Dose - Response Relationships

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Learning Objectives

Part 1: Understand the quantitative relationship between toxicant exposure and induced（引起的） effects (Dose - Response Curves).

Part 2: Know about Joint Toxic Effect and Types.

Part 3: Know about four Toxicokinetic（毒物代谢动力）Phases: Absorption, Distribution, Metabolism/Storage, Elimination.

Part 1

1.1 The Father of Modern Toxicology

Swiss physician（医师）**Paracelsus** (1493-1541) credited with being

"The Father of Modern Toxicology."

"All substances are poisons: there is none which is not a poison. The right dose differentiates（区分）a poison from a remedy（药物）."

1.2.1 What is a Dose?

- The amount of a substance entering the body. 机体一次接触某种外源化学物质的量

- Exposure is characterized by
  - Number of doses. 量
  - Frequency of dosing. 次数、频率
  - The total period of time for the exposure. 持续的时间

1.2.2 Quantifying the Dose 剂量的定量

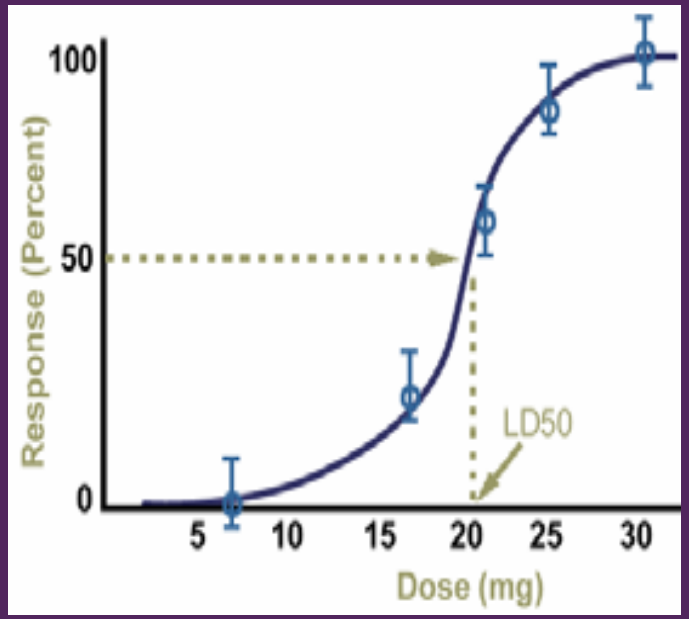
- Gram (g) is the standard unit but mg is typical of most exposures in toxicology.
- Dosage: mg (dose) / kg (bw) / day (duration)
  - mg/kg/d
- Exposures are quantified in relation to the media.
  机体生存环境中的浓度
  - mg/L in water.
  - mg/kg in food.
  - mg/m^3 in air.
- Variation in units common (ppm, ppb).

1.2.3 Lethal Dose(LD)：数值越小，毒性越强

LD_{100} (absolute lethal dose，绝对致死量)：引起一群个体全部死亡所需的最低剂量。

LD_{50} (half lethal dose，半数致死量)：引起一群个体50%死亡所需的剂量。 Or

LC_{50} (half lethal concentration，半数致死浓度)：引起一群个体50%死亡所需的剂量。



LD_{01} (minimum lethal dose，最小致死量)：仅引起一群个体中个别个体死亡的最低剂量。

LD_0 (maximal lethal dose，最大耐受量)：在一群个体中不引起死亡的最高剂量。

1.3.1 Effect & Response

Effect（效应）是指一定剂量的外源化学物与机体接触后可引起的生物学变化。此种变化的程度用计数或计量单位如若干个、mg等来表示。

Response（反应）是指一定剂量的外源化学物与机体接触后，呈现某种效应并达到一定程度的比率，或者产生效应的个体数在某一群体中所占的比率，一般以%或比值表示。

1.3.2 Types of Response

按所观察的效应指标的不同按性质分类：

- Graded Response (量反应)：（药理）效应强弱是连续增减的量变，可用具体数量或最大反应的百分率表示。如血压、心率、血脂浓度、平滑肌收缩或松弛强度等。

