

1595

**"THREE TREE"
POISON**

"URARI"

**"HE TO WHOM IT COMES,
FALLS"**

CURARE



CLAUDE BERNARD

1844

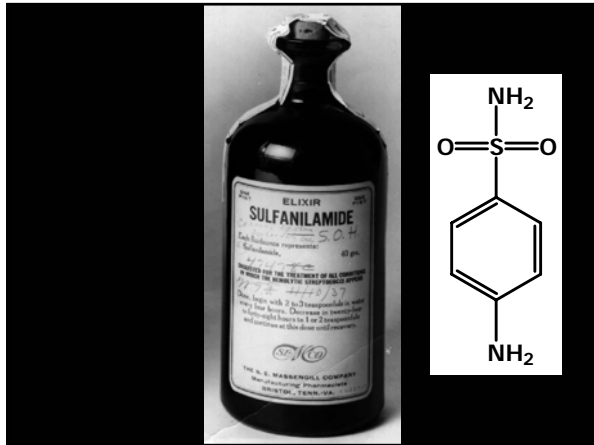


**DR. HAROLD GRIFFITH IN MONTREAL
BECAME THE FIRST PHYSICIAN TO USE
CURARE TO RELAX THE MUSCLES OF A
PATIENT UNDERGOING AN APPENDECTOMY
(1942)**

1937

SOME PATIENTS WHO HAD TAKEN A NEW MEDICATION FOR BACTERIAL INFECTION EXPERIENCED EXCRUCIATING ABDOMINAL PAIN, THRASHED ABOUT, VOMITED, WENT BLIND AND THEN DIED.

AUTOPSIES REVEALED CATASTROPHIC KIDNEY AND LIVER FAILURE.



DIETHYLENE GLYCOL



“THE RATS THAT TOOK IT GOT SICK AND SHRIVELLED AND THE URINE GOT RED AND THEY WOULD SHORTLY AFTER DIE.”

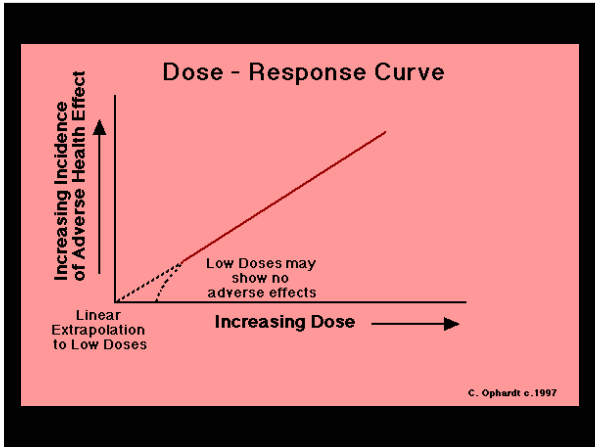
**FRANCES KELSEY
UNIVERSITY OF CHICAGO**

FDA INSPECTORS RECOVERED 234 OF THE 240 GALLONS THAT HAD BEEN MANUFACTURED, BUT 107 PEOPLE DIED AND 260 WERE LEFT WITH PERMANENT DISABILITIES.

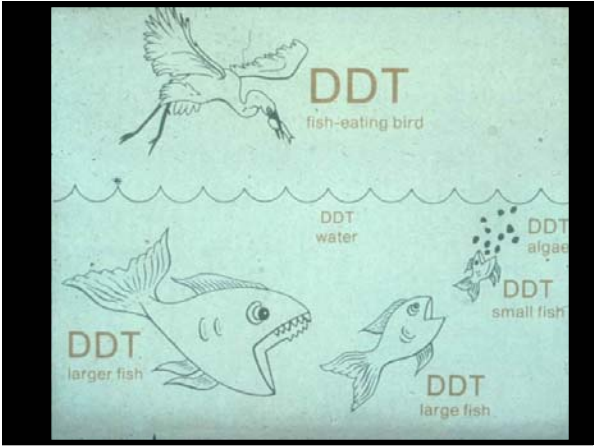
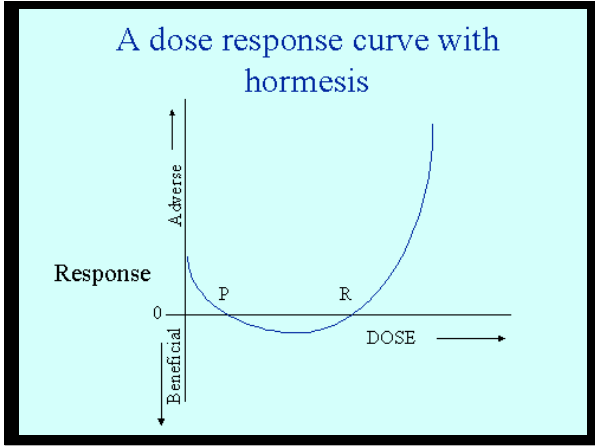
ON JUNE 15, 1938 PRESIDENT ROOSEVELT SIGNED INTO LAW THE FEDERAL FOOD, DRUG AND COSMETIC ACT. COMPANIES NOW HAD TO PROVE THEIR PRODUCT WAS SAFE.

TOXICOLOGY
THE STUDY OF THE
EFFECTS OF CHEMICALS
ON LIVING ORGANISMS

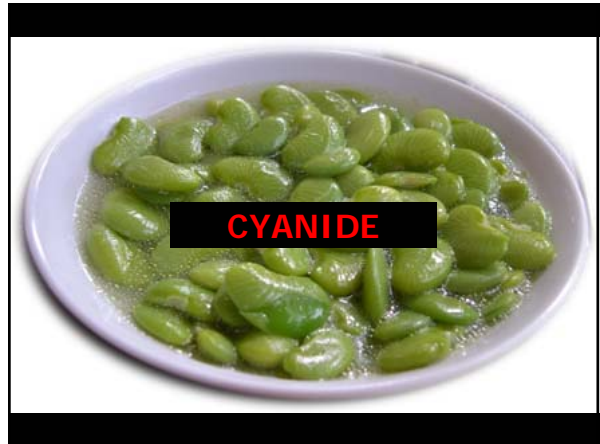
"Sola dosis facit venenum"
Paracelsus
"Only the dose makes the poison"
Paracelsus



"HORMESIS"



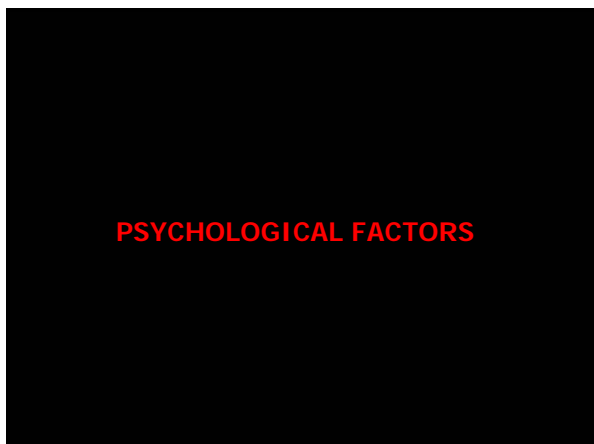
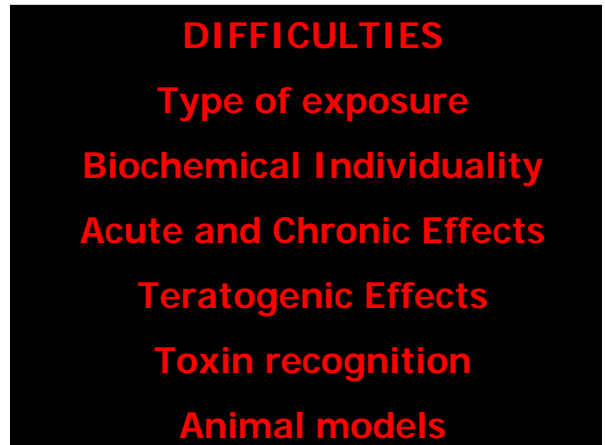
RISK = TOXICITY x EXPOSURE



