

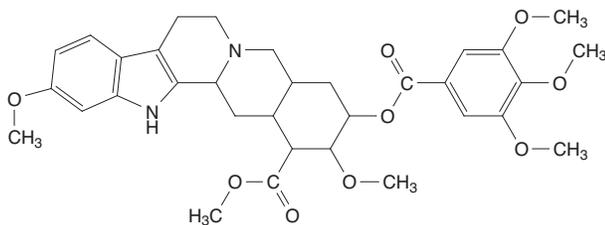
## Reserpine

### CAS No. 50-55-5

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as methyl 18 $\beta$ -hydroxy-11,17 $\alpha$ -dimethoxy-3 $\beta$ ,20 $\alpha$ -yohimban-16 $\beta$ -carboxylate 3,4,5-trimethoxybenzoate (ester)



### Carcinogenicity

Reserpine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

#### Cancer Studies in Experimental Animals

Oral exposure to reserpine caused tumors in two rodent species and at several different tissue sites. Dietary administration of reserpine caused cancer of the mammary gland in female mice, cancer of the genitourinary tract (undifferentiated carcinoma of the seminal vesicles) in male mice, and benign tumors of the adrenal gland (pheochromocytoma) in male rats (Griesemer and Dunkel 1980, IARC 1980, NTP 1982). Since reserpine was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Reserpine administered by subcutaneous injection also caused mammary-gland tumors in mice and adrenal-gland tumors (pheochromocytoma) in rats (IARC 1987).

#### Cancer Studies in Humans

Several case-control epidemiological studies examined the relationship between breast cancer and the use of reserpine (or *Rauwolfia* derivatives; see Properties); most of these studies reported statistically nonsignificant risk estimates of between 1 and 2. These studies do not provide conclusive evidence of a causal association between reserpine use and cancer (IARC 1976).

Since reserpine was listed in the *Second Annual Report on Carcinogens*, additional epidemiological studies have been identified. Case-control and cohort studies on the relationship between breast cancer and exposure to reserpine reviewed by the International Agency for Research on Cancer reported inconsistent results (IARC 1982, 1987). However, one large study reported a significantly increased risk of breast cancer among individuals who had used reserpine for over 10 years (Stanford *et al.* 1986). A review and pooled analysis of all published case-control studies found a small but significant increase in the risk of breast cancer with reserpine use; however, this finding was not confirmed by prospective studies (Grossman *et al.* 2002).

### Properties

Reserpine is a biologically active naturally occurring alkaloid (NