What are Chemicals?

Everything in your life except light, radiation and sound waves.

Chemicals are plants, food, cars, other living things

Rachel Carson	**1962**
Clean Water Act	**1972**
Clean Air Act	**1970**
Resource Conservation & Recovery Act	**1976**
Toxic Substances Control Act	**1976**

Comprehensive Environmental Response, Compensation and Liability Act CERCLA (Superfund) 1980

Worker Right to Know	**1986**
Superfund Amendments and Reauthorization Act (SARA)	**1986**

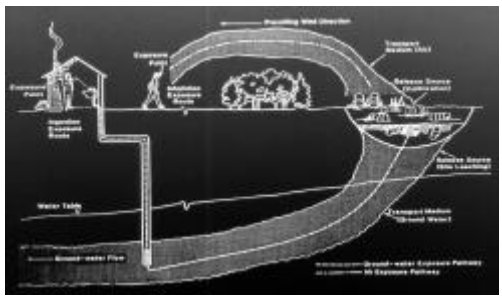
Chemical-Induced Effects

- **Acute- mucous membrane irritation, drowsiness-immediate/transient**
- **Delayed-hepatotoxicity- 48/72 hours**
- **Chronic toxicity-cirrhosis of the liver**
- **Carcinogenicity-hepatocarcinoma**

Chemical-Induced Effects

(cont.)

- **Mutagenicity- germ cells/somatic cells**
- **Teratogenicity- birth defects**
- **Organ toxicity:**
  - **Neurotoxicity**
  - **Hepatotoxicity**



As Stated by Admiral Crowe:

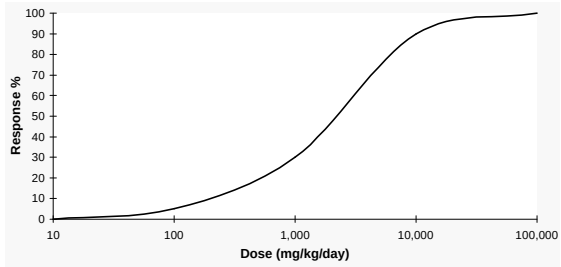
The Hallmark of an educated person is the ability, when facts warrant to change one's mind.

F Admiral William Crowe
- Retired Chairman of the Joint Chiefs of Staff

The number of storks in Europe has been decreasing for decades. At the same time, the European birth rate has also been decreasing. We would be foolish to accept this high correlation as evidence that storks bring babies.

Doses of Common Substances

Example of a Dose-Response Curve



What concentration of chemicals in air, water, soil, food, consumer products are safe?

Chemicals produce specific effects and these are dose related.

R = T x E

Risk = Toxicity x Exposure

where

T = toxicity of a specific chemical

E = amount of exposure a population has to a specified chemical

Problem Statement

Acceptable risk levels

Public alarmist reaction to any risk

Placing risk in perspective

Types of Risk Assessments

Linear: Used to portray the risk of carcinogenicity

Threshold: Used to model all other forms of toxicity

Actual Toxicity and Ranking

Agents	LD_{50}	Expected Human Dose
PCBs	14,000	1 Quart
Alcohol	10,000	1 Pint-1 Quart
Table salt	4,000	1 Pint
Iron	1,500	1 Ounce-1 Pint
DDT	100	1 Teaspoon-1 Ounce
Strychnine	2	4 Drops
Nicotine	1	1 Drop
TCDD	0.001	Less Than 1 Drop
Botulinus toxin	0.00001	Less Than 1 Drop

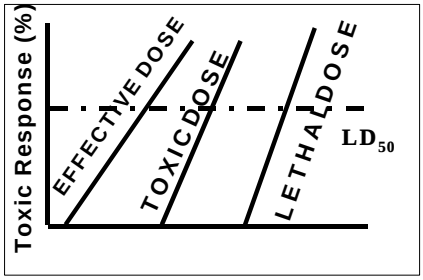
	Teratogenicity	Mutagenicity	Carcinogenicity
1. Insidious Nature (Cause is Mild Relative to the Effect)	Yes	Yes	Yes
2. Duration and Time Between Cause and Effect	Weeks	Generations	Years
3. Irreversible	Yes	Yes	Yes
4. Greater Susceptibility of Immature Tissues	Yes	No	Yes/No
5. Differences	Altered Develop-at Tissue/ Organ Level	Altered Nucleotide Sequence-Molecular Level: DNA	Uncontrolled ment Proliferation at Cellular Level

Hazard Identification-

What adverse health effects can the chemical produce?

Hazard Evaluation-

what are the dose response relationships for the adverse health effects?



Sources of Toxicity Information

Material Safety Data Sheets (MSDS)
Integrated Risk Information System (IRIS)
Hazardous Substances Database (HSDB)

Arsenic trioxide MSDS

Route of entry
- F **inhalation: yes**
- F **skin: yes**
- F **ingestion: yes**

Carcinogenicity
- F **NTP: yes**
- F **IARC: yes**
- F **OSHA: yes**

F **symptoms may include chest pain, dyspnea, pulmonary edema, cyanosis, giddiness, restlessness, lassitude, headache, hypotension**

Arsenic trioxide MSDS

Emergency/First Aid Procedure

- **inhalation: remove to fresh air, artificial respiration or oxygen**
- **skin: may cause itching, burning, sensitization**
- **ingestion: lethal dose is 120 mg**

Chloroform MSDS

Route of entry

- **inhalation: yes**
- **skin: yes**
- **ingestion: yes**

Carcinogenicity

- **NTP: no**
- **IARC: yes**
- **OSHA: no**

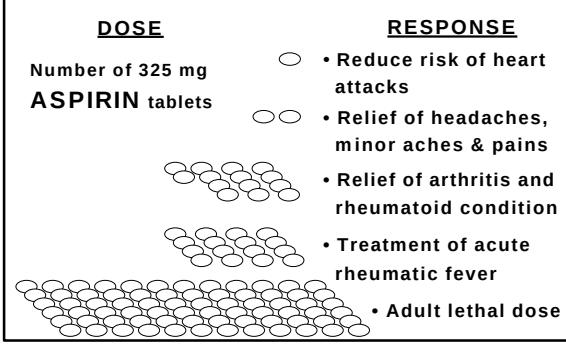
- **exposure may cause burns, nausea, headache, dizziness, vomiting, severe inflammation, swelling, disorientation**

Chloroform MSDS

Emergency/First Aid Procedure

- **inhalation: remove to fresh air, artificial respiration or oxygen**
- **skin: flush with water 15-20 min.**
- **ingestion: induce vomiting**

An Example of Dose and Response



Risk Assessment

--is the process used to determine if there is excess risk, above that allowed by public policy

The four basic components of risk assessment include:

- **Hazard Identification**
- **Hazard Evaluation**
- **Exposure Evaluation**
- **Risk Estimation**

R = T x E

Risk = Toxicity x Exposure

where

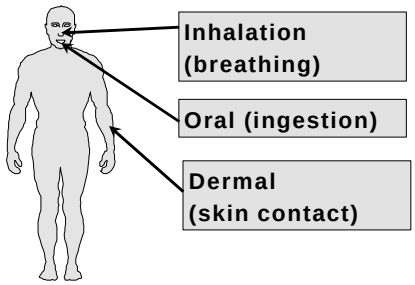
T= toxicity of a specific chemical

E= amount of exposure a population has to a specific chemical

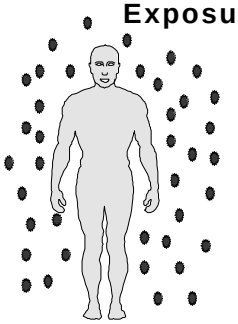
TOXICITY

is a measure of the potential of a substance to produce a harmful effect on a living system.