LETHAL DOSE

BOTULIN	0.03 mcg
TETRODOTOXIN	10.0 mcg
CYANIDE	10,000 mcg







**DR. HARVEY W. WILEY
CHIEF OF THE BUREAU OF CHEMISTRY**

**BORAX
SALICYLIC ACID
SULFURIC ACID
SODIUM BENZOATE
FORMALDEHYDE
COPPER SULFATE**

**DOSAGE RANGED
FROM 0.5 TO 4
GRAMS DAILY**

**ALL MEALS EATEN AT
"HYGIENIC TABLE"
CHEMICALS CONSUMED IN
GELATIN CAPSULES
URINE AND FECES COLLECTED**

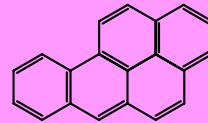
**NAUSEA, VOMITING, STOMACH
ACHES
NO LONG TERM CONSEQUENCES**

**NAUSEA, VOMITING, STOMACH
ACHES
NO LONG TERM CONSEQUENCES
PURE FOOD AND DRUG ACT OF
1906**

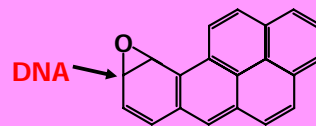
BORAX
SALICYLIC ACID
SULFURIC ACID
SODIUM BENZOATE
FORMALDEHYDE
COPPER SULFATE

DETOXICATION
PHASE I ENZYMES
PHASE 2 ENZYMES

THE CYTOCHROME P450
FAMILY OF ENZYMES ARE
THE MOST IMPORTANT
PHASE 1 ENZYMES

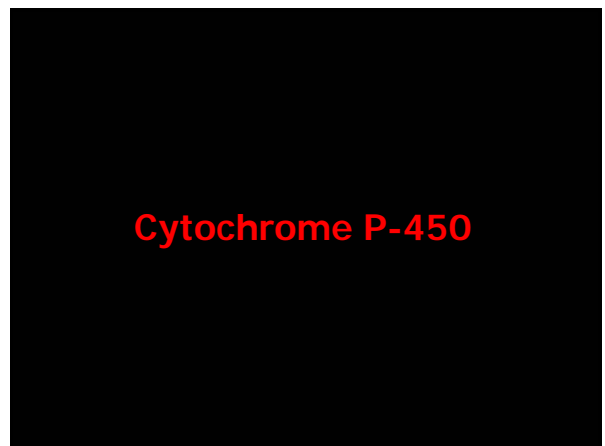


CARCINOGEN



CARCINOGEN

DETOXICATION ENZYMES CAN BE INDUCED

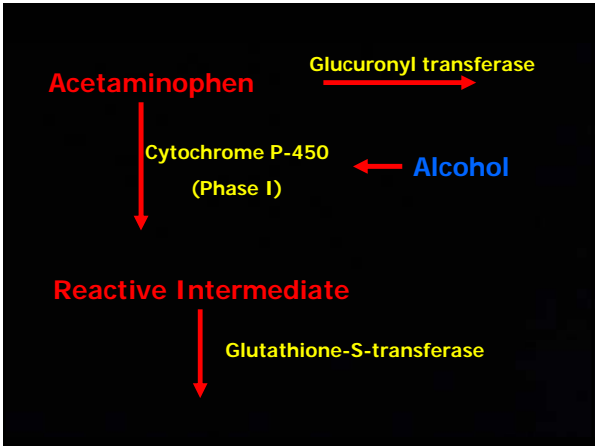
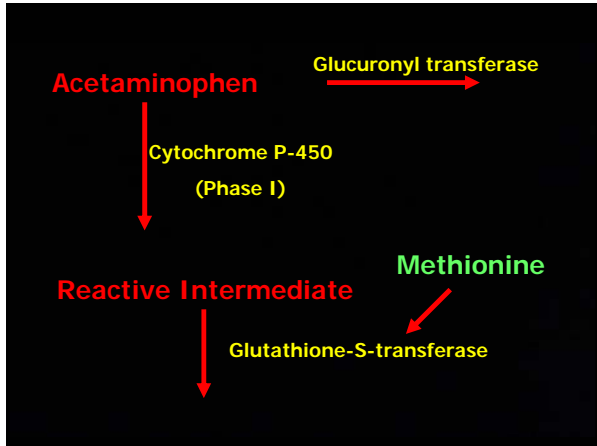
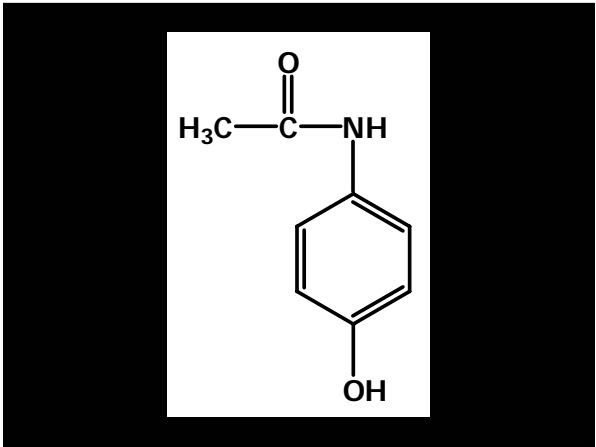


