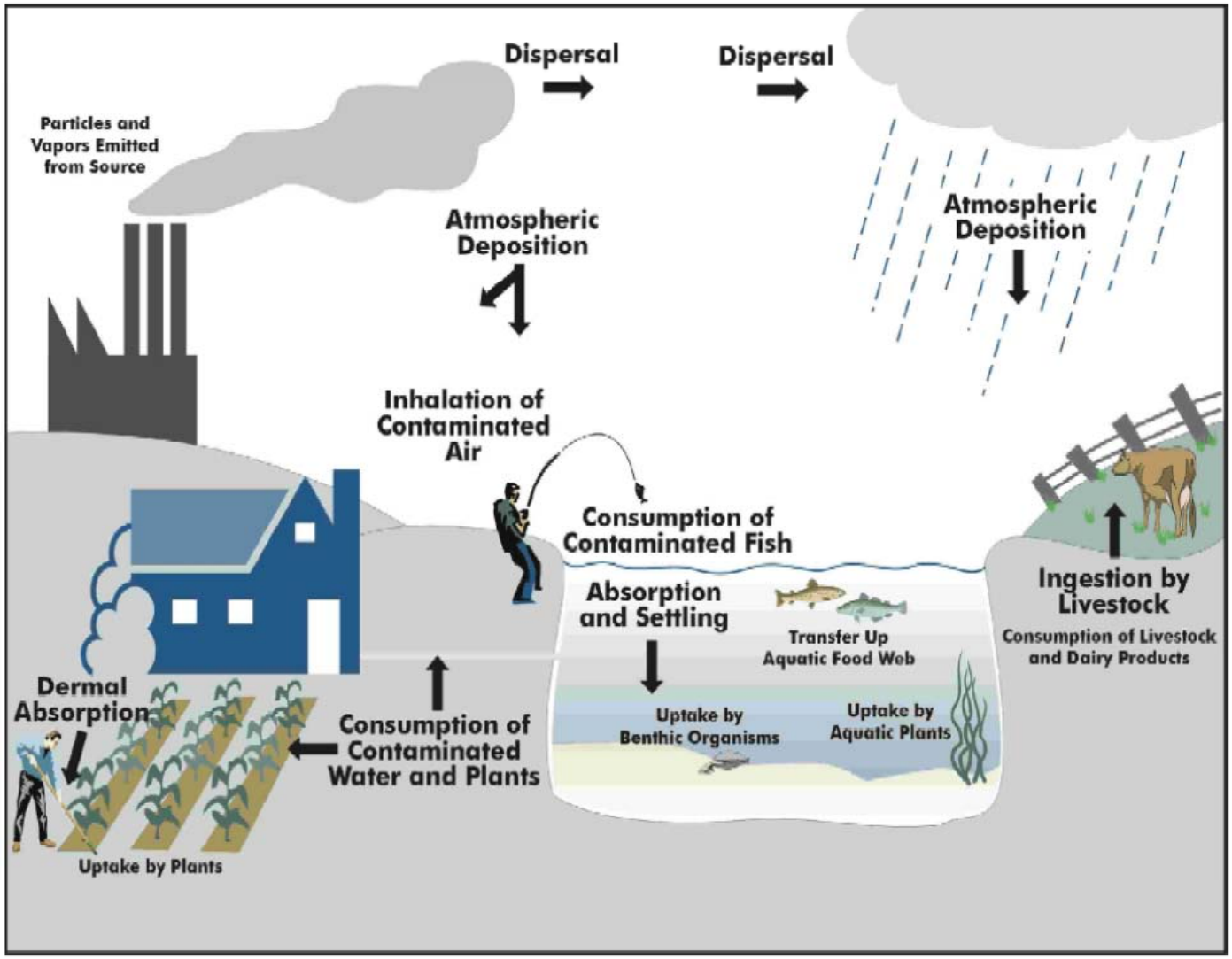
CHAPTER 6

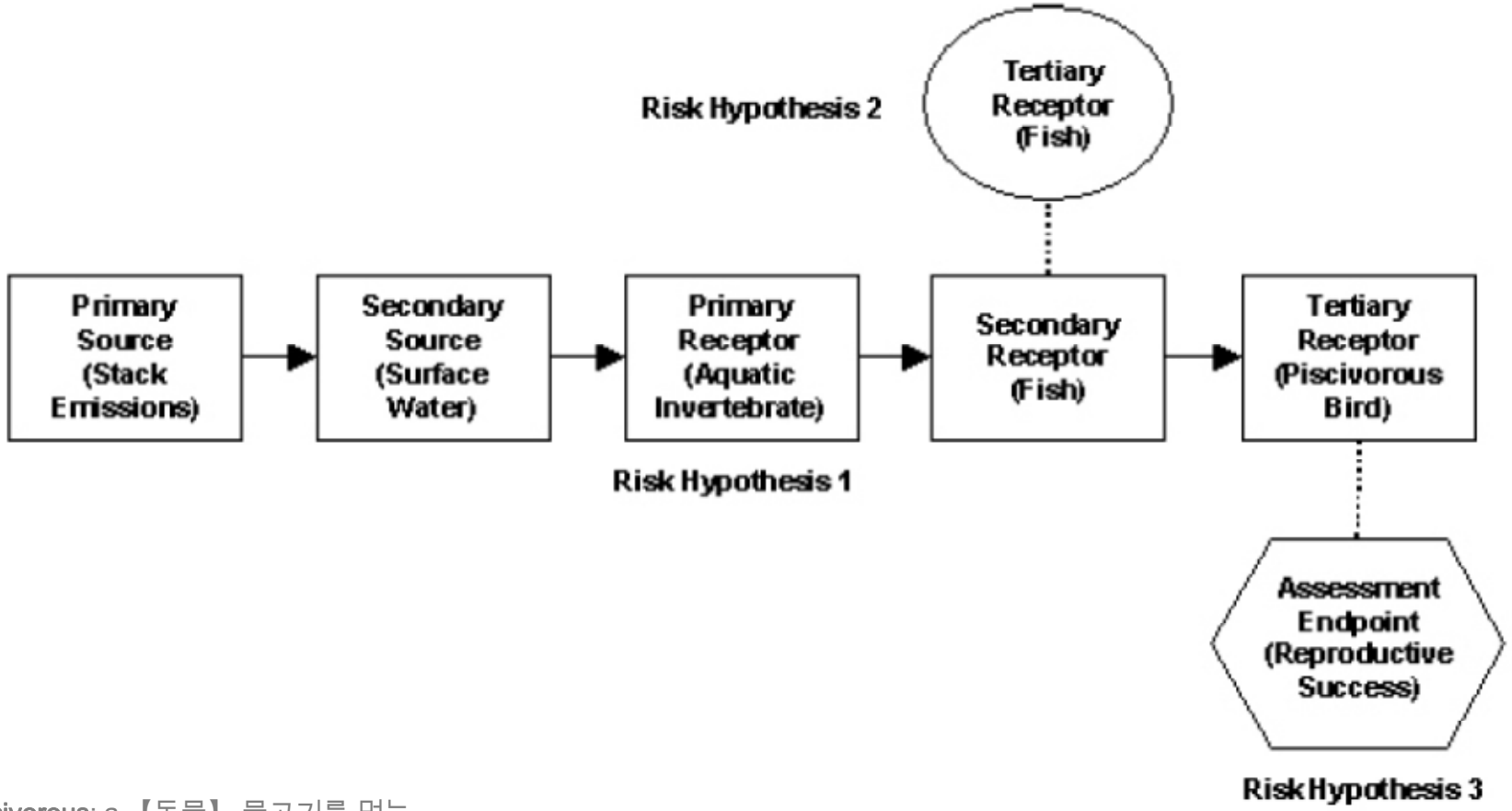
Evaluating Exposures

Potential Multimedia Exposure Pathways of Concern



http://www.epa.gov/ttnmain1/fera/data/risk/vol_1/chapter_20.pdf

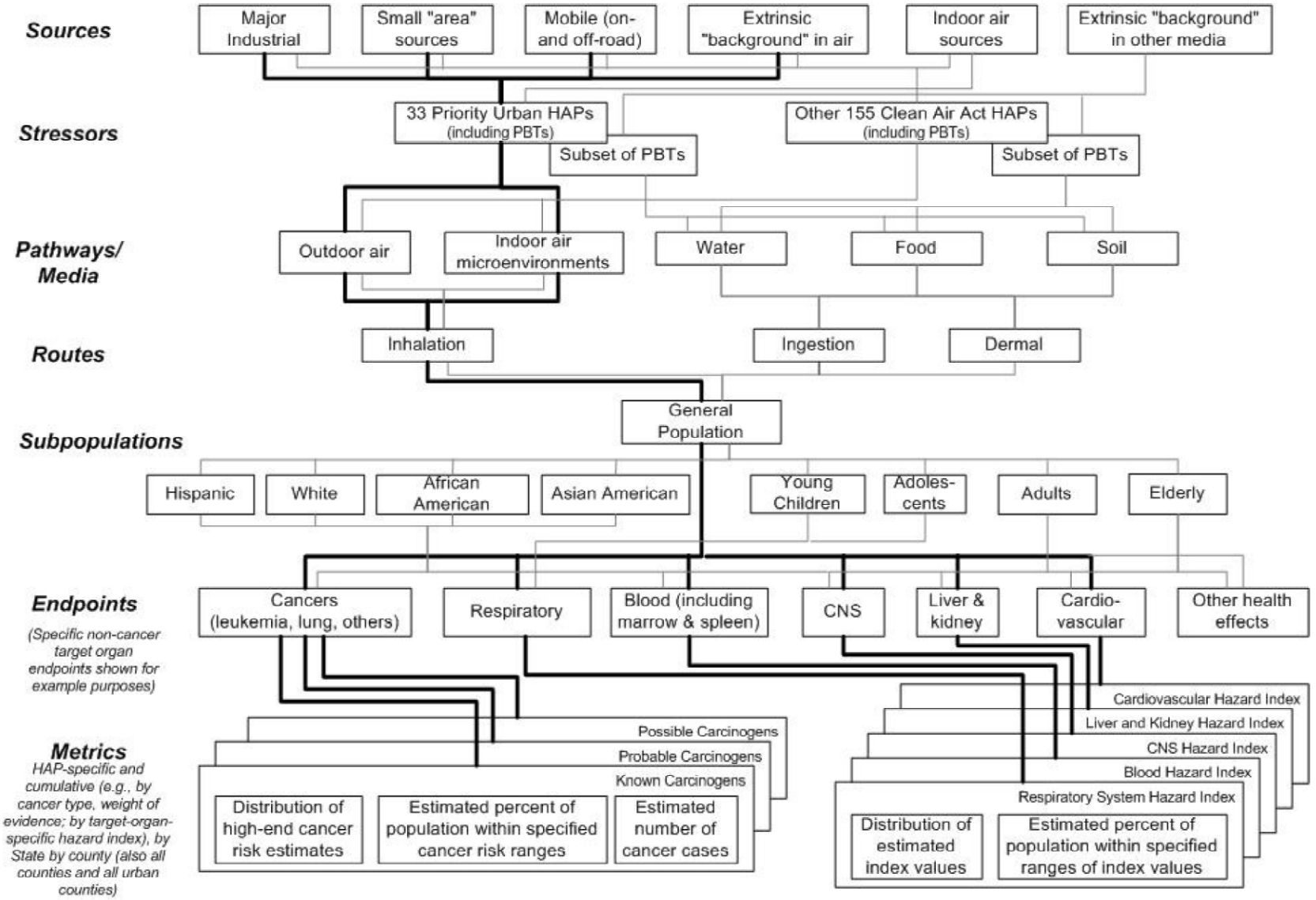
Conceptual Model Diagram for Exposure of Piscivorous Birds to Air Toxics



piscivorous: a.【동물】 물고기를 먹는
invertebrate: a.【동물】 무척추 동물의

http://www.epa.gov/ttnmain1/fera/data/risk/vol_1/chapter_23.pdf

Generalized Conceptual Model for Air Toxics Risk Assessments



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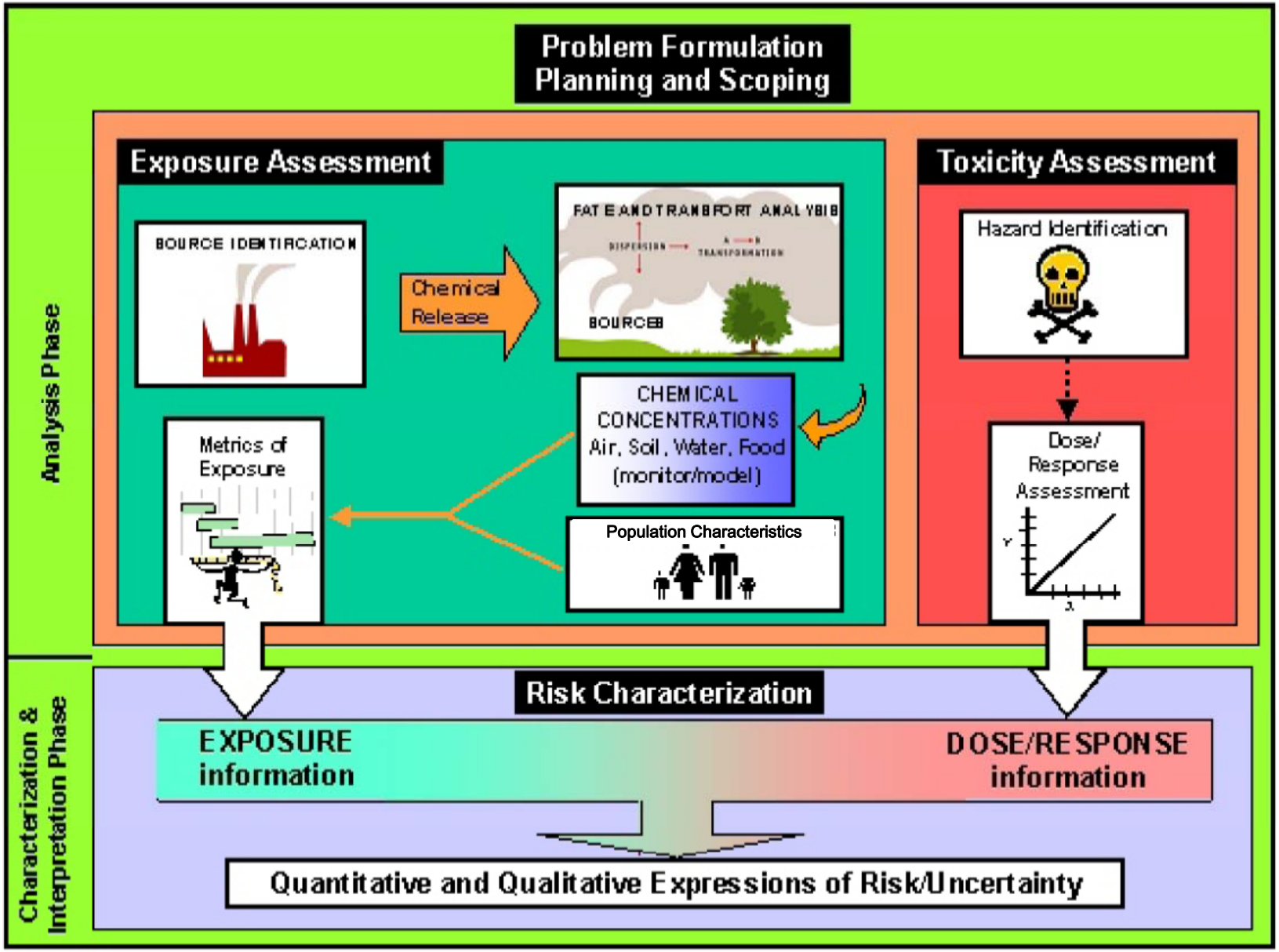
The Detailed Air Toxics Risk Assessment Process



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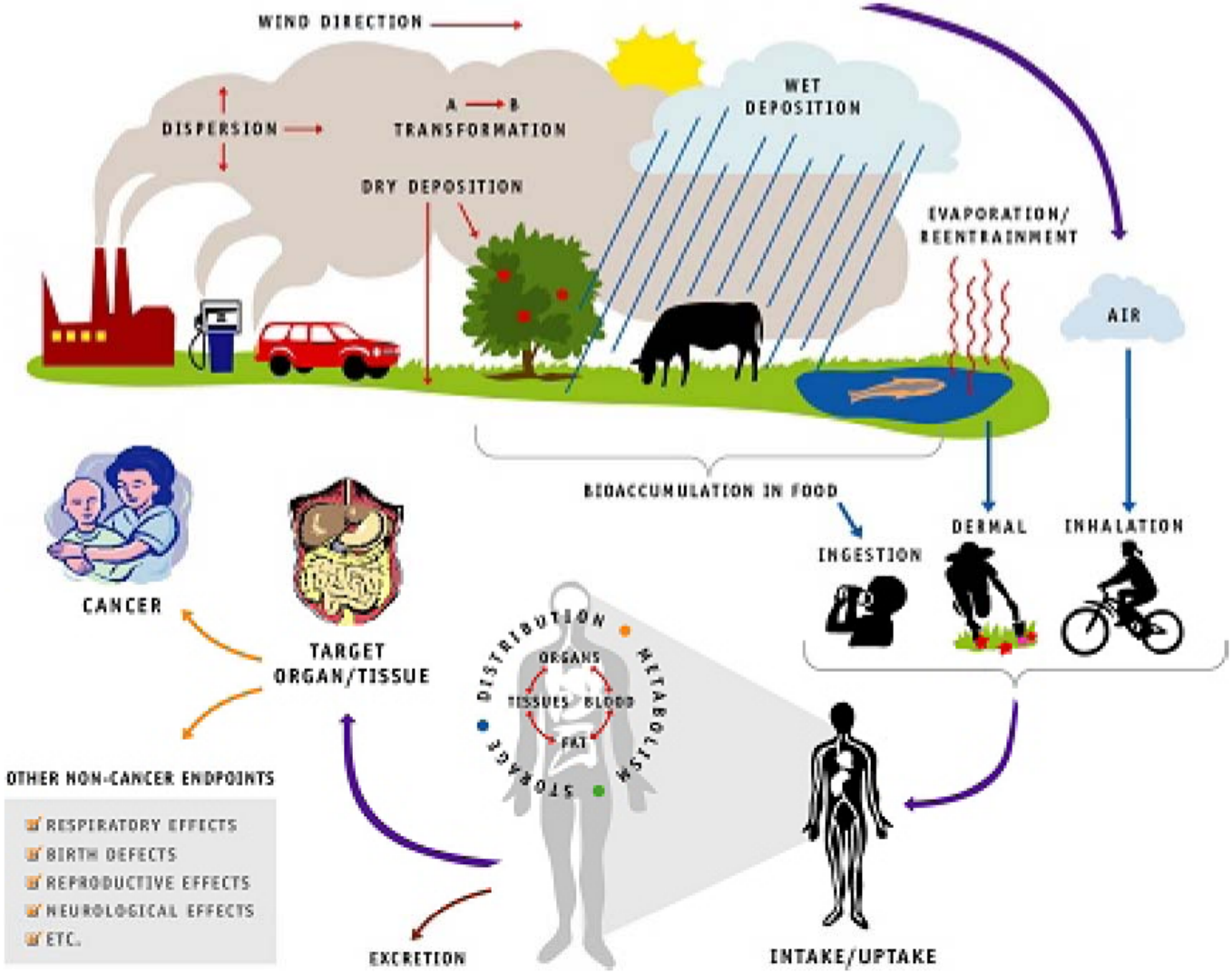
Generic Conceptual Model of How Air Toxics Releases May Result in Injury or Disease



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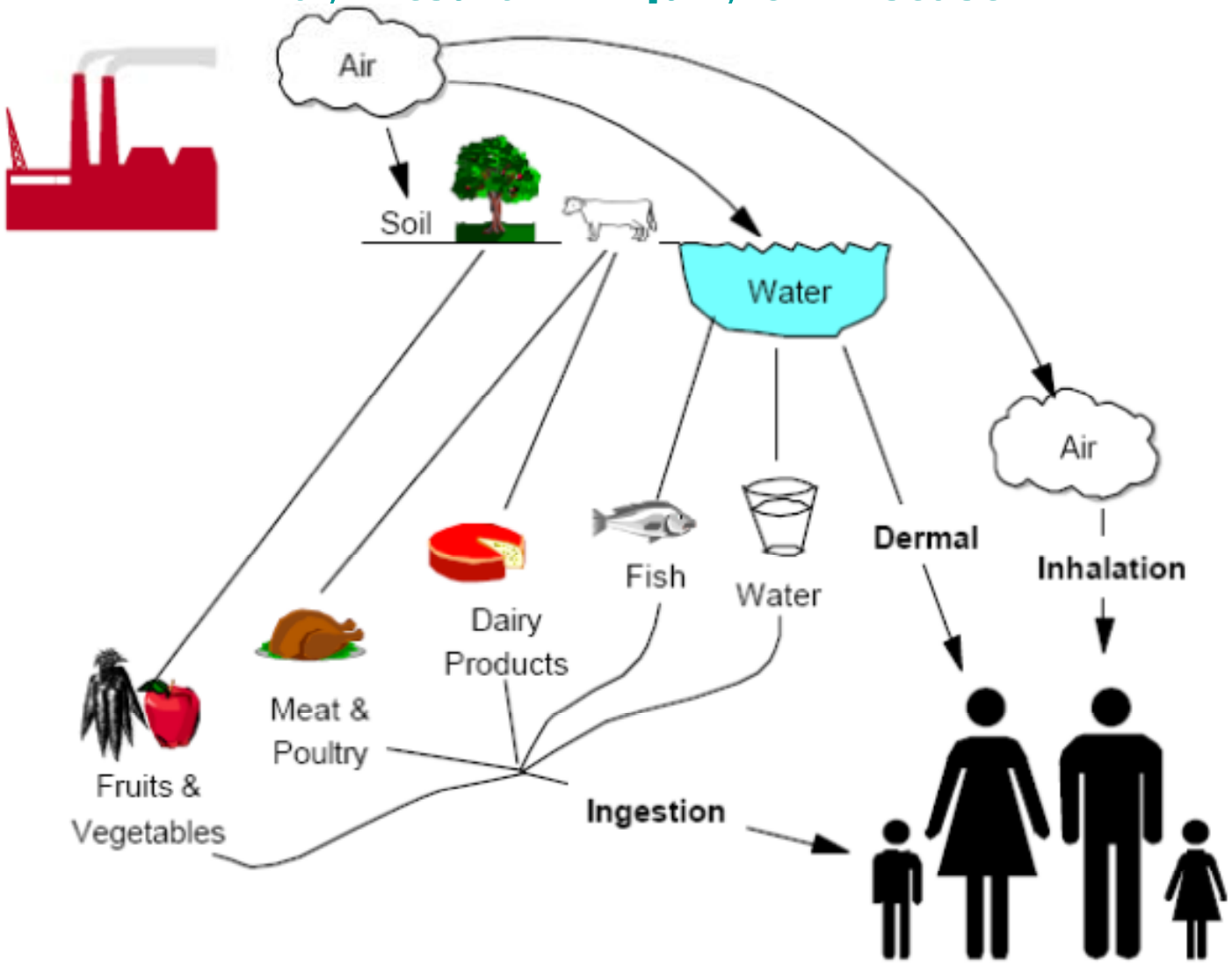
Generic Conceptual Model of How Air Toxics Releases May Result in Injury or Disease



People may be exposed to air toxics in ways other than direct inhalation

Questions Addressed by the Exposure Profile

- How may exposure occur?
- What may be exposed?
- How much exposure may occur?
- When and where may exposure occur?
- How may exposure vary?
- How uncertain are the exposure estimates?
- What is the likelihood that exposure will occur?

http://www.epa.gov/ttnmain1/fera/data/risk/vol_1/chapter_24.pdf

Contents

6.1 Introduction

(http://www.epa.gov/ppt/exposure)

The human health risk associated with a chemical is dependent on

- **the rate at which the chemical is released,**
- **the fate of the chemical in the environment,**
- **human exposure to the chemical,**
- **human health response resulting from exposure to the chemical**

6.1 Introduction

(http://www.epa.gov/ppt/exposure)

The methods for estimating exposure will be separated into two sections - **occupational and community**.

Occupational exposure

~ occur in workplace by inhalation of workplace air, ingestion of dust or contaminated food, or from contact of the chemicals with the skin of eyes.

6.1 Introduction

(http://www.epa.gov/ppt/exposure)

Community Exposure

Chemical releases to rivers, lakes, and streams may accumulate in fish and other marine life, which are subsequently used as a source of food, or may be ingested by persons using the downstream reaches of rivers as a supply of potable water.

Person living downwind of a chemical manufacturing facility may be exposed to fugitive and point source releases of chemical toxins to the atmosphere.

Disposal of solid and hazardous wastes on the land, either in repositories such as landfills or into subterranean strata by injection into wells may result in contamination of potable groundwater is not isolated from the water supplies.

stratum: 【지질】 지층;층

6.1 Occupational Exposure

Recognition, Evaluation and Control

Basic Assessment Items

- Recognize all sources of exposure to chemicals
  - *developing a list of sources of chemical exposure in the work environment*

- Determine if the exposure is within permissible limits
  - *level and duration* ***(Table 6.2-1)***

- Control those exposures that exceed permissible limits
  - *require on the source, pathway, workers exposed (control by process change, adjustment in ventilation systems, protective equipment, etc.)*

OSHA PEL

OSHA Permissible Exposure Limits for Air Contaminants

- Set by OSHA (Occupational Safety and Health Administration), a division of the U.S. Department of Labor.

- Listed in Title 29, Part 1910.1000 of the code of Federal Regulations)

- Hydrogen Cyanide (known poison) and Ammonia (irritating but nontoxic) are the basis for relative toxicity

- Expressed as time-weighted averages for the chemical substance in any 8-hour work shift of a forty-hour work week.

- For PELs the action level is not the actual PEL but one-half the PEL, meaning action must be taken at this level to reduce the emission.

Table 6.2-1

OSHA Permissible Exposure Limits for Air Contaminants

Chemical Substance	CAS No.*	ppm by volume**	mg/m^3***
Acetic acid	64-19-7	10	25
Acetone	67-64-1	1000	2400
Acrolein	107-02-8	0.1	0.25
Ammonia	7664-41-7	50	35
Bromine	7726-95-6	0.1	0.7
2-Butanone(Methyl ethyl ketone)	78-93-3	200	590
Ethyl benzene	100-41-4	100	435
Hydrogen Cyanide	74-90-8	10	11
Nitric oxide	10102-43-9	25	30
Dichlorodifluoro-methane (CFC 12)	75-71-8	1000	4950

*The CAS Number is a unique number assigned as a means of identification to distinct chemical substances by the Chemical Abstracts Service.

**Parts of vapor or gas per million parts of contaminated air by volume at 25° C and 760 torr.

***Milligrams of chemical substance per cubic meter of air.

OSHA: Occupational Safety and Health Administration,
a division of the U.S. Department of Labor.

6.2.1 Characterization of the Workplace

The first step in an occupational exposure assessment is to characterize the work place.

Description of Workplace: Schematic or Written Description

- Schematic Description
  - *Identification of unit operations where exposure may occur (process flow diagram, production activities, process chemistry, identify ventilation, other mechanism reduce exposure)*

- Written description
  - *release and exposure from transportation, disposal*
  - *area and location where chemical exposure may occur*
  - *component stream, concentration, operating temp and pressures*
  - *use of protective equipment, ventilation, open-top vessels*
  - *frequency and duration of sampling events*
  - *duration of batch processes*
  - *type and frequency of transfer operation*
  - *number of workers involved in each operation*

6.2.1 Characterization of the Workplace

▶ Detailed Description

- A relative complete inventory of chemicals that encountered in workplace
- The rate or generation of each chemical
- Collect physical property data (b.p., v.p., …)
- PSD of solid particles (airborne fraction) will give the potential respirable.
- MSDS (nuisance, irritant, toxicity, carcinogenicity, birth defects) will provide occupational exposure guidelines established by regulatory or consensus organization.
- These include

☑ The Occupational Safety and Health Administration PELs
☑ The American Conference of Governmental Industrial Hygiene Associations' Threshold Limit Values (TLVs)

} **Chap. 8**

☑ The American Industrial Hygiene Association's Workplace Environmental Exposure Level (WEEL) guides

6.2.1 Exposure Pathways

- Exposure to Chemicals in Work Environment can occur through inhalation, skin absorption, or ingestion.
- Exposure pathway model from process to worker (Fig. 6.2-1)
- Inhalation is most significant route (volatilize, evaporate)

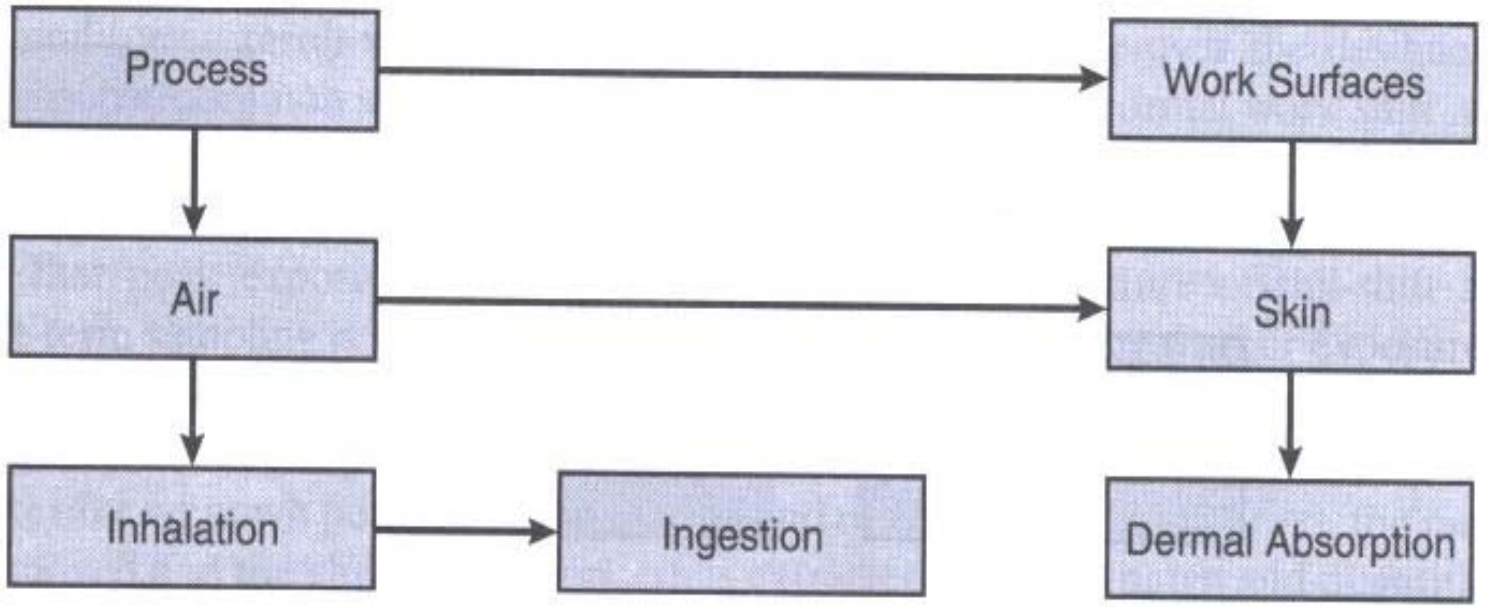


Fig. 6.2-1 Exposure pathway model

Framework for Calculating Exposure by Inhalation

Exposure (mass)
= **Severity** of exposure (mass/time) × **Duration** of exposure (time)

- **Severity** (mass/time)
  = Environ-Concentration (mass/volume) × Breathing rate (volume/time)

- **Duration** (time)
  = Frequency (No. of exposure) × Period (time/exposure)

*A separate estimate of the **rate of absorption** of inhaled materials is necessary to calculate the intake of a chemical into body*

Framework for Dermal Contact and Oral Ingestion

Dermal exposure

Exposure (mass)

= **Severity** $\times$ **Frequency**

(mass absorbed/incident) (number of incidents)

$$\text{Severity} = \text{Surface area exposed skin} \times \frac{\text{Mass absorbed/area}}{\text{Incident}}$$

Dermal intake into the body requires a separate estimate of the rate of uptake of the chemical from exposed skin surface.

Oral Ingestion

Oral Ingestion (relatively minor route), however, may be an important route of exposure that accumulate in the body over long periods of time

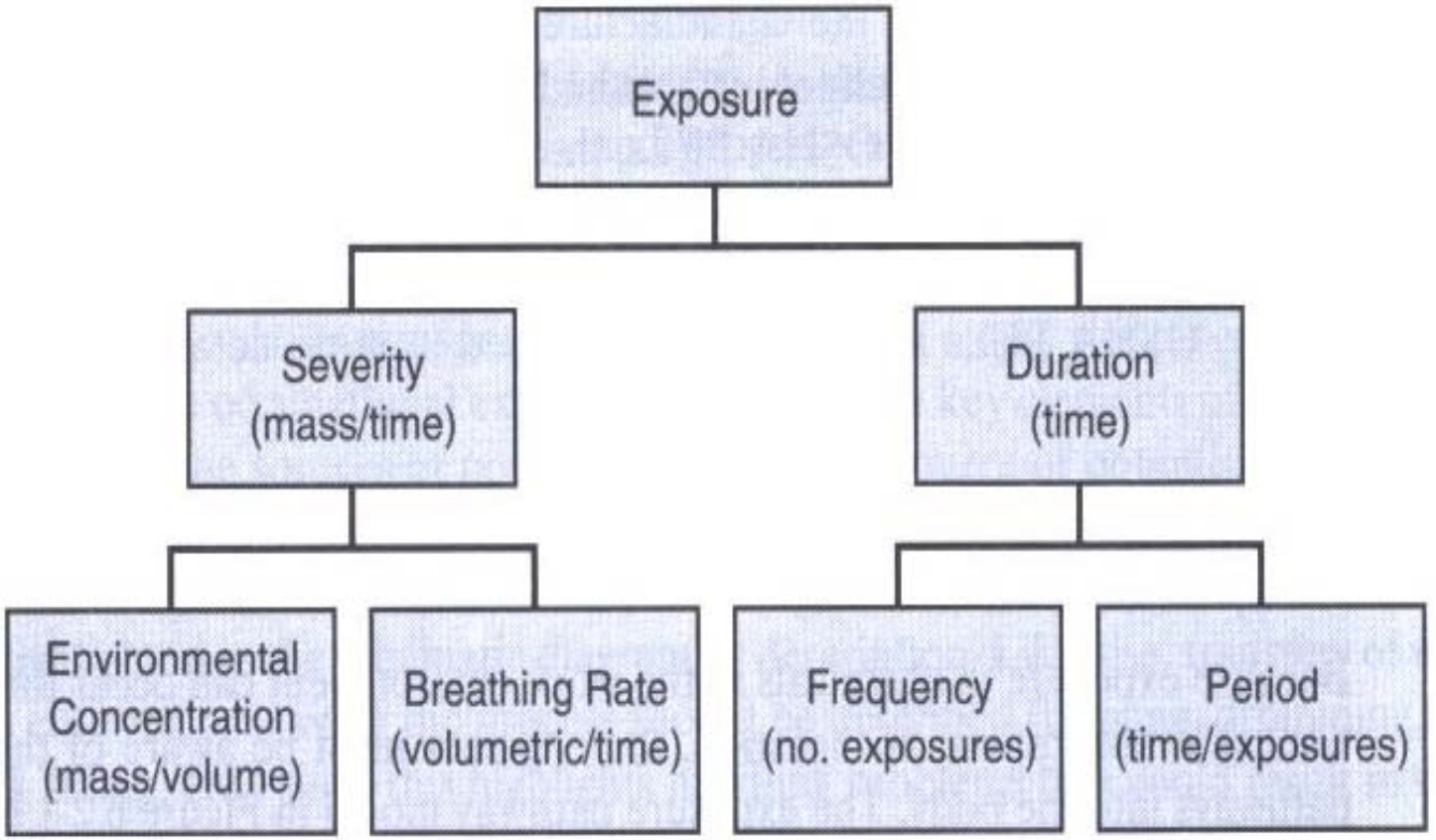


Fig. 6.2-2 Inhalation exposure framework

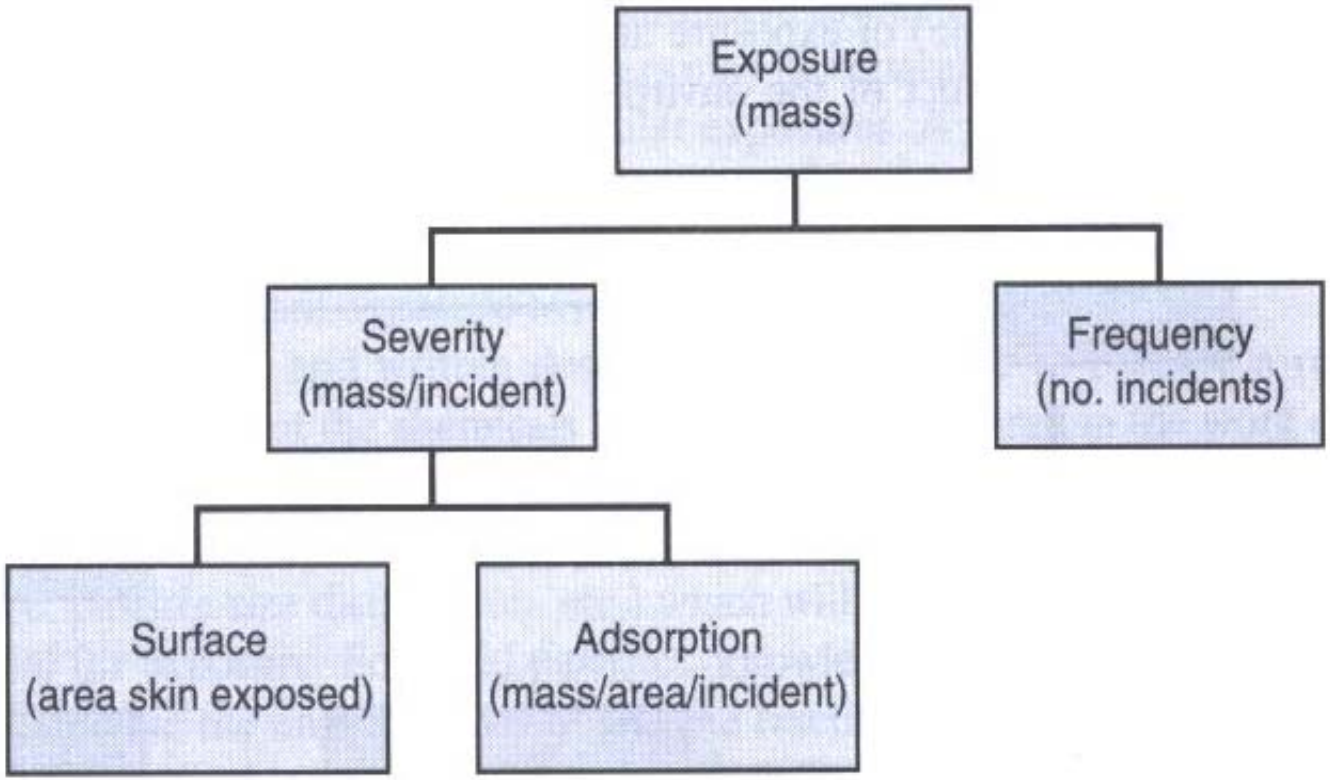


Fig. 6.2-3 Dermal exposure framework

Monitoring Worker Exposure

Monitoring objectives can be grouped into three categories:

- Baseline Monitoring (기준 감시)
  - Evaluate the range of worker exposure
  - Baseline date are to determine the acceptability of exposures to chemicals and the need for controls to reduce exposures

- Diagnostic Monitoring (진단 감시)
  - Identify principal sources and tasks contributing to exposure to specific chemicals
  - Used to select appropriate control strategies for reducing exposure to known sources

- Compliance Monitoring (준수 감시)
  - Demonstrate conformance with government regulations
  - Monitor the most exposed worker using a collection device attached to worker near his breathing zone

Monitoring Methods: Personal Monitoring

Personal Monitoring

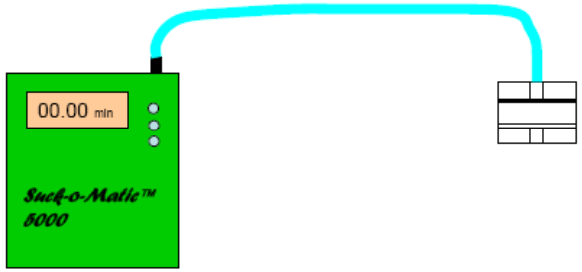
- Characterize the exposure of a worker to the chemical substances of interest

Common Method

- Breathing zone measurement (battery-powered pump is attached to the worker to draw air through a collection tube)
- Two common sampling averaging times:
  - ❶ 8 hrs for a normal work shift
  - ❷ 15-min for a common short-term exposure time limit
- By patch testing, skin absorption also can be quantified

Monitoring Methods: Personal Monitoring

Basic Personal Air Sampling System



Pump
Adjustable flow.
Constant air flow.
Worker "wearable".
Operates for full work shift.

Sampler
Efficiently collect particles.
Retain particles for analysis.
Known particle size cutoff.
Practical to use.

Inhalable Samplers

PM Sampler

AEROTRAK™ 9000
Nanoparticle Aerosol Monitor

Monitoring Methods: Area Monitoring

Area Monitoring of ambient air is used to

- To measure background level of chemical contaminants
- To warn of toxic concentrations of acutely hazardous chemicals
- To demonstrate the effectiveness of ventilation controls by measuring the level of chemical contaminants before and after the controls are installed
- Identify deficiencies in maintenance or operation of control system
- Includes investigation of surface contamination by wipe test method (useful for tracking level of contaminations by dermal route)

6.2.4 Modeling Inhalation Exposures

- It is not always possible for new process to undertake a monitoring program to determine airborne concentrations of chemicals
- Rapid estimate of potential worker exposure is needed

Mass Balance Model (Box Model)

~ work area is modeled as a box in which the contaminant is uniformly distributed

$$V\frac{dC}{dt} = G - kQ(C - C_0)$$

C : airborne contaminant in work area(mass/L^3)
V : work area volume (L^3)
t : time duration which contaminants emitted
G : emission rate of contaminant to air(mass/time)
Q : ventilation rate (L^3/time)
k : mixing factor account for incomplete mixing
C_0: initial concentration

6.2.4 Modeling Inhalation Exposures

If G and Q are constant, C will reach a steady state

$$C = C_0 + G/kQ \qquad (6\text{-}2)$$

At times, emissions are episodic. Consider a work area that initially contains contaminant at concentration C_0. At some time, t=0, an emission source, releasing contaminant at rate G, is placed in the work area.

Rise of Contaminant Concentration by Box Model

Assume ventilation rate is constant

$$C = C_0 + \frac{G}{kQ}[1 - \exp(-kQt/V)] \qquad (6\text{-}3)$$

k (mixing factor) = 0.3~0.7 in small room without fan

0.5 in work area with average ventilation

0.1 in work area with poor ventilation

6.2.4 Modeling Inhalation Exposures

Penetration Model to Determine G **(Example 6.2-1)**

Assume that the source is a pool of liquid
that is evaporating at constant rate

$$\frac{G}{A} = 8.79 \times 10^{-5} \frac{(MW^{0.883})(VP)[(1/MW + 1/29)^{0.25}](v^{0.5})}{(T^{0.05})(\Delta x^{0.5})(P^{0.5})} \quad (6\text{-}4)$$

G	:	evaporation rate(g/sec)
A	:	surface area of the pool/air interface
MW	:	molecular weight of the evaporating species(g/mole)
VP	:	vapor pressure of evaporating contaminant (atm)
v	:	air velocity parallel to the surface of the evaporating liquid (cm/sec)
T	:	surface temperature (K)
Δx	:	length of the evaporating pool in the direction of air flow
P	:	ambient pressure (atm)

Box Model for Non-Ventilatory Removal

When exposure may be mitigated by adsorption of chemical to wall and other surface in the work room

$$V\frac{dC}{dt} = G - kQ(C - C_0) - rC \qquad (6\text{-}5)$$

r : non-ventilatory removal coefficient of airborne contaminant

- If ventilation and emission rates are constant, box model predicts a steady state concentration of

$$C = \frac{kQC_0 + G}{(kQ + r)} \qquad (6\text{-}6)$$

Modified Box Model

Modified Box Model~ work area is divided into 2 zones
(one near the source and the other is removed from the source)

$$C = \frac{G(B+Q)}{(BQ)} \qquad (6\text{-}7)$$

C : near the source
G : rate of vaporization of contaminant(m/time)
B : rate of exchange of air between the zones
Q : ventilation rate of the zone removed from the source

Example 6.2-2

6.2.4.2 Dispersion Models

- Spread of the contaminant is aided by the convective mass transfer driven by the ventilation system
- Describe the variation of contaminant concentration with distance from the source

$$u\frac{dC}{dx} = \frac{D}{r^2}\frac{d}{dr}\left[\frac{rdc}{dr}\right] \qquad (6\text{-}8)$$

u : wind velocity in x direction(L/time)
C : concentration of airborne contamination
D : diffusion coefficient (L^2/time)
x : distance downwind from the source
r : distance from the source to the sampling point

6.2.4.2 Dispersion Models

- Concentrations from emissions into infinite space

$$C = \frac{G}{4\pi D r} \exp[(-u/2D)(r-x)] \qquad (6\text{-}9)$$

G : contaminant emission rate from the source

- ***Evaluated ranges of D (Diffusion coefficient)***
  0.05~11.5 m^2/min, with 0.2 m^2/min being a typical value indoor industrial environments

(Example 6.2-3)

6.2.5 Assessing Dermal Exposures

Dermal hazards : *damage the skin and chemicals can enter the body and cause toxic effects in other organs*

- *acids, alkalis and corrosive chemicals*

Mechanism of Dermal Exposures

- Direct contact from splashing or immersion
- Transfer of a chemical from a contaminated surface to skin following direct contact
- Deposition or impaction on the skin as a vapor or aerosol

Assessing Dermal Exposures

Measurement Methods

- Direct methods *(absorbed pads, clothing, wipe sampling of contaminated surface)*
- Computerized image analysis with fluorescent whitening agents
- Control devices *(gloves, apron, clothing, etc)*

Table 6.2-2

Surface area by region of the body for adults in cm^2

Region of the Body	Men		Women	
	Median	*5th to 95th Percentiles*	*Median*	*5th to 95th Percentiles*
Head	1300	1190–1430	1110	1060–1170
Trunk	7390	5910–9350	5790	4900–7520
Arms	2910	2410–3540	2300	2100–2530
Hands	990	850–1170	817	730–966
Legs	6400	5390–7620	5460	4600–6830
Feet	1310	1140–1490	1140	1000–1340
Total	19,400	16,600–22,800	16,900	11,450–20,900

Source: U.S. Environmental Protection Agency, *Exposure Factors Handbook, Volume I* (EPA 600/P-95/002Fa), Washington, D.C. (1997).

Modeling Dermal Exposures

To estimate the exposure to a chemical that is absorbed through skin

$$\mathbf{DA = (S)\,(Q)\,(N)\,(WF)\,(ABS)} \qquad (6\text{-}10)$$

DA : dermal absorbed dose rate of the chemical (m/time)
S : surface area of the skin contacted by the chemical
Q : quantity deposited on the skin/event (m/L^2/event)
N : number of exposure events / day
WF : weight fraction of the chemical in the mixture
ABS : fraction of applied dose absorbed during the event

In the absence of monitoring data, value in **Table 6.2-3** may be used to estimate dermal exposure to liquids in plant operation

Table 6.2-3

Q: Quality of chemical deposited on the skin per exposed event

Activity	Quantity Transferred to the Skin per Event (mg/cm^2)
Handling wet surfaces	6.0–10.3
Spray painting	6.0–10.3
Manual cleaning of equipment	0.7–2.1
Filling drums with liquid	0.5–1.8
Connecting transfer lines	0.7–2.1
Sampling	0.7–2.1
Ladling liquid/bench scale transfer	0.5–1.8

Source: US Environmental Protection Agency, *Occupational Dermal Exposure Assessment—A Review of Methodologies and Field Data*, Office of Pollution Prevention and Toxics, 1996.

Modeling Dermal Exposures

The skin is resistance to hydrophilic or water soluble chemical and permeability constant is unlikely to exceed **0.001 cm/hr**.

(6-10)

Hydrophobic compounds are more readily absorbed and the penetration of organic solvents such as toluene and xylene may approach **1 cm/hr**.

Uptake Absorbed through the skin

Estimate the uptake of a chemical that is absorbed through the skin when evaporation and organic solvent carrier effects are negligible.

$$DA = (S)\,(K_P)\,(ED)\,(WF)\,(\rho) \qquad (6\text{-}11)$$

DA : dermal absorbed dose of the chemical (M)

S : surface area of the skin contacted by the chemical (L^2)

K_P : permeability coefficient for the chemical (L/time)

ED : exposure duration (time)

WF : weight fraction of the chemical in the mixture (-)

ρ : density of the mixtures (M/L^3)

Permeability Coefficient

Based on diffusion of organics in aqueous solution through the skin (US EPA 1992)

$$\log(K_P) = -2.72 + 0.71\log(K_{OW}) - 0.0061(MW) \qquad (6\text{-}12)$$

K_P : permeability coefficient of the chemical through the skin (cm/hr)
K_{OW} : oil-water partition coefficient (-)
MW : molecular weight of the chemical of concern (mass/mole)

(Example 6.2-5)

6.3 Exposure Assessment
for Chemicals in the Ambient Environment

Exposure to Toxic Air Pollutants

Four-Step Process

- **1st - Step**: *identify pollutants likely to be in ambient air*
  (factories, consumer goods, wastes can be released toxic pollutants to air)

- **2nd - Step**: *estimate the quantities of pollutants released by point, area, and mobile sources*
  - *Point sources : plants, mills, refineries, waste incinerators, etc. (sites with specific location)*
  - *Area sources : many small sources releasing pollutants to air in a defined area (dry cleaner, metal plating operations, gas stations, etc)*
  - *Mobile : automobiles, buses, etc. (important sources of NOx, SOx, HCs, etc.)*

6.3 Exposure Assessment
for Chemicals in the Ambient Environment

Exposure to Toxic Air Pollutants

Four-Step Process

- **3rd - Step**: *estimate the concentration of toxics at the location where exposure occurs*
  - *Dispersion of air pollutants is a function of wind direction, speed, and terrain shapes such as hill, flat, mountains, etc.*

  (Gaussian Dispersion Model)

- **4th - Step**: *estimate the number of persons exposed to a toxic air pollutant*
  - *Demographers can estimate the number of persons living in source areas*
  - *Combining the concentration estimates and the census data, one can estimate numbers of people exposed to toxic air pollutants*

  (http://www .epa.gov/enviro/index.java.html)

Gaussian Dispersion Model

characterize the dilution of toxic air pollutants with distance from the source

$$C = Q(\pi\sigma_x\sigma_y U)^{-1} \times \exp(-0.5H^2\sigma_z^{-2})$$

C : concentration of toxic air pollutant (μg/m^3)
Q : source release rate ((μg/sec)
U : mean wind speed at the stack height (m/s)
H : effective height of release above the earth (m)
y : distance in a direction transverse to the wind
Z : height at which the observation is made
σ : standard deviation of the concentration

$$\sigma_y\sigma_z = ax^b$$

A, b : constant (nondimensional)
x : distance downwind from the source(length)

- Parameters are in **Table 6.3-1** **(Example 6.3-2)**

Table 6.3-1 Regression equations for dispersion coefficients

a. Rural release, neutral atmosphere, x<500m:	$\sigma_y\sigma_z = 0.01082\ x^{1.78}$
b. Rural release, neutral atmosphere, x>500m:	$\sigma_y\sigma_z = 0.04487\ x^{1.56}$
c. Rural release, stable atmosphere, x<2000m:	$\sigma_y\sigma_z = 0.0049\ x^{1.66}$
d. Rural release, stable atmosphere, x>2000m:	$\sigma_y\sigma_z = 0.01901\ x^{1.46}$
e. Urban release, neutral atmosphere, x<500m:	$\sigma_y\sigma_z = 0.0224\ x^{2}$
f. Urban release, neutral atmosphere, x>500m:	$\sigma_y\sigma_z = 0.394\ x^{1.54}$
g. Urban release, stable atmosphere, x<500m:	$\sigma_y\sigma_z = 0.008\ x^{2}$
h. Urban release, stable atmosphere, x>500m:	$\sigma_y\sigma_z = 0.34\ x^{1.37}$

Dermal Exposure to Chemicals
in ambient environment

Activities Cause Dermal Exposure

- Swimming (in river, lake, stream) : high frequency
  (low frequency : water skiing, fishing, standing in the rain)
- Frequency of swimming in natural surface water : number and duration

Exposure Scenarios

- Inherent assumption: clothing prevents dermal contact and subsequent absorption of contaminants
- Swimming and bathing scenarios, past exposure assessments have assumed that 75~100 % skin surface is exposed.
- Data on surface area of body : **Table 6.2-1**

Example 6.3-3

Effect of Chemical Release to Surface Waters on Aquatic Biota

Wastewater Contaminant and Treatment

- Contain a fraction of chemical produced and raw materials
- They must be either treated by facilities at the plant site, or at a publicly owned treatment works *(POTW)*
- Removal of chemicals during wastewater treatment follows
  1. *Adsorption to suspended solids in the primary clarifier, aeration basin, and secondary clarifier*
  2. *Volatilization through surface vaporization in the primary and secondary clarifiers and through air-stripping in aeration basins*
  3. *Biodegradation by aeration microorganisms, commonly in an activated sludge basin*

Models to Predict chemical Fate in a POTW

- Fugacity approach , Clark et al , 1995 ***(Table 6.3-2)***

(http://www.usgs.gov/usa/nwis/sw)

Table 6.3-2

Removal efficiencies in a POTW Calculated by Clark et al , 1995

	Removal Efficiency	Volatilization	Biodegradation	Settled Solids	Effluent
1,1,1-trichloroethane	88%	73%	13%	1%	12%
1,1,2-trichloroethane	85%	69%	15%	1%	15%
toluene	87%	38%	48%	1%	13%
1,4-dichlorobenzene	72%	19%	46%	7%	28%
naphthalene	68%	7%	53%	7%	32%
anthracene	86%	<1%	47%	39%	14%
pyrene	87%	<1%	14%	73%	12%
dibutyl phthalate	81%	<1%	27%	54%	19%
2-ethyl hexyl phthalate	91%	<1%	27%	63%	9%
phenol	99%	<1%	99%	1%	1%
pentachlorophenol	87%	<1%	81%	6%	13%
2,4-D	83%	<1%	79%	4%	17%

Models to Predict Chemical Fate in a POTW

Surface water concentrations of the chemical of concern in free flowing rivers and streams

$$SWC = [Release \times \frac{(1 - WWT/100)}{StreamFlow}]$$

SWC : surface water concentration (mass/volume)
Release : quantity of chemical released in wastewater (mass/time)
WWT : percent removal in wastewater treatment
Stream flow : measured or estimated flow of the receiving stream (volume/time)

(Example 6.3-4)

Ground Water Contamination

Typical Solid waste Treatments

- land disposal or landfills
- less commonly, surface impoundments and land treatment

(problems)

1. Chemicals may leach from the wastes $\Rightarrow$ carry into soils $\Rightarrow$ solubilize in water $\Rightarrow$ drinking water

2. Not discovered until long after the actions leading to the contamination is occurred (delay in detection)

Drinking Water Standards

- US National primary Drinking Water Standards by EPA

(Table 6.3-3)

Modeling Contaminants Migration in Groundwater

- Equations governing flow, physical equilibrium and chemical rxn.

Modeling Contaminants Migration in Groundwater

- Equation for convection and dispersion for dissolved, non-reactive constituents in a homogeneous sediment

$$D\frac{\partial^2 C}{\partial x^2} - u\frac{\partial C}{\partial x} = \frac{\partial C}{\partial t}$$

C : concentration of dissolved solute in the groundwater (mass/volume)
D : hydrodynamic dispersivity in the flow direction (length^2/time)
U : average interstitial groundwater velocity (length/time)
x : distance along the flow path (length)
T : the temporal variable (time)

- Hydrodynamic dispersion is due to mixing of groundwater and molecular diffusion of the dissolved species

$$D = \alpha u + D^*$$

α : dynamic dispersivity of porous media (length, typical value is 0.1)
D*: coefficient of molecular diffusion of the solute (length^2/time)

$$D\frac{\partial^2 C}{\partial x^2} - u\frac{\partial C}{\partial x} = \frac{\partial C}{\partial t}$$

Boundary Condition and Analytical Solution

$$C(x,0) = 0, x \geq 0$$
$$C(0,t) = C_0, t \geq 0$$
$$C(\infty,t) = 0, t \geq 0$$

- Solution for saturated, homogeneous porous media

$$C(x,t) = C_0\{erfc[(x-ut)/(4Dt)^{1/2}] + \exp(u/D)erfc[(x+ut)/(4Dt)^{1/2}]\}$$

erfc : complementary error function tabulated in data books

- Solution for contamination is carried away from the source in x-direction, the concentration distribution from instantaneous release of mass M is

$$C(x,y,z,t)=\frac{M}{8(\pi t)^{2/3}[D_x D_y D_z]^{1/2}}\exp\{-[(x-ut)^2/4D_x t]-[y^2/4D_y t]-[z^2/4D_z t]\}$$

  - Maximum occurs where x = ut, y = 0, z = 0

- Zone in which 99.7% of the contamination mass occurs is described by ellipsoid of $d_i = (2D_i t)^{1/2}$ **(Example 6.3-5)**

6.4 Designing Safer Chemicals

A challenge for chemical engineers is to the general principle in designing chemicals that will reduce toxicity. The semi-quantitative principle and guideline (DeVito, 1996) that can be used in designing safer chemicals.

In designing safer chemicals, it is useful to think about modifying properties so that

- persistence and dispersion in the environment are minimized, ***reducing exposures***
- uptake by the body is minimized, ***reducing dose***, and
- **toxicity is minimized**

This section will consider property modifications that can lead to reduced exposure, dose, and toxicity.

6.4 Designing Safer Chemicals

6.4.1 Reducing Dose

Converting an exposure (e.g., inhaling a chemical) into a dose (e.g., absorption by the blood through the lung membrane) generally involves the transport of a chemical across a membrane.

The three primary membranes of interest are
the lung, which controls uptake of chemicals that are inhaled;
the skin, which controls uptake of chemicals from dermal exposures;
the gastrointestinal tract, which controls uptake of chemicals that are ingested.

Some of the characteristics of these membranes are listed in Table 6.4-1.

Table 6.4-1
Characteristics of membranes that control chemical uptake by the body

Membrane	*Surface area (m^2)*	*Thickness of absorption barrier (μm)*	*Blood flow (L/min)*
Skin	1.8	100-1000	0.5
Gastrointestinal tract	200	8-12	1.4
lung	140	0.2 – 0.4	5.8

Exposure route	*High water solubility*	*Moderate water solubility*	*Low water solubility*
Inhalation			
Ingestion	Potentially high uptake	Potentially high uptake	Low uptake due to poor mass transfer within g.i. tract
Dermal contact			

It is apparent that
the gastrointestinal tract has one of
the greatest surface areas available
for uptake of chemicals
by the body.

gastrointestinal: a. 위장(胃腸)의

6.4 Designing Safer Chemicals

6.4.1 Reducing Dose

The uptake of chemicals across this membrane is controlled by
lipid solubility, water solubility, dissociation constant and molecular size.

High water solubility enhance uptake through gastrointestinal tract because water soluble materials are more easily mobilized in the large and small intestine and the materials therefore experience less mass transfer resistance in migrating to the intestine wall.

In contrast, high lipid solubility enhance uptake and transport across the membrane. Thus, the compounds that are likely to be transported from the gastrointestinal tract into the blood streams are compounds with moderate water solubility and moderate lipid solubility.

Highly water soluble (lipid insoluble) and highly lipid soluble (log Kow > 5, water insoluble) compounds are less likely to be taken up through the gastrointestinal tract.

6.4 Designing Safer Chemicals

6.4.1 Reducing Dose

Molecular weight also plays a role in determining uptake through the gastrointestinal tract. A general guideline is that molecules with molecular weight less than 300 that are both water and lipid soluble are well absorbed, and those with molecular weights in excess of 1000 are sparingly absorbed.

The lung also provides a relatively large surface area for uptake of chemicals. The lung is a relatively thin membrane and because the membrane is so thin, lipid solubility plays less of a role in chemical uptake than for the gastrointestinal tract. High water solubility will promote uptake through the lung, as will the delivery of the compound on fine particles (less than 1 micron in diameter). Small particles can be inhaled deeply and will deposit deep in the lung, allowing the chemicals adsorbed on or dissolved in the particles to reside in the lung for very long periods.

6.4 Designing Safer Chemicals

6.4.1 Reducing Dose

The skin presents a formidable barrier to chemical transport. For a chemical to be taken up through the skin, it must pass through multiple layers. As with the gastrointestinal tract, moderate lipophilicity (log K_{ow} < 5) promotes absorption through skin because transport must occur through both largely lipid and largely aqueous layers.

Finally, note that once a compound is absorbed into the blood stream, it must still reach a target organ. Many organs have their own barrier to uptake that may influence dose (e.g., the blood-brain barrier is more easily crossed by lipophilic materials).

In addition, chemicals may be removed by the body through urine and feces before the target organ is reached (water solubility enhances elimination via this mechanism).

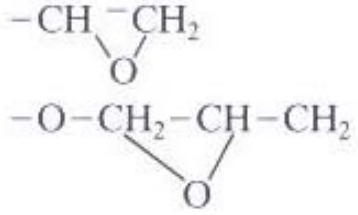
6.4 Designing Safer Chemicals

6.4.2 Reducing Toxicity

Design safer chemicals by reducing toxicity requires knowledge of the mechanisms by which compounds exert a toxic effect. While these mechanisms are not known in many cases, there are a few general mechanisms for toxicity that can be examined, leading to safer chemical designs.

One group of mechanisms associated with toxic effects are the reactions of electrophilic species with nucleophilic substituents of cellular macromoleclues such as *DNA*, *RNA*, *enzymes, and proteins*. Table 6.4-2 presents the possible effects of a number of common electrophilies**.**

Table 6.4-2 examples of Electrophilic substituents and reactions they undergo with biological nucleophilies, and the resulting toxicity

Electrophile	General Structure	Nucleophilic Reaction	Toxic effect
Alkyl halides	R−X where X= Cl,Br,I,F	substitution	Various; e.g., cancer
α,βunsaturated carbonyl and related groups	C=C−C=O C≡C−C=O C=C−C≡N	Michael addition	Various; e.g., cancer, mutations, hepatoxicity, nephrotoxicity, neurotoxicity, hematoxicity
γ diketones	$R_1-C(=O)-CH_2-CH_2-C(=O)-R_2$	Schiff base formation	Neurotoxicity
Terminal epoxides		addition	Mutagenicity, testicular lesions
Isocyanates	−N=C=O −N=C=S	addition	Cancer, mutagenicity, immunotoxicity

*The presence of these substituents in a substance does not automatically mean that the substance is or will be toxic. Other factors, such as bioavailability, and the presence of other substituents that may reduce the reactivity of these electrophiles can influence toxicity as well.

6.4 Designing Safer Chemicals

6.4.2 Reducing Toxicity

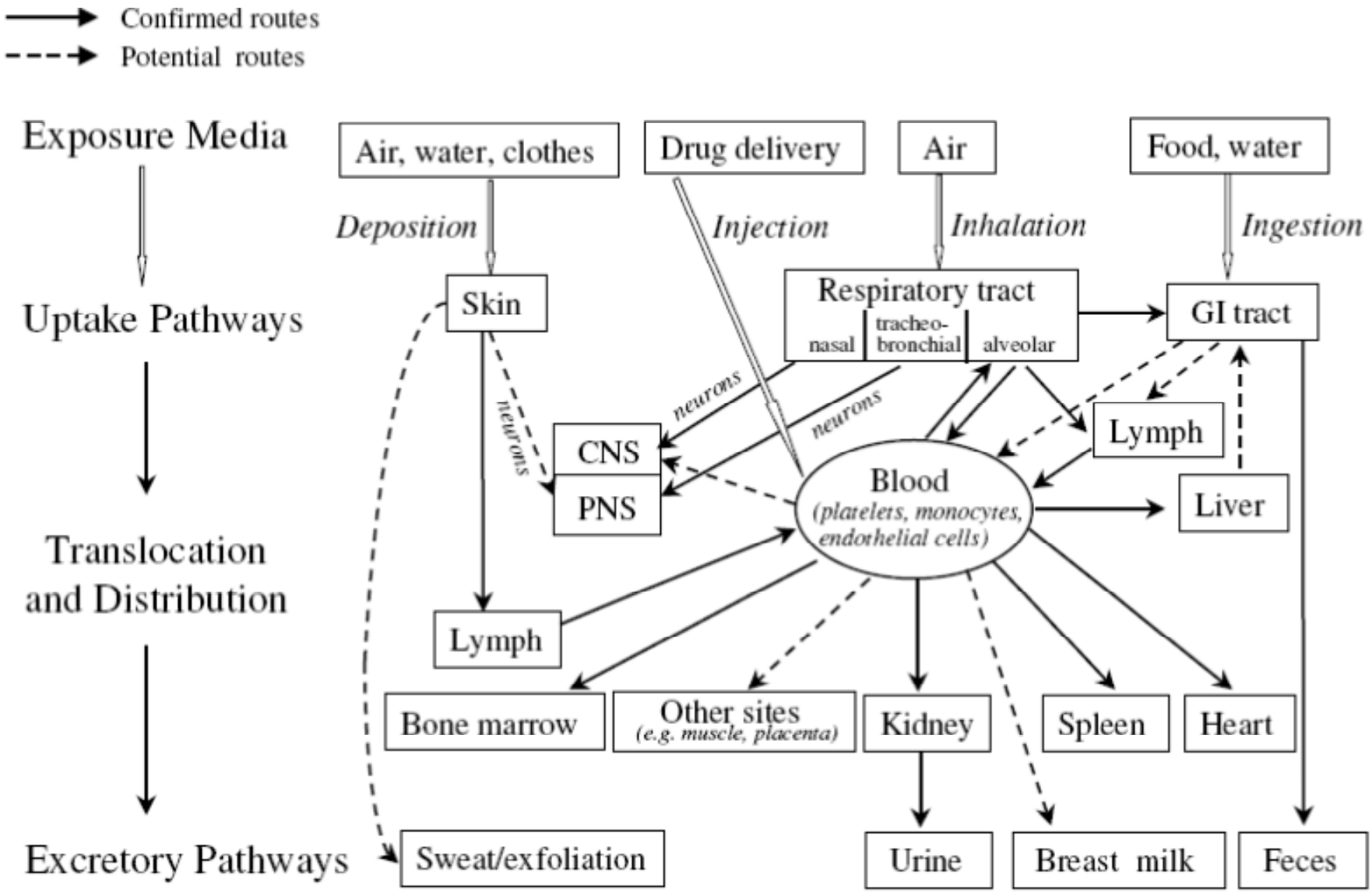
Ideally, the use of these groups would be avoided, however, in many cases the electrophilic groups are necessary to produce a desired property.

For example, for the case of the unsaturated carbonyls, the Michael addition reaction that causes the toxic effect may be the desired commercial property. Nevertheless, the toxic effects can sometimes be reduced by introducing selected substituents.

For example, the addition of a methyl substituent to ethyl acrylate reduces potential health effect. Isocyanates present another example. In this case, the electrophilic nature of the isocyanate can be masked in some applications by converting the material to a ketoxime derivative. The ketoxime derivative is then removed, in situ, during the use of the componds. This reduces potential exposures and the resultant toxicity.

- Case study of structural modification leading to reduce toxicities ***(http://www.epa.gov/greenchemistry/gces.htm)***

Biokinetics of Nano-sized Particles.



Biokinetics of Nano-sized Particles.

Table 3: Applicability of a range of analytical techniques to providing specific physicochemical information on engineered nanomaterials, in the context of toxicity screening studies

		Analytical technique														
		Transmission Electron Microscopy (TEM)	Scanning Electron Microscopy (SEM)	X-Ray Diffraction (XRD)	X-ray Photon Spectroscopy (XPS)	Auger Spectroscopy (AES)	Secondary Ion Mass Spectrometry (SIMS)	Scanning Probe Microscopy	Dynamic Light Scattering (DLS)	Zeta potential	Size Exclusion Chromatography	Analytical Ultracentrifugation	Differential Mobility Analysis (DMA)	Isothermal Adsorption (e.g. BET)	Spectroscopic techniques (UV vis, IR, Raman, NMR)	Elemental analysis (eg ICP-MS/AA etc)
Physicochemical Characteristic	Size distribution (primary particles)	▲	●	●				●	●		●	●	●			
	Shape	▲	●					●	✓				✓			
	Surface area	●	◊					◊	◊			◊	✓	●		
	Composition	●	●	●			▲								●	▲
	Surface chemistry	●	✓		●	●	✓	✓		◊					✓	
	Surface contamination	✓			●	●		✓							✓	
	Surface charge – suspension/ solution									▲						
	Surface charge – powder (use bio fluid surrogate)									▲						
	Crystal structure	●	◊	▲												
	Particle physicochemical structure	▲	●				✓									
	Agglomeration state	▲	●	✓				●	✓		✓	✓	●			
	Porosity	◊											●	●		
	Heterogeneity	▲	●					◊							✓	

Other applicable techniques are available that have not been listed.
▲Highly applicable
● Capable of providing information in some cases
✓ Capable of providing information in some cases, with validation from more accurate/applicable techniques
◊ Capable of providing qualitative or semi-quantitative information

Biokinetics of Nano-sized Particles.

While many uptake and translocation routes have been demonstrated, others still are hypothetical and need to be investigated. Largely unknown are translocation rates as well as accumulation and retention in critical target sites and their underlying mechanisms.

These as well as potential adverse effects will be largely dependent on physicochemical characteristics of the surface and core of nano-sized particles. Both qualitative and quantitative changes in nanosized particles' biokinetics in a diseased or compromised organism need also to be considered.

US Presidential Green Chemistry Challenge

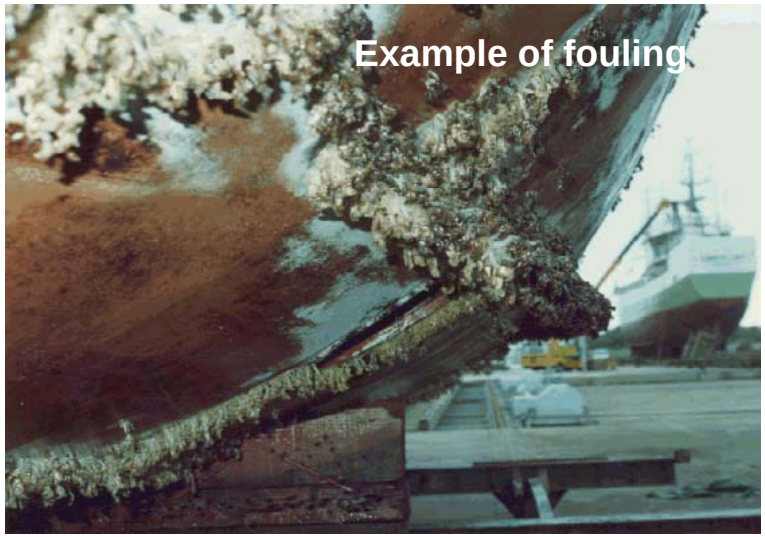
1996: Designing Safer Chemicals Award

Sea Nine™ Biocide

Sea Nine™

4,5-dichloro-2-n-octyl-4-isothiazolin-3-one

- **Attributes**
  - No heavy metals
  - Reduces drag due to growth build up on ship's surface
  - Conserves fuel and reduces emissions
- **Markets**
  - Marine anti-foulants
  - Paint film (in container and on surface)
  - Paper industry (wet pulp)



Which of the 12 Principles are supported by each product ?

- **Sea Nine ™ Biocide**
  - 1 prevent waste (of final product)
  - 3 less hazardous synthesis
  - 4 design safer chemicals
  - 6 design for energy efficiency (of final product)
  - 8 reduce derivatives
  - 10 design for degradation