Three Pathways through which People Can Be Exposed to Chemicals:



The Difference Between Exposure and Dose



Exposure = opportunity for contact

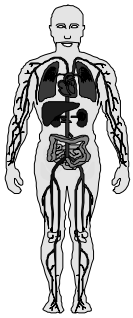
The Difference Between Exposure and Dose

Dose = the amount of a chemical in the body

Exposure Evaluation

- Absorption
- Distribution
- Metabolism
- Execretion

Absorption Distribution Metabolism Excretion



Absorption into gastrointestinal tract, lungs, and through the skin

Distribution from blood stream to rest of body, including fat, brain, liver

Metabolism X —*enzymes*→ Y

x = absorbed, distributed chemical
y = metabolite

Excretion via exhaled breath; from liver through bile/feces; from kidneys through urine

The HALF-LIFE

of a chemical in the body is defined as the amount of time it takes the body to get rid of ONE HALF of an amount of the chemical.

Biological Half-Life

CHEMICALS	HALF-LIFE (in humans unless otherwise noted)
Benzene	1-3 hours
Cadmium	10-30 years
Caffeine	3.5 hours
Ethanol	2-4 hours
Toluene	72 hours (whole blood)
Ethylbenzene	4-7 hours (for metabolite)
Xylene	20-30 hours
Tetrachlorethylene	33-72 hours

CHEMICALS OF CONCERN =

chemical species studied in detail in the risk assessment process

Since different chemicals cause different types of health effects, results of the risk assessment are different for each different type of health effect.

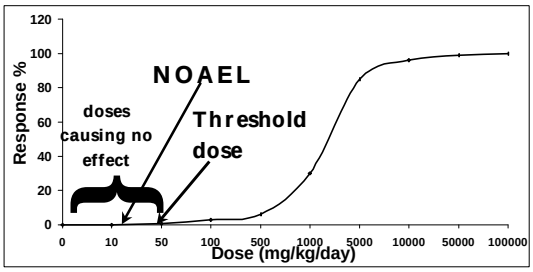
Type 1:

Chemicals that Cause Health Effects After Chronic Exposures

- **Threshold = Dose below which no effect is seen**
- **NOAEL = No Observable Adverse Effect Level**

Chronic Toxicity

Threshold/NOAEL



What is a Safe Dose? Who Determines that Value?

- Safe Values are set by public policy to be protective of the public health
  - IRIS (Integrated Risk Information System, USEPA)
  - HEAST (Health Effects Assessment Summary Tables, USEPA)

What is a safe dose? Who determines that value?

- Values are called Reference Doses (ingestion and dermal pathways) -- RfD
- Reference Concentrations (for the inhalation pathway) -- RfC

$RfD = \frac{NOAEL}{(UF \times MF)}$

Where: UF = Uncertainty Factor

MF = Modifying Factor

Because the threshold dose value is difficult to know for certain, the UF and MF provide a factor of safety that is protective of the public health.

Safety Factor = SF

Multiples of 10

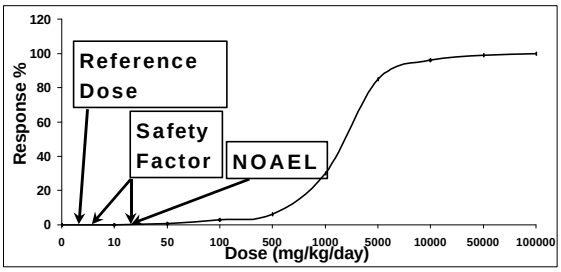
Accounts for:

- uncertainty in using animal studies to determine doses for humans
- variation in susceptibility among people exposed
- professional judgment and knowledge of the substance itself

Does the Safety Factor Work?

YES.

Chronic Toxicity
Safety Factor/Reference Dose



Hazard Quotient

- a method to assess whether a dose may potentially have a health effect
- ratio of exposure (dose) of a substance to the reference dose (RfD) for that substance

Generalized Hazard Quotient Equation

$$\text{Hazard Quotient} = \frac{CC \cdot CR \cdot CF \cdot EF \cdot ED}{BW \cdot AT} \Big/ RfD$$

RfD: reference dose
CC: Conc. of contaminants
CR: contact rate
CF: conversion factor
ED: exposure duration
AT: averaging time
EF: exposure frequency
BW: body weight

$$\text{Hazard Quotient} = \frac{\text{Dose (mg/kg/day)}}{\text{RfD (mg/kg/day)}}$$

If the hazard quotient is greater than one (a person is exposed to more of the substance than is acceptable under public policy), there is a *possibility* that a health effect may occur.