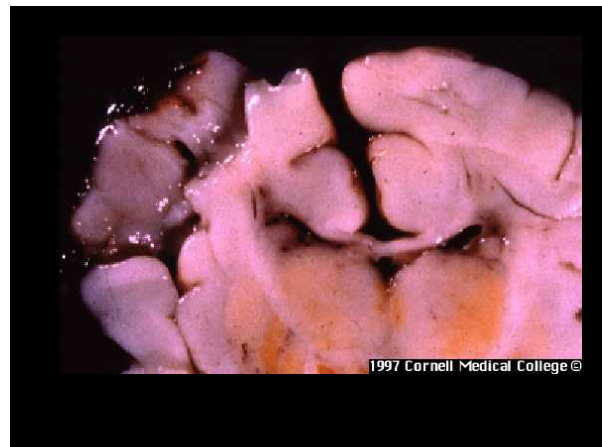
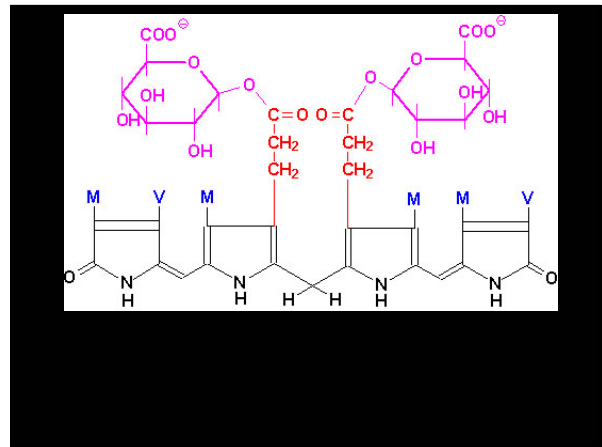
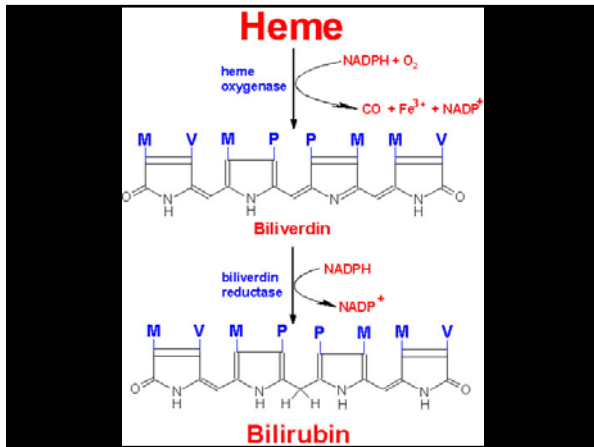
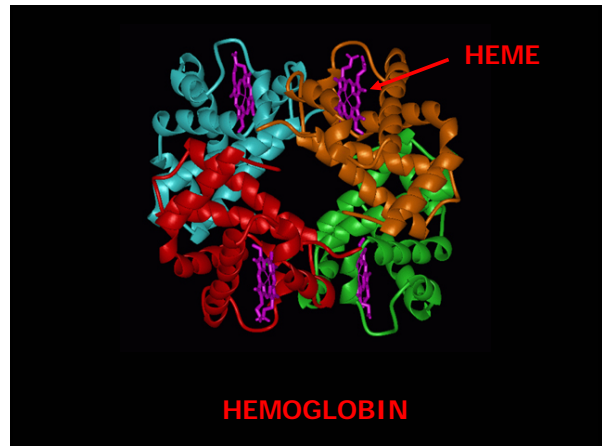
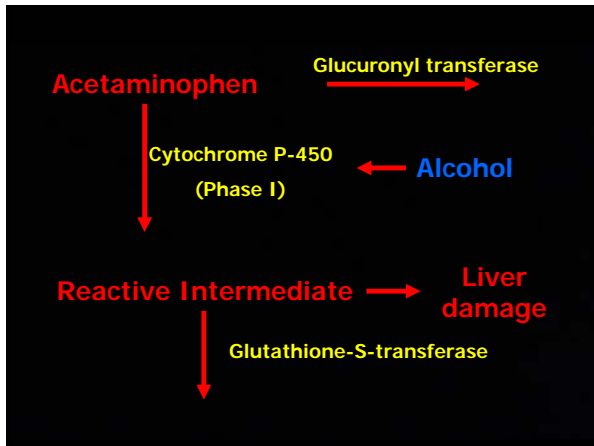
- Tetracycline
- Tamoxifen
- MAO Inhibitors
- Protease inhibitors
- Corticosteroids
- Antidepressants
- Anesthetics
- Contraceptives

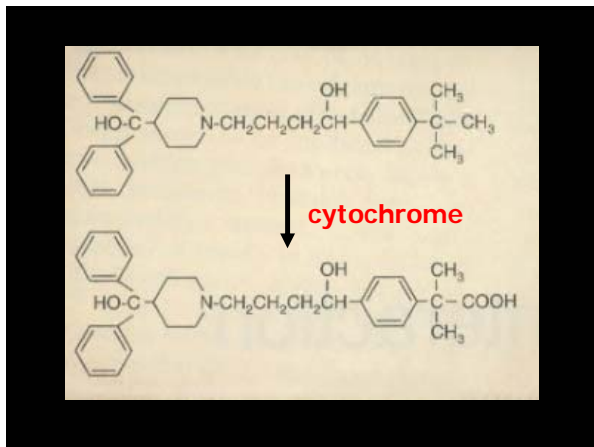
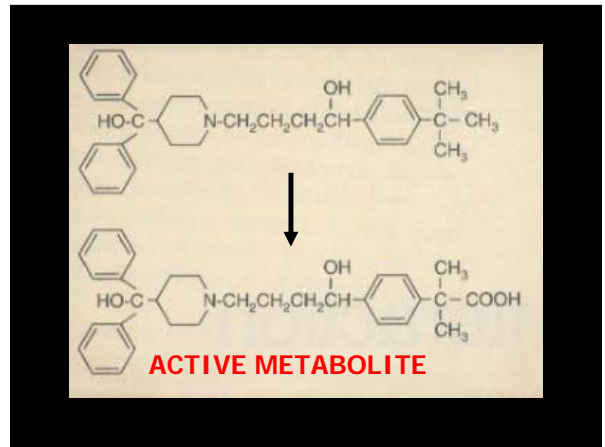
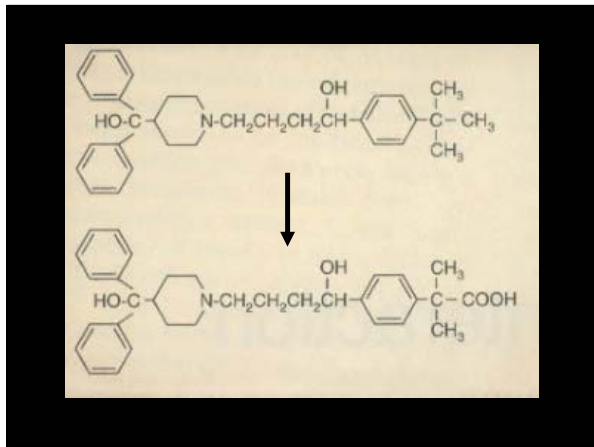
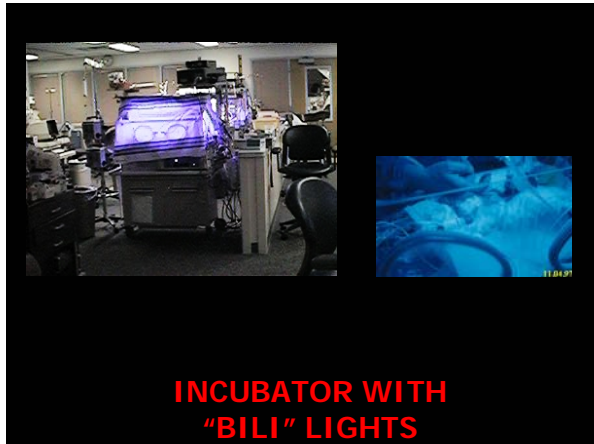


Xanax .25 mg
Chemical name:
alprazolam

COMMON ANTI-ANXIETY AGENT







Terfenadine-Ketoconazole Interaction
 Pharmacokinetic and Electrocardiographic Consequences

Carl E. Foyok, M.D., MPH, Dale C. Williams, M.D., Edwin J. Sargent, Ph.D., Eric W. Corwin, Pharm.D., and C. Miller, M.D., Todd R. Callahan, M.D., PhD.

Objective.—To examine prospectively the effects of ketoconazole on the pharmacokinetics and electrocardiographic conduction parameters (corrected QT interval) of terfenadine in men and women.

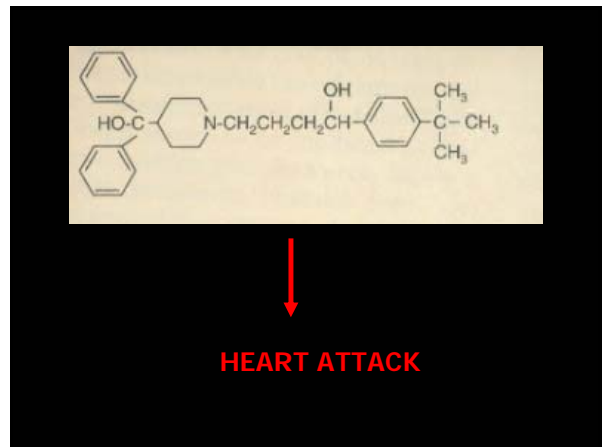
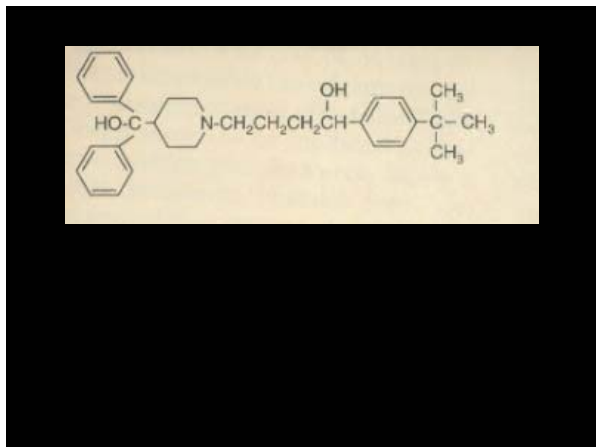
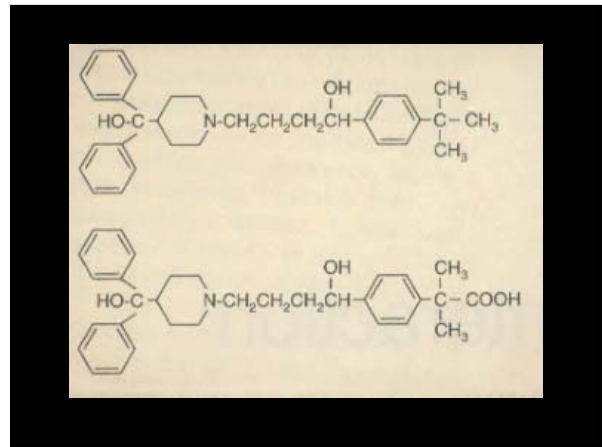
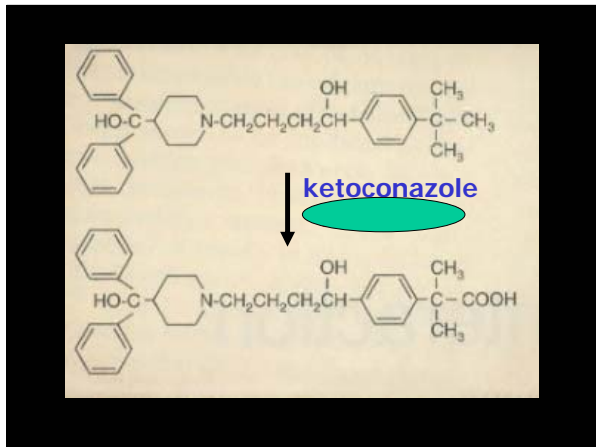
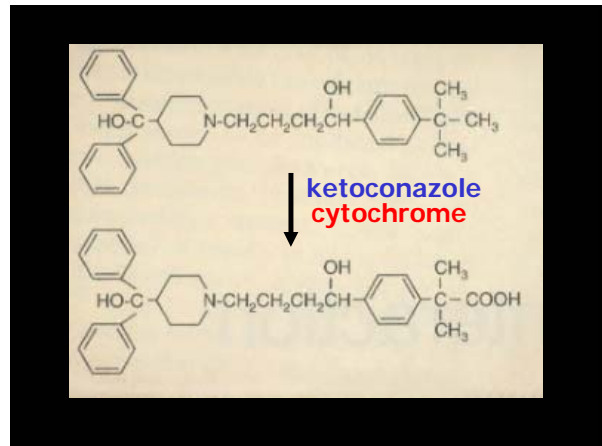
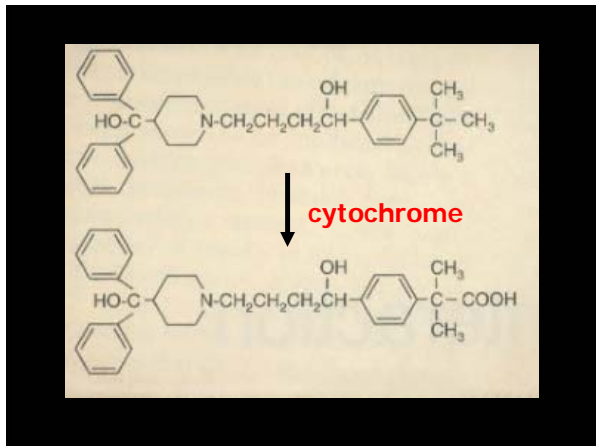
Design.—Prospective crossover study with each subject serving as his or her own control.

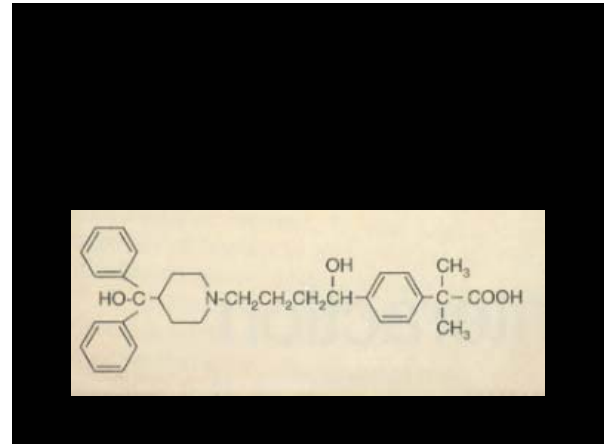
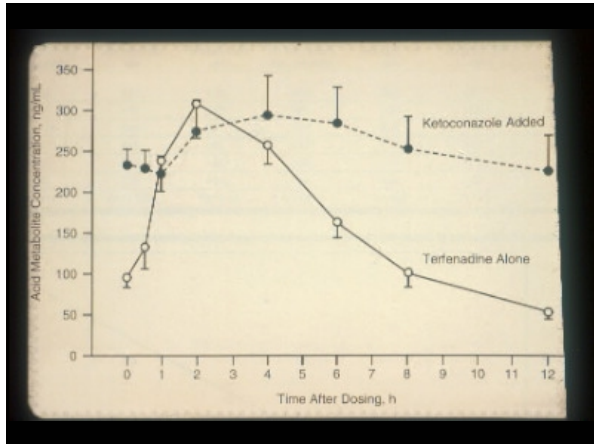
Setting.—Outpatient cardiology clinic and inpatient telemetry unit for continuous ECG.

Participants.—Six healthy volunteers (four men and two women, aged 24 to 35 years) not taking any drugs (prior or during the study) medications.

Intervention.—After achieving a steady state while taking terfenadine (60 mg every 12 hours for 7 days), daily concentrations of terfenadine (200 mg every 12 hours) were added to the study regimen. Pharmacokinetic profiles were obtained 16 hours after each 200 mg oral dose and after the addition of ketoconazole. Electrocardiograms were obtained at baseline, after 1 week of taking terfenadine alone, and at the time of the second (final) ketoconazole profile after the addition of ketoconazole to the regimen.

Results.—Ketoconazole significantly increased the plasma concentration of terfenadine (Fig. 1). As a result, it is assumed that the metabolite period (half-life) in the plasma of patients who are taking terfenadine. However, an important note is that the interaction to be a potent inhibitor of CYP3A4 (the cytochrome P-450 isozyme that metabolizes terfenadine) was not reported by the manufacturer's Reporting System of the FDA. The drug's safety profile is similar to that of terfenadine and ketoconazole. The results indicate that the FDA's safety profile is similar to that of terfenadine and ketoconazole. The results indicate that the FDA's safety profile is similar to that of terfenadine and ketoconazole.





Popular Antibiotic Increases Cardiac Arrest Risk; Erythromycin's Drug Interactions Heighten Danger

Columbian 09/09/2004

A widely used antibiotic long considered safe dramatically increases the risk of cardiac arrest, particularly when taken with some popular drugs for infections and high blood pressure, a huge study found.

