Appendix 1-1 U.S. Laws That Have a Basis in Toxicology

Responsible agency	Law
Food and Drug Administration (FDA)	Federal Food, Drug, and Cosmetic Act
Environmental Protection Agency (EPA)	Federal Insecticide and Rodenticide Act
	Clean Air Act
	Resource Conservation and Recovery Act
	Safe Drinking Water Act
	Toxic Substances Control Act
Consumer Product Safety Commission (CPSC)	Consumer Product Safety Act
	Federal Hazardous Substances Act
Occupational Safety and Health Administration (OSHA)	Occupational Safety and Health Act

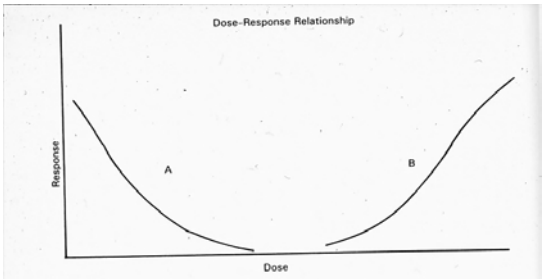

Figure 4-1 Schematic representation of dose-response relationship. Curve A: certain essential nutrient, with which the response (deficiency syndrome) increases along with decreased intake. Curve B. Most chemicals: with which the response (toxic effects) increases along with increased intake. Certain substances, e.g. selenium, exhibit both types of responses.

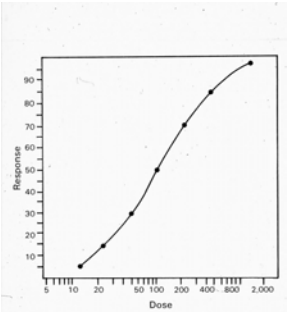

Figure 2–2. Diagram of dose-response relationship. Dosage is most often expressed as mg/kg and plotted on a log scale.

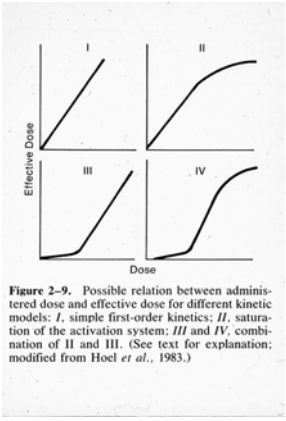

Figure 2–9. Possible relation between administered dose and effective dose for different kinetic models: *I*, simple first-order kinetics; *II*, saturation of the activation system; *III* and *IV*, combination of II and III. (See text for explanation; modified from Hoel *et al.*, 1983.)

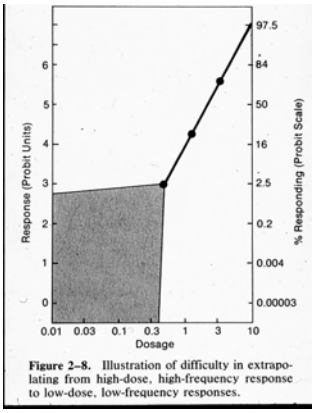

Figure 2–8. Illustration of difficulty in extrapolating from high-dose, high-frequency response to low-dose, low-frequency responses.

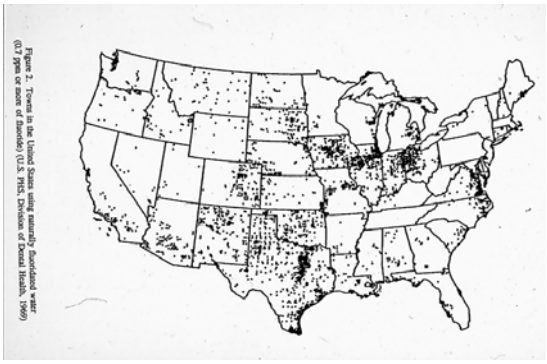

Figure 2. Towns in the United States using naturally fluoridated water (0.7 ppm or more of fluoride) (U.S. PHS, Division of Dental Health, 1969)

finding. This observation set the stage for fluoride measurements of drinking water as related to the degree of mottling (a historical term used to describe discolored teeth of any etiology).

ASSOCIATION BETWEEN MOTTLED ENAMEL AND DENTAL CARIES, AND DOSE-RESPONSE EFFECT

Mottling was classified by degree, from barely detectable flecks of white on the normally translucent teeth, through yellow to deepening brown and even corroded-looking teeth (Dean, 1938). In 1916 Black noted that caries were less frequent among residents with mottled teeth in Colorado Springs than among people living in areas where mottling did not occur. Elsewhere in the world others also suggested an association between mottled teeth and reduced caries scores (reviewed by Dean, 1938). Next, Dean and coworkers (1942a) conducted a systematic survey of dental caries in relation to the fluoride content in the water of 21 U.S. cities. These investigators found that the frequency of caries decreased as the content of fluoride in the water supplies increased (Figure 1). This dose-response effect provided evidence that fluoride was related to a reduction in dental caries.