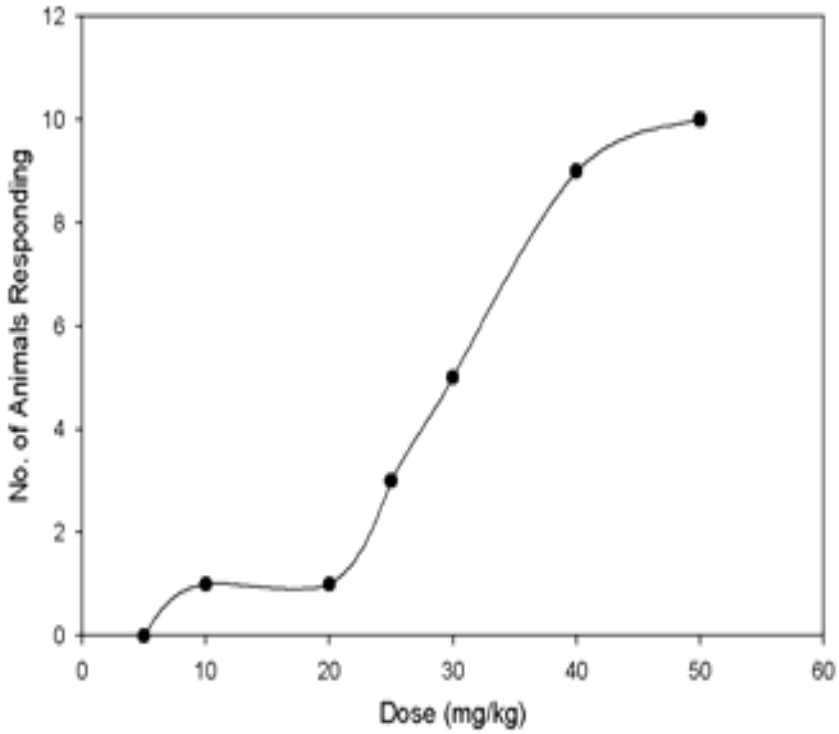
- All-or-none Response (质反应)：（药理）效应只能用全或无，阳性或阴性表示，必需用多个动物或多个实验标本以阳性率表示。如死亡与生存、抽搐与不抽搐等