The drug is erythromycin, which has been on the market for 50 years and is prescribed for everything from strep throat to syphilis.

The new study shows the need for continuing research on the safety of older medicines, including how they interact with newer drugs, said researcher Wayne A. Ray, a professor of preventive medicine at Vanderbilt University School of Medicine in Nashville.

Taken alone, erythromycin doubled the very low risk of sudden cardiac death among patients in the study.

In patients taking other drugs those that increase erythromycin's concentration in the blood the risk of cardiac death was more than five times greater, Ray and his colleagues found. That translates to six deaths for every 10,000 people taking erythromycin for the typical two weeks while on the other drugs.

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KETOCONAZOLE
CLARITHROMYCIN
CALCIUM CHANNEL BLOCKERS
PROTEASE INHIBITORS

among patients in the study.

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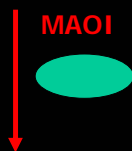
DEPRESSION

**MONOAMINEOXIDASE
INHIBITOR
MAOI**

**NOREPINEPHRINE,
SEROTONIN,
DOPAMINE**



**NOREPINEPHRINE,
SEROTONIN,
DOPAMINE**

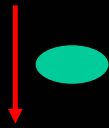


TYRAMINE

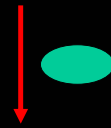
TYRAMINE

MAO
↓

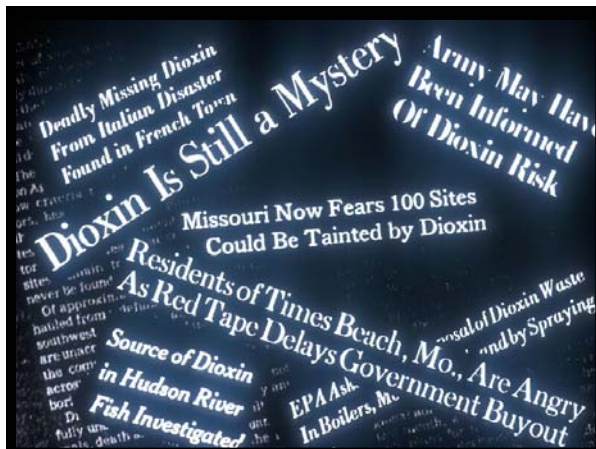
TYRAMINE



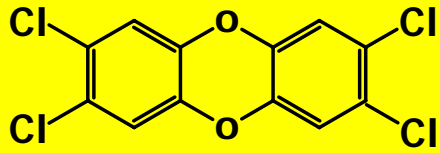
TYRAMINE



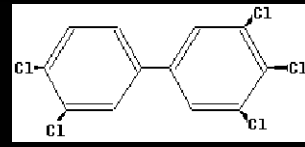
HYPERTENSION



**"THE MOST TOXIC
MAN-MADE
CHEMICAL"**



TETRACHLORODIBENZODIOXIN
TCDD



**PCBs ARE ALSO
REGARDED AS
"DIOXINS"**



PLANT HORMONES

AUXIN-1928

2,4-DICHLOROPHENOXYACETIC ACID
2,4-D

2,4,5-TRICHLOROPHENOXYACETIC ACID
2,4,5-T





**CHLORACNE
1953**



**CHLORACNE
1953
TETRACHLORODIBENZODIOXIN
TCDD**

**1969
2,4,5-T
BIRTH DEFECTS IN
MICE
TCDD**

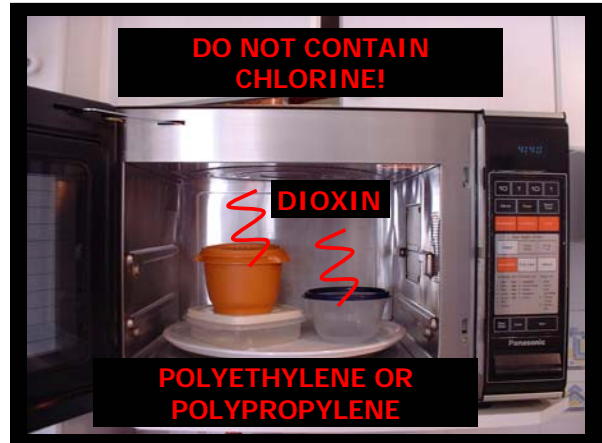
LD₅₀ DIOXIN (mg/kg body weight)

GUINEA PIG	0.001
MONKEY	0.007
RAT	0.2
DOG	3.0
HAMSTER	5.0
HUMAN	???

**THE MOST POTENT
CARCINOGEN EVER
TESTED IN ANIMALS**



**INCINERATORS CAN
PRODUCE DIOXINS**



**SEVESO, ITALY
1976**

Preliminary Report: 2,3,7,8-Tetrachlorodibenzo-p-dioxin Exposure to Humans—Seveso, Italy

AT APPROXIMATELY noon on Saturday, July 23, 1976, an explosion occurred during the production of 2,4,5-trichlorophenoxyacetic acid (TCPOA) in a factory at Seveso, about 20 km south of Milan, in the

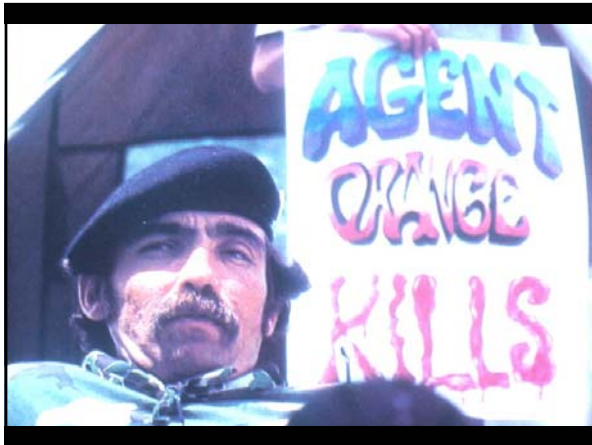
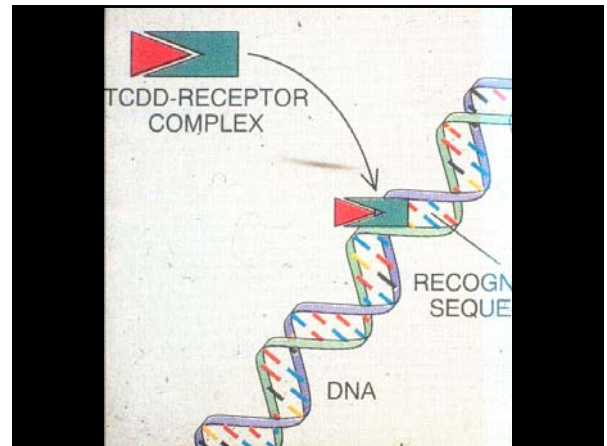
Lombardy region of Italy. A cloud of toxic material was released and settled on 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Within three days fall

of about 2.5 km² (500 acres), including parts of the towns of Inverigo, Meda, Cassinetta Marone, and Daino. The size of the contaminated area was estimated primarily by measuring TCDD in the

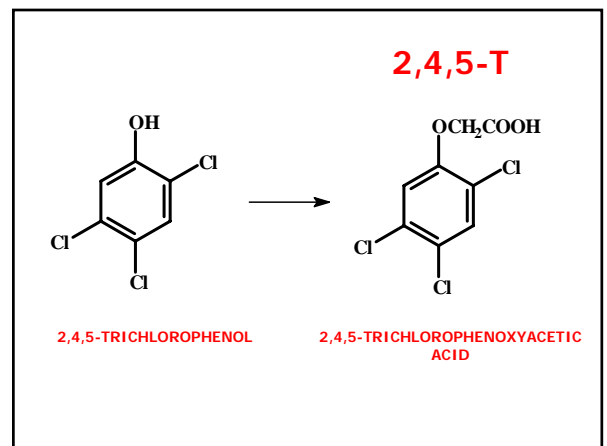
OSHA, February 10, 1980—OSHA 201, 74, 5

OSHA/HAZARDOUS WASTE 831

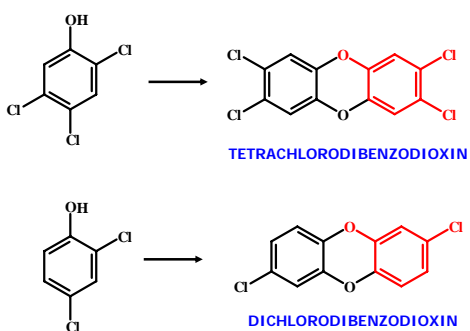
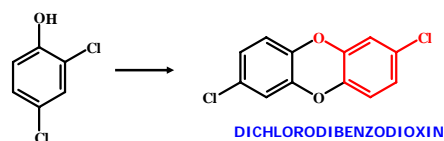
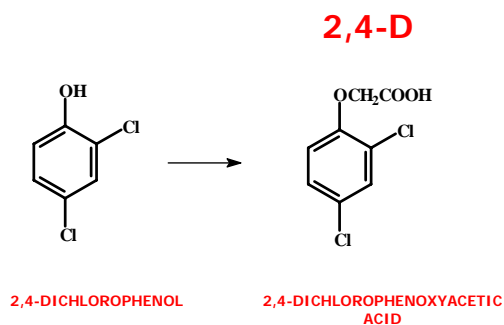
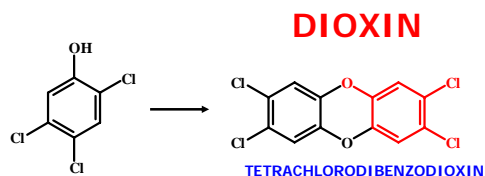
**EXPOSED MEN
FATHERED A
DISPROPORTIONATE
NUMBER OF GIRLS**



**"Post hoc, ergo propter hoc"
"After it, therefore because of it"**



SIDE REACTION



Ban urged on lawn chemicals

*Commons committee to propose act
for reducing health threat of pesticides*

**CORRELATION DOES NOT
IMPLY CAUSE AND EFFECT**

**THE BIRTH RATE IN EUROPE
DECLINED AS STORK
POPULATIONS DECLINED**



**"You don't have to be a
scientist, you don't have to do
a survey to find out - common
sense will tell you that there is
something wrong at Love
Canal"**