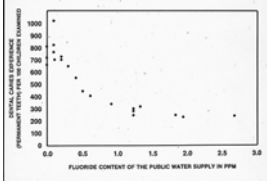

Figure 1. Relationship between the amount of dental caries (permanent teeth) observed in 7,257 selected 12-14 year old white school children of 21 cities of 4 states and the fluoride content of public water supply (Dean et al., 1942)

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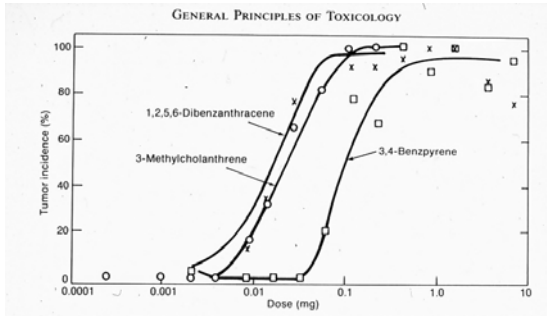


Figure 2–5. Dose-response relationship for carcinogens. Three carcinogenic polycylic aromatic hydrocarbons were administered subcutaneously in a single dose, each to a group of 20 mice. The incidence of sarcomas at the site of injection was noted. (Modified from Bryan and Shimkin, 1943.)

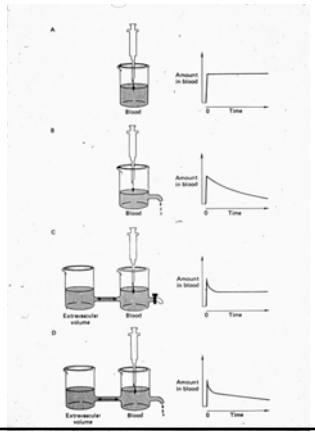
Table 2–1. APPROXIMATE ACUTE LD50'S OF SOME REPRESENTATIVE CHEMICAL AGENTS

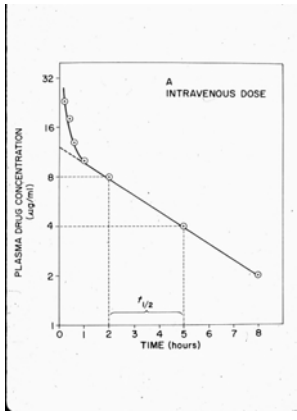
AGENT	LD50 (mg/kg)*
Ethyl alcohol	10,000
Sodium chloride	4,000
Ferrous sulfate	1,500
Morphine sulfate	900
Phenobarbital sodium	150
Picrotoxin	5
Strychnine sulfate	2
Nicotine	1
d-Tubocurarine	0.5
Hemicholinium-3	0.2
Tetrodotoxin	0.10
Dioxin (TCDD)	0.001
Botulinum toxin	0.00001

* LD50 is the dosage (mg/kg body weight) causing death in 50 percent of the exposed animals.

Table 5-2 Effect of Age on Acute Toxicity of Malathion, DDT, and Dieldrin in Rats

Pesticide	Age	LD_{50} (mg/kg) with 95% confidence limits
Malathion	Newborn	134.4 (94.0–190.8)
	Pre-weaning	925.5 (679.0–1261.0)
	Adult	3697.0 (3179.0–4251.0)
DDT	Newborn	>4000.0
	Pre-weaning	437.8 (346.3–553.9)
	Adult	194.5 (158.7–238.3)
Dieldrin	Newborn	167.8 (140.8–200.0)
	Pre-weaning	24.9 (19.7–31.5)
	Adult	37.0 (27.4–50.1)





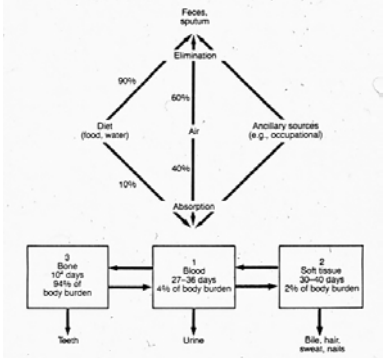


Figure 4. A simple three-compartment model for absorption, retention, and elimination of lead in humans
Quantitative estimates apply to adult males. Adapted with permission from Reference 5

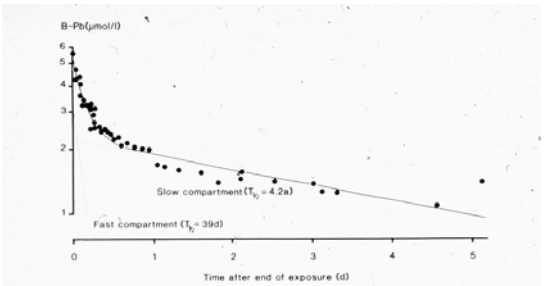


Fig. 2. Decay of blood lead level (logarithmic) after end of exposure in an ex-lead worker. A linear two-compartment model was fitted to the data. A "background" of 0.3 μmol/l has been subtracted. Biological half-times ($T_{1/2}$) for the compartments are given.