1.3.3 Graded Response & All-or-none Response

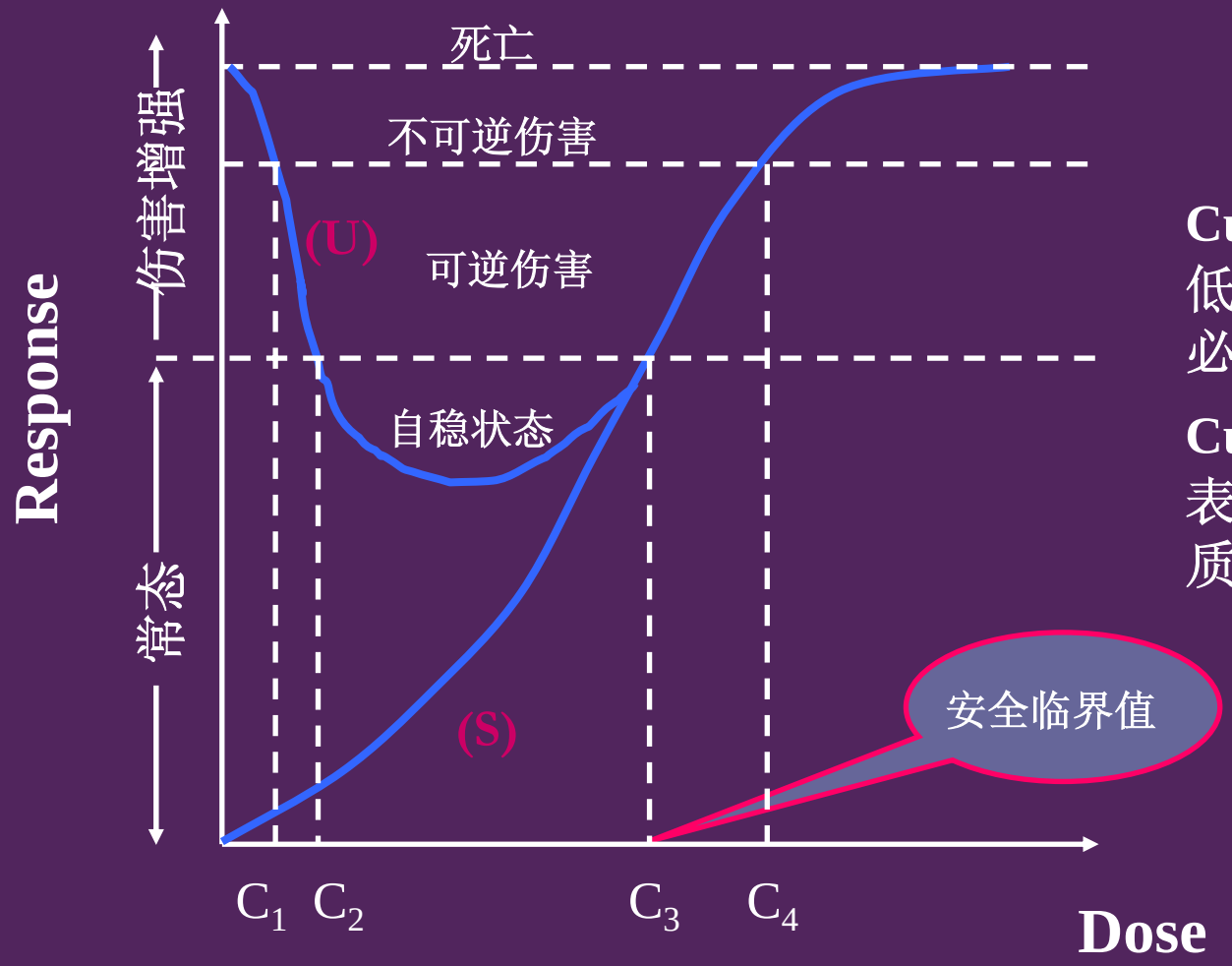
- 量反应决定效应的因素是剂量
- 量反应的量效曲线是测定不同剂量下药物效应强度的指标
- 量反应所研究的对象是个体
- 质反应决定效应的因素是个体反应的差异性
- 质反应的量效曲线是测定某一剂量下某种效应发生频数的指标
- 质反应所研究的对象是群体

1.4.1 Example Dose-Response Relationship

Dose (mg/kg)	No. of animals responding
5	0
10	1
20	1
25	3
30	5
40	9
50	10



1.4.2 Dose-Response Relationship:
S-shaped Curve & U-shaped Curve



Curve(U):
低浓度下表现为生命必需物质效应。

Curve(S):
表现为生命非必需物质的效应。

Part 2

2.1 Joint Toxic Effect 联合毒性作用

Toxic Effect：毒性作用，又称为毒效应，是化学物质对机体所致的不良或有害的生物学改变，故又可称为不良效应、损伤作用或损害作用。
是其本身或代谢产物在作用部位达到一定数量并停留一定时间，与组织大分子成分互相作用的结果。

Joint Toxic Effect：凡两种或两种以上的化学物同时或短期内先后作用于机体所产生的综合毒性作用。

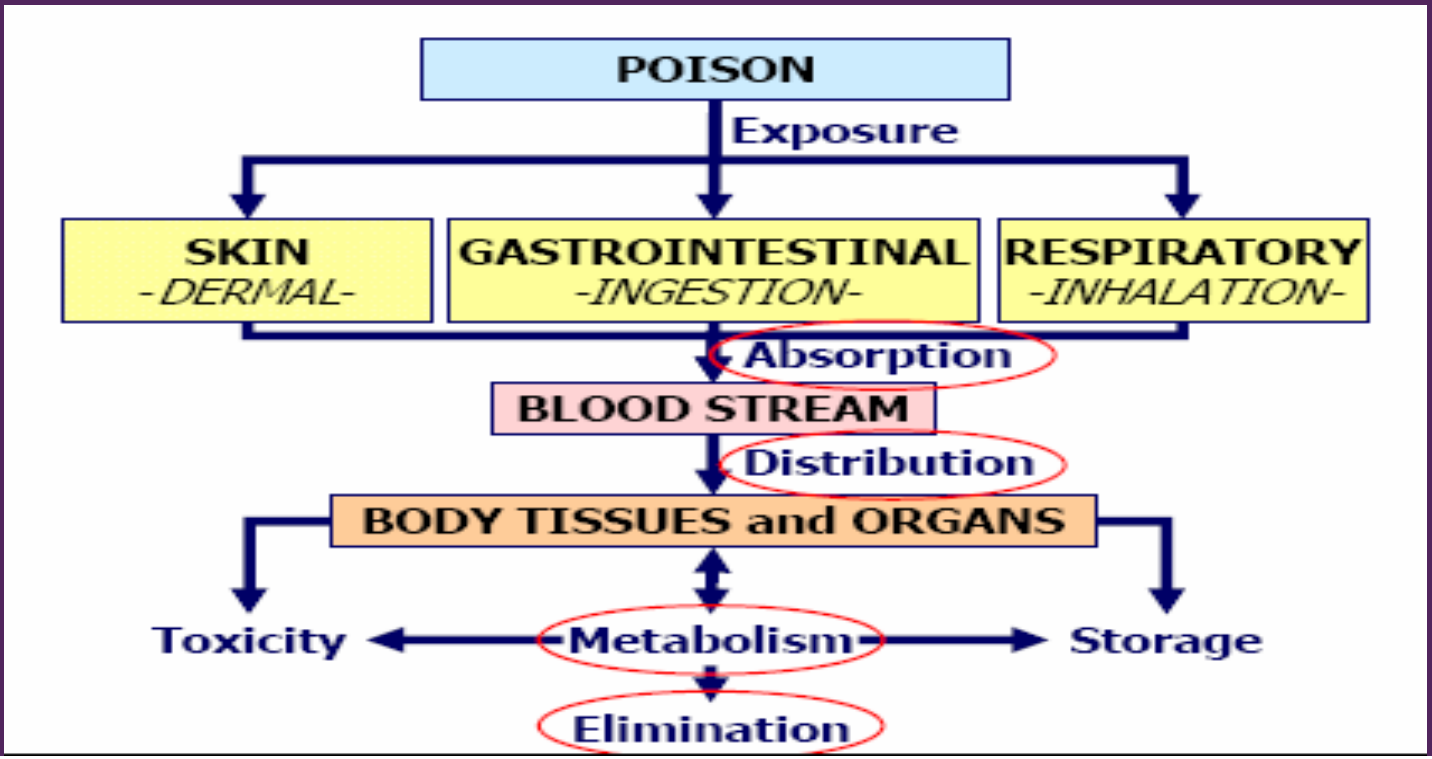
2.2 Types of Joint Toxic Effect

- Additional Joint Action（相加作用）：单独作用的总和
- Synergism（协同作用）：远远超过单独作用强度的总和
- Potentiation（增强作用）：本身无毒，但能增加其他化学物的毒性
- Antagonism（拮抗作用）：相互干扰，降低毒性
- Independent Joint Action（独立作用）：彼此无影响

Part 3

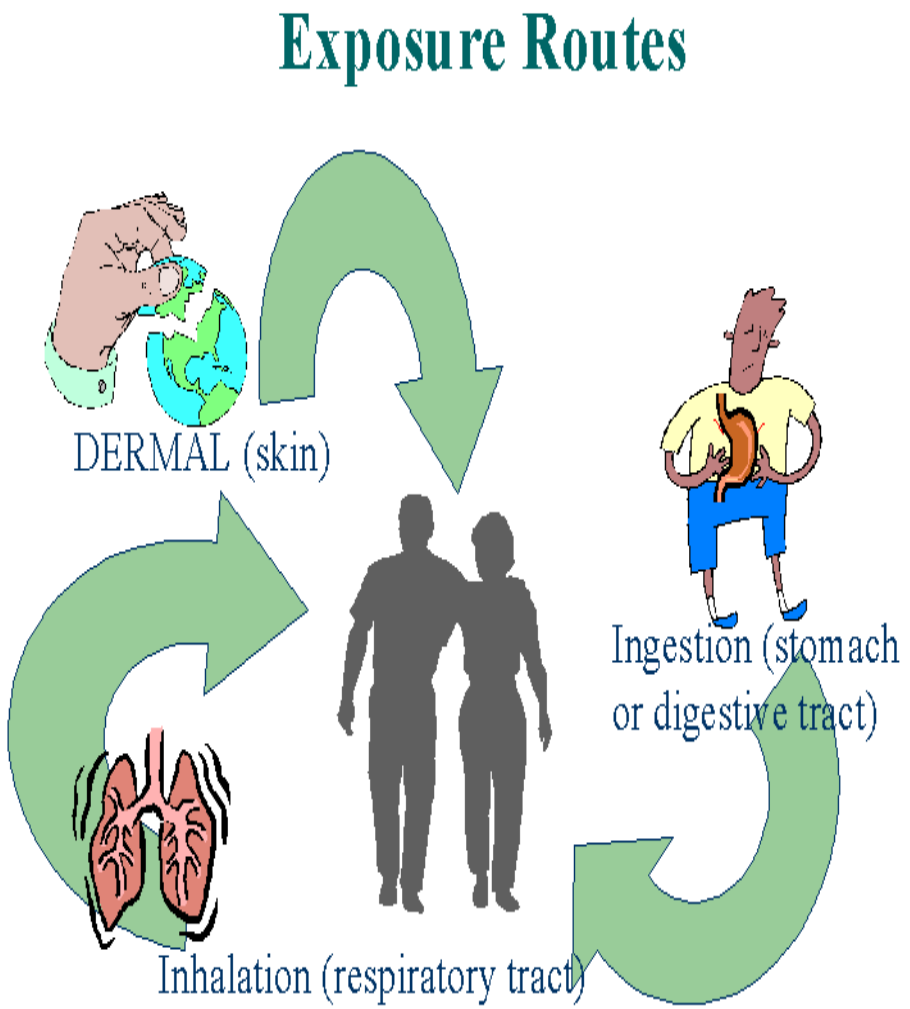
3 Toxicokinetic（毒物代谢动力）phase

- Four processes are involved:
  - Absorption: how toxicants enter an organism.
  - Distribution: how transported.
  - Metabolism/Storage: where they aggregate（聚集）.
  - Elimination: how removed.



3.1 Absorption

- Ingestion
  - 口腔：停留时间短，吸收量少
  - 胃：易吸收酸性物质
  - 小肠：弱有机碱易被吸收
- Inhalation
  - 肺是呼吸道中最主要的吸收器官
- Dermal
  - 表皮&毛囊、汗腺及皮脂腺



3. 2 Distribution

污染物被吸入血液和体液后，随血液和淋巴液的流动分散到全身各组织器官的过程

- Blood-Brain Barrier：阻止毒物进入中枢神经系统
- Placental Barrier：阻止毒物由母体透过胎盘进入胚胎

3. 3 Metabolism/Storage

- Storage Depot
  - Plasma protein (血浆蛋白): 可逆性非共价结合
  - Liver & Kidney：含有特殊的结合蛋白
  - Adipose tissue (脂肪组织) :脂溶性化合物易被吸收和贮存
  - Skeletal tissue (骨骼组织) ：某些成分和化学物有特殊亲和力
- Significance
  - Protection from acute effect
  - Potentially risk for chronic effect

3. 4 Elimination

- Kidney
- Bile(胆汁)
- Lung
- Sweat, Saliva(唾液), tears, Breast milk
- Nail & Hair
- Dejection(粪便)