Hazard Index

- Calculated as sum of hazard quotients
- Hazard Index = sum of Hazard Quotients (individual organ or system)
- Used when potential exists for exposure to more than one substance that may affect a specific target organ or organ systems

Results of the Risk Assessment for Chemicals Causing Health Effects After Chronic Exposures:

The Answer is NOT:

- **A Number**
- **A Probability**
- **A "Yes"/"No"**

The Answer IS:

- **"Maybe"/"No"**

TYPE 2:

CARCINOGENIC CHEMICALS

EPA Weight-of-Evidence Classification System

Group A. Human Carcinogen--indicates that there is sufficient evidence from epidemiological studies to support a cause-effect relationship between substance and cancer.

Group B. Probable Human Carcinogen--
B_1: classified on the basis of sufficient evidence from animal studies and limited epidemiological evidence
B_2: classified on basis of sufficient evidence from animal studies and epidemiological data that is inadequate or non-existent

EPA Weight-of-Evidence Classification System (cont.)

Group C. Possible Human Carcinogen--indicates that there is limited evidence from animal studies and no epidemiological data

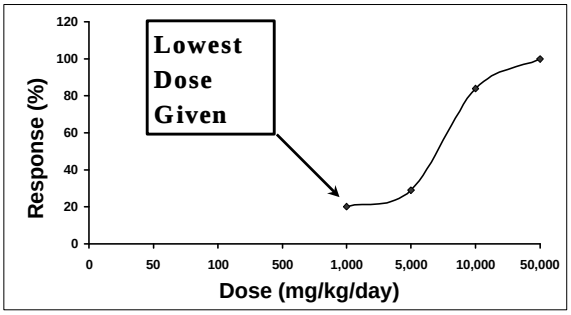
Group D. Not Classifiable as to Human Carcinogenicity-data from human epidemiological and animals studies are inadequate or completely lacking, so no assessment as to the substance's cancer -causing hazard is possible

EPA Weight-of-Evidence Classification System (cont.)

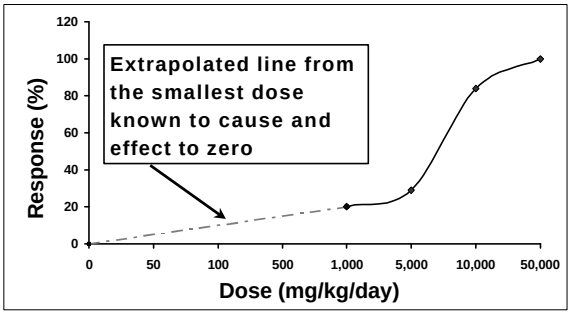
Group E. Evidence of Noncarcinogenicity for Humans- substances in this category have tested negative in at least two adequate (defined by EPA) animal cancer tests in different species and in adequate epidemiological and animal studies. Classification in group E is based on available evidence; substance may prove carcinogenic under certain conditions.

To be protective of the public health, EPA has established policy that there is no threshold value for any carcinogen

Dose Response for Carcinogens



Dose Response for Carcinogens



$$\text{Risk} = \frac{\text{CSF} \cdot \text{CC} \cdot \text{CR} \cdot \text{CF} \cdot \text{EF} \cdot \text{ED}}{\text{BW} \cdot \text{AT}}$$

CSF: cancer slope factor
CC: Conc. of contaminants
CR: contact rate **CF: conversion factor**
ED: exposure duration **AT: averaging time**
EF: exposure frequency **BW: body weight**

Food-Related Risks

Risk	Average Lifetime Risk
Eating one tablespoon of peanut butter per day	1.4×10^{-4}
Drinking one pint of milk per day	1.4×10^{-4}
Eating one-half pound of steak per week	2.1×10^{-5}

Everyday Cancer Risks

Incident	Average Lifetime Risk
All cancers	0.25
One transcontinental round trip by air per year*	7×10^{-5}
Natural background radiation at sea level	1.4×10^{-4}
Average diagnostic X-ray	1.4×10^{-4}
Smoking	8.4×10^{-2}
Sharing A room with a smoker	7.0×10^{-4}

*Estimated based on exposure to cosmic rays
Source: Crouch and Wilson, 1982

Estimated Average Annual and Average Lifetime Risks of Death for United States Residents from Specific Incidents

Incident	Average Annual Risk	Average Lifetime Risk
Motor vehicle accident	2.4×10^{-4}	1.7×10^{-2}
Falls	6.2×10^{-5}	4.3×10^{-3}
Drowning	3.6×10^{-5}	2.5×10^{-3}
Fires	2.8×10^{-5}	1.7×10^{-3}
Firearms	1.0×10^{-5}	7.0×10^{-4}
Electrocution	5.3×10^{-6}	3.9×10^{-4}
Floods	6.0×10^{-7}	4.2×10^{-5}
Lightning	5.0×10^{-7}	3.5×10^{-5}
Animal bite or sting	2.4×10^{-7}	1.7×10^{-5}

Source: Crouch and Wilson, 1982

For carcinogens, risk will be additive.

$Risk_{Total} = Risk_{Benzene} + Risk_{Chromium}$

$Risk_{Nickel} + Risk_{Tetrachlorethylene}$

Results of the Risk Assessment for Carcinogens

- **Compare Calculated Risk Number with Public Policy**
- **Answer is "Yes"/ "No"**

"It should be emphasized that the linearized multistage procedure leads to a plausible upper limit to the risk that is consistent with some mechanism of carcinogenesis. Such an estimate, however, does not necessarily give a realistic prediction of the risk. The true value of the risk is unknown and may be as low as zero."

--US Environmental Protection Agency, 1986

Cancer risk is unverifiable

It is lost in the noise of natural occurrence.

Indoor Air as a Source of Chemical Exposures and Discomfort

Indoor air concentrations of chemicals are typically much greater than outdoor concentrations and these indoor levels are derived from sources unrelated to outdoor air.

Indoor Air as a Source of Chemical Exposure and Discomfort

For example:

We have shown that about 20 common activities can result in sharply increasing personal exposures over 5-11 hr may be increased by factors of 10-100 compared to exposures during periods of little activity... These common activities and indoor sources result in personal exposures that far exceed observed outdoor concentrations, even in chemical manufacturing and petroleum refining areas.

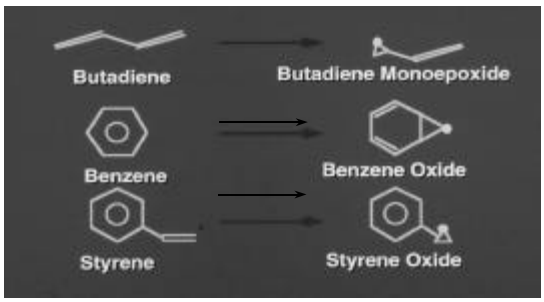
(Wallace et al., 1989)

Rational Approach to Medical Evaluation of Possible Toxic Exposures to Environmental Chemicals

Exposure → Dose → Health Effects

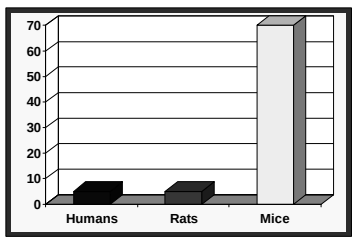
Environmental Testing	Biological Testing	Medical Testing
a) Air	a) Blood	a) History
b) Water	b) Urine	b) Physical Exam.
c) Soil	c) Breath	c) Laboratory
d) Food	d) Tissue	d) Radiology

Structures

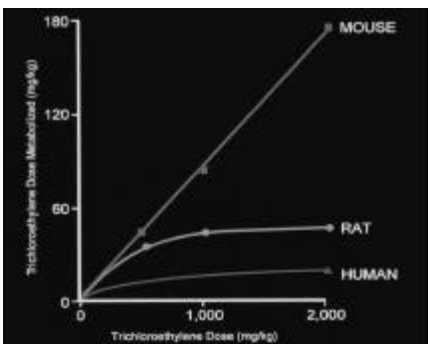


Butadiene Metabolism

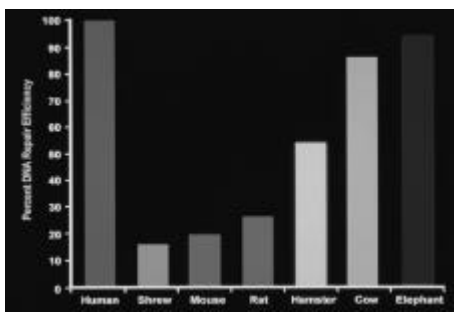
Activation
Detoxification



Cancer ? ? ?