Releases of bioaccumulators to air, water, and land, 1991

Chemical	Total Air/Water/Land Releases (Pounds)
Anthracene	59,085
Benzoic trichloride	7,947
Chlordane	1,428
Decabromodiphenyl oxide	271,632
Dibutyl phthalate	164,008
1,2-Dichlorobenzene	443,567
1,4-Dichlorobenzene	338,730
Di-(2-ethylhexyl) phthalate	1,203,035
Heptachlor	5
Hexachlorobenzene	953
Hexachloro-1,3-butadiene	4,093
Hexachlorocyclo-pentadiene	25,484
Hexachloroethane	22,711
Mercury	22,823
Mercury compounds	2,905
Methoxychlor	580
4,4'-Methylenebis(2-chloroaniline)	1,362
Pentachlorophenol	16,296
Polychlorinated biphenyls (PCBs)	10
1,2,4-Trichlorobenzene	415,891
Total	**3,002,545**

Source: Selected U.S. industries reporting to the Environmental Protection Agency.

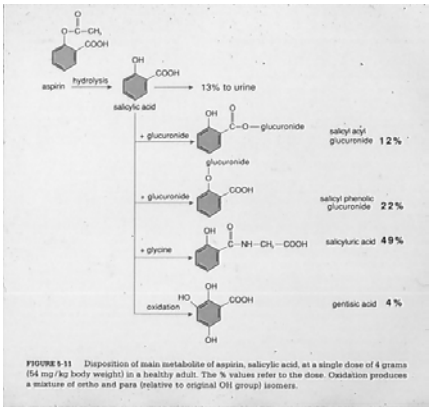
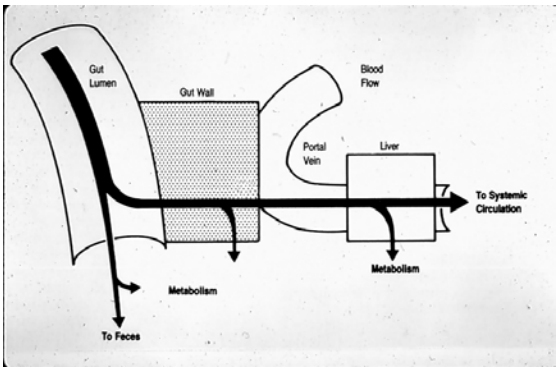


FIGURE 5-11 Disposition of main metabolite of aspirin, salicylic acid, at a single dose of 6 grams (94 mg/kg body weight) in a healthy adult. The % values refer to the dose. Oxidation produces a mixture of ortho and para (relative to original OH group) isomers.



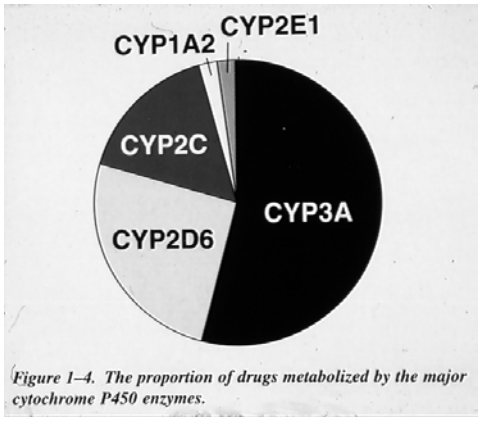


Figure 1–4. The proportion of drugs metabolized by the major cytochrome P450 enzymes.

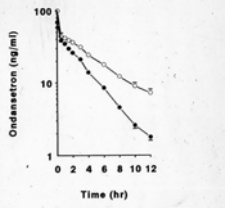


Figure 2. Plasma concentrations (mean ± SEM) of ondansetron in 10 subjects after intravenous administration of 8 mg ondansetron following pretreatment with 600 mg rifampin or placebo once daily for 5 days. *Open circles*, After placebo; *solid circles*, after rifampin.

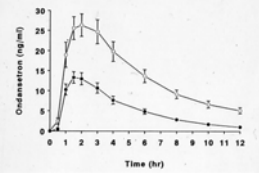


Figure 1. Plasma concentrations (mean ± SEM) of ondansetron in 10 subjects after oral administration of 8 mg ondansetron following pretreatment with 600 mg rifampin or placebo once daily for 5 days. *Open circles*, After placebo; *solid circles*, after rifampin.

