride) Ethylene oxide Etoposide Firefighters, occupational exposure Glyphosate Hepatitis B virus Magnetic fields, extremely low frequency (childhood leukaemia) Malaria (caused by infection with *Plasmodium falciparum* in holoendemic areas) Malathion Mitoxantrone Nitrogen mustard Painting (childhood leukaemia

List of Classifications by cancer sites with *sufficient* or *limited evidence* in humans, Volumes 1 to 125[a]

Cancer site	Carcinogenic agents with *sufficient evidence* in humans	Agents with *limited evidence* in humans
	Semustine (methyl-CCNU) Thiotepa Thorium-232 and its decay products Tobacco smoking Treosulfan X-radiation, gamma-radiation	from maternal exposure) Petroleum refining, occupational exposures Polychlorinated biphenyls Polychlorophenols or their sodium salts (combined exposures) Radioiodines, including Iodine-131 Radon-222 and its decay products Styrene Teniposide 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin Tobacco smoking (childhood leukaemia in smokers' children) Trichloroethylene
Multiple or unspecified sites		
Multiple sites (unspecified)	Cyclosporine Fission products, including strontium-90 X-radiation, gamma-radiation (exposure in utero)	Chlorophenoxy herbicides Plutonium
All cancer sites (combined)	2,3,7,8-Tetrachlorodibenzo-*para*-dioxin	

[a] This table does not include factors not covered in the *IARC Monographs*, notably genetic traits, reproductive status, and some nutritional factors.

[b] For benzene, the evidence in humans is sufficient for acute non-lymphocytic leukaemia, including acute myeloid leukaemia; and the evidence in humans is limited for non-Hodgkin lymphoma, chronic lymphoid leukaemia, multiple myeloma, chronic myeloid leukaemia, and acute myeloid leukaemia in children

Adapted from Table 4 in Cogliano *et al.* (2011) available at: http://jnci.oxfordjournals.org/content/early/2011/12/11/jnci.djr483.short?rss=1

Last update: 29 November 2019

Preventing Exposure

Levels of prevention in the workplace

- Engineering controls
- Work Practice controls
- Administrative controls
- Personal Protective Equipment (PPE)

Principles for the introduction of population screening (WHO)

The condition should be an **important** health problem

There should be a **recognizable latent or early symptomatic stage**

The **natural history** of the condition, including development from latent to declared disease, should be adequately understood

There should be an **accepted treatment** for patients with recognized disease

There should be a **suitable test or examination** that has a high level of accuracy

There should be an **agreed policy on whom to treat** as patients

Facilities for diagnosis and treatment should be available

Sensitivity

Specificity

Cancer Council of Australia National Cancer Control Policy https://wiki.cancer.org.au/policy/Principles_of_screening

Assessing Risk of Exposure

Patient history
Occupations
Onset, Length
Chemicals / Processes
Carcinogenic?
Intensity of exposure
Other Explanations? Causes?

Assessment of the Exposed

Observation
Palpation
Lab work
Imaging
Histology

Causality

Sir Bradford Hill's ~~criteria~~ Guidelines

Strength of association

Consistency

Specificity

Temporality

Biological gradient

Plausibility

Coherence

Experiment

Analogy

Hill, 1965