Comparison of DNA Repair



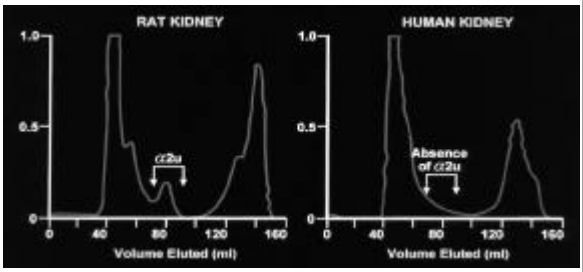
Chemicals that Induce a2u-Globulin Nephropathy and Kidney Tumors in Male Rats

Chemical	α2u-Nephropathy	Kidney Tumor Response (Male Rats Only)	
Unleaded Gasoline	+	+	
1,4-Dichlorobenzene	+	+	
d-Limonene		+	+
Isophorone	+	+	

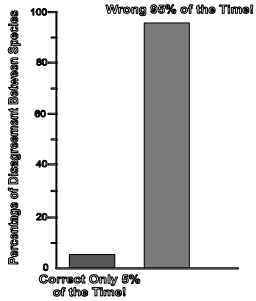
Chemicals that Induce a2u-Globulin Nephropathy and Kidney Tumors in Male Rats (Cont.)

Chemical	α2u-Nephropathy	Kidney Tumor Response (Male Rats Only)
Dimethyl Methylphosphonate	+	+
Perchloroethylene	+	+
Pentachloroethane	+	+
Hexachloroethane	+	+

Absence of a2u-Globulin in Human Kidneys



Rodents Are Poor Predictors of Carcinogens For Humans



The Standard carcinogen tests that use rodents are an obsolescent relic of the ignorance of past decades. At that time, extreme caution made sense. But now tremendous improvements of analytical and other procedures make possible a new toxicology and far more realistic evaluation of the dose levels at which pathological effects occur.

Philip H. Abelson. *Science*, Volume 29, Number 4975: 1357. September 21, 1990.

Toxicity Data Evaluation

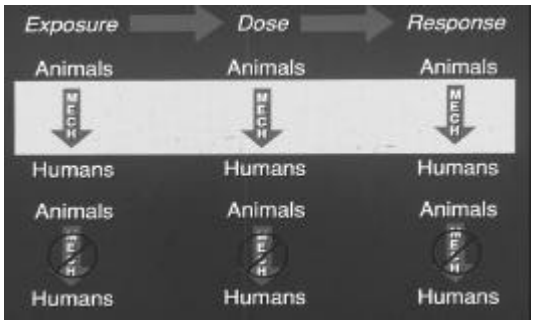
A rational approach towards assessing the risk that a chemical might pose requires mechanism-of-action-oriented research to four principal points.

For example, let us look at the maximum tolerated dose (MTD). Approximately two-thirds of the NTP carcinogens would not be positive, i.e., not be considered as carcinogens, if the MTD was not used.

Federal Register Vol. 57, No. 138
July 17, 1992, Pg. 31723

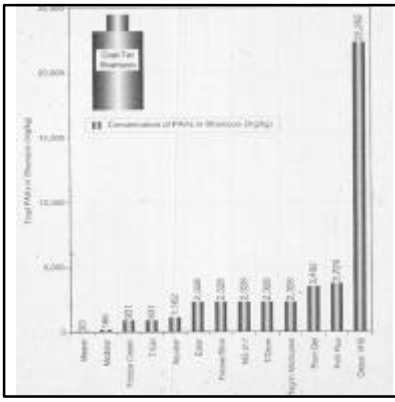
Rebuttals of Animal Data to Use in Toxic Torts

- Poor predictor of target organ toxicity
- Low degree of concordance
- High degree of false positives



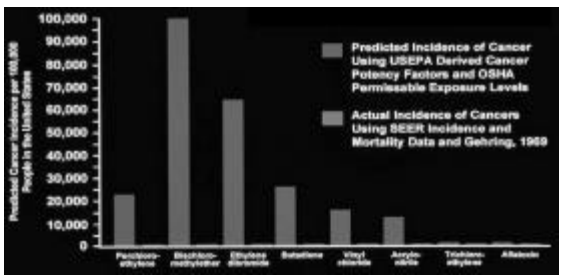
Chemical Essential to Health that Causes Cancer in Rodents

USEPA	→	safe dose calculated by USEPA procedures	=	less than 2 Units
National Research Council	→	dose recommended by National Research Council	=	400 Units



PAHs in Coal-Tar Shampoo (mg/kg)

Cancer Potency Factors Overestimate Actual Risk



Regulations Protect

They Do Not Predict

Carcinogens and Neurotoxicants Released During 1991

Carcinogens - 15,850,466 lbs.

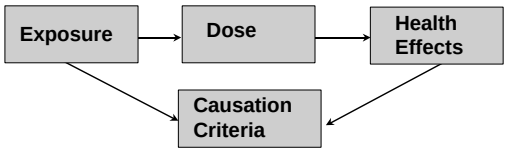
- Known Human Carcinogens (A) - 6,128,266 lbs.
- Probable Human Carcinogens (B1) - 802,583 lbs.
- Probable Human Carcinogens (B2) - 8,919,618 lbs.

Neurotoxicants - 10,329,084 lbs.

Neurotoxicants Released in Houston/Galveston Area, 1991

N-Butyl Alcohol - 3,067,693 lbs
Carbon Disulfide - 962,663 lbs
Styrene - 2,455,353 lbs
Xylenes - 2,361,747 lbs
Cumene - 1,215,434 lbs
Freon 113 - 263,970 lbs
2,6-Dinitrotoluene - 1,500 lbs
Acrylamide - 714 lbs

Rational Approach to Medical Evaluation of Possible Toxic Exposures to Environmental Chemicals and Causation Criteria



a) **Exposure and dose**
b) **Literature precedence**
c) **Confounder analysis**
d) **Temporality**
e) **Biological plausibility and consistency**

Symptoms

There are very few symptoms that are relatively specific for a particular disease and thus useful in the diagnosis of the disease.

Symptoms are medically defined as:

…any subjective evidence of disease or of a patient's condition, i.e., such evidence as perceived by the patient; a change in a patient's condition indicative of some bodily or mental state. (Dorland's Illustrated Medical Dictionary, 27th edition)

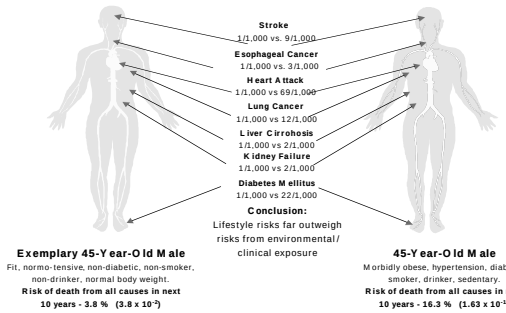
Signs

Signs provide some tangible form of evidence which assists in the final determination of the true cause of the symptoms and the disease.

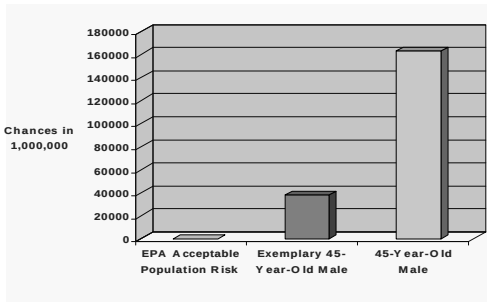
A sign is defined as

…any objective evidence of a disease, such evidence as is perceptible to the examining physician, as opposed to the subjective sensations (symptoms) of the patient. (Dorland's Illustrated Medical Dictionary, 27th edition)

Individual Risk Evaluation



Comparison of Risk of Death



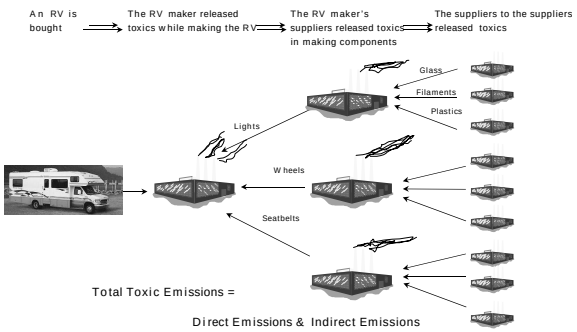
Contributory Risk

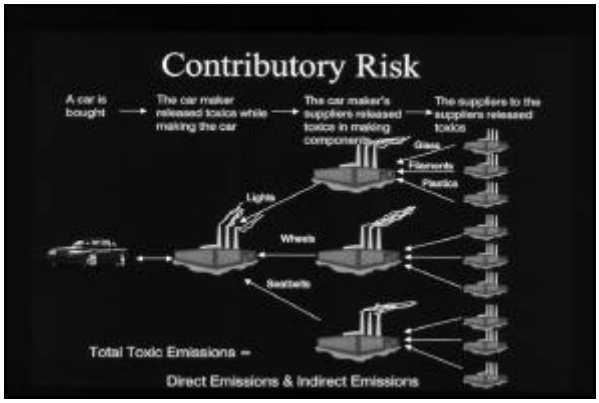
Qualitative characterization of contributory risk

Need to account for direct and indirect sources of risk in an assessment

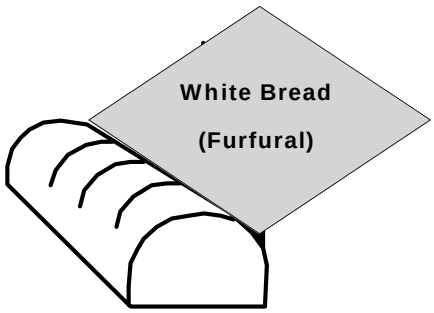
Voluntary actions (such as buying a jet ski, RV or snowmobile) contribute to involuntary risk in others

Contributory Risk

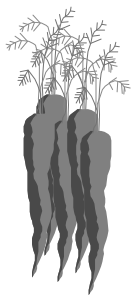




Common Carcinogenic Hazards



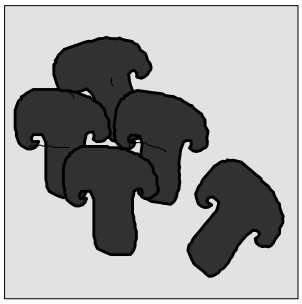
Common Carcinogenic Hazards



CARROTS

(Caffeic acid)

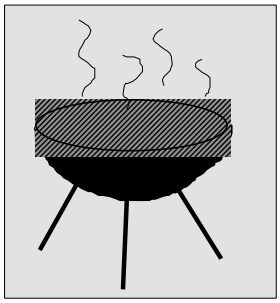
Common Carcinogenic Hazards



MUSHROOMS

(Hydrazines)

Common Carcinogenic Hazards



All chargrilled food contains Polycyclic Aromatic Hydrocarbons (PAHs)

Common Carcinogenic Hazards Associated with Daily Lifestyle, 1:100,000

Cosmic ray risks	
•one transcontinental flight per year	21
•airline pilot, 50 hrs/month at 35,000 feet	35
Other radiation risks	
•natural background at sea level	105
Smoking	
•cancer only	8,400
•all effects (including heart disease	21,000
Miscellaneous	
•regular use of contraceptive pills	140

Post Risk Assessment Follow-up

Where risk assessment stops, risk management begins

Risk Management

- **If the answer is "YES" for carcinogens, and/or**
- **If the answer is "MAYBE" for chemicals causing health effects after chronic exposures,**

Undertake appropriate risk management

Risk Management

- **Will be undertaken by controlling exposures**
- **Will be undertaken as part of the permitting process**
- **Will be undertaken to protect public health**