Grapefruit juice substantially increases plasma concentrations of buspirone

Background: Buspirone has a low oral bioavailability because of extensive first-pass metabolism. The effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of orally administered buspirone is not known.
Methods: In a randomized, 2-phase crossover study, 10 healthy volunteers took either 200 mL double-strength grapefruit juice or water 3 times a day for 2 days. On day 3, each subject ingested 10 mg buspirone with either 200 mL grapefruit juice or water, and an additional 200 mL was ingested ½ hour and 1½ hours after buspirone administration. Timed blood samples were collected up to 12 hours after ingestion, and the effects of buspirone were measured with 6 psychomotor tests up to 8 hours after ingestion.
Results: Grapefruit juice increased the mean peak plasma concentration of buspirone 4.3-fold (range, 2-fold to 15.6-fold; $P < .01$) and the mean area under the plasma buspirone concentration–time curve 9.2-fold (range, 3-fold to 20.4-fold; $P < .01$). The time of the peak concentration (t_{max}) of buspirone increased from 0.75 to 3 hours ($P < .01$), and the elimination half-life ($t_½$) was slightly increased ($P < .01$) by grapefruit juice. A significant increase in the pharmacodynamic effects of buspirone by grapefruit juice was seen only in subjective overall drug effect ($P < .01$).
Conclusions: Grapefruit juice considerably increased plasma buspirone concentrations. The probable mechanism of this interaction is delayed gastric emptying and inhibition of the cytochrome P450 3A4–mediated first-pass metabolism of buspirone caused by grapefruit juice. Concomitant use of buspirone and at least large amounts of grapefruit juice should be avoided. (Clin Pharmacol Ther 1998;64:655-60.)

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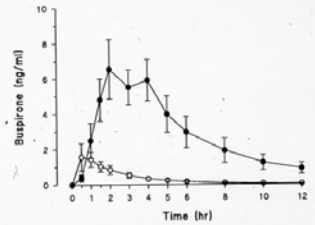

Figure 1. Plasma concentrations (mean value ± SEM) of buspirone among 10 healthy volunteers after a single oral dose of 10 mg buspirone, after ingestion of 200 mL double-strength grapefruit juice *(solid circles)* or water *(open circles)* 3 times a day for 2 days, and on day 3 with buspirone administration and ½ hour and 1½ hours later.

Inhibition of chlorzoxazone metabolism, a clinical probe for CYP2E1, by a single ingestion of watercress

To investigate the effect of watercress on the metabolism of chlorzoxazone, an in vivo probe for CYP2E1, the oral pharmacokinetics of chlorzoxazone was studied in 10 healthy volunteers before and after a single ingestion of a watercress homogenate (50 gm). A third chlorzoxazone pharmacokinetic study was performed after a 1-week treatment with isoniazid (300 mg/day), a well-known CYP2E1 inhibitor. Ingestion of watercress or isoniazid did not affect the oral absorption of chlorzoxazone. The area under the chlorzoxazone plasma concentration–time curve was significantly increased by 56% ($p < 0.05$) after watercress ingestion and by 135% ($p < 0.001$) with isoniazid treatment. Similarly, chlorzoxazone elimination half-life was prolonged after watercress (53%; $p < 0.05$) and isoniazid (104%; $p < 0.01$) administration. These results show that a single ingestion of watercress inhibits the hydroxylation of chlorzoxazone, an in vivo probe for CYP2E1. (Clin Pharmacol Ther 1998;64:144-9.)

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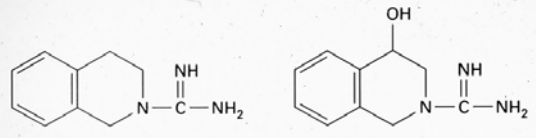

Debrisoquine 4–Hydroxydebrisoquine

Fig. 7.1. Chemical structure of debrisoquine and its major metabolite, 4-hydroxydebrisoquine. (From Mahgoub *et al.* 1977.)

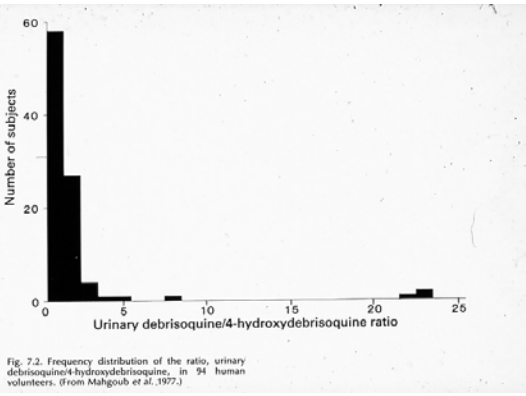

Fig. 7.2. Frequency distribution of the ratio, urinary debrisoquine/4-hydroxydebrisoquine, in 94 human volunteers. (From Mahgoub *et al.*,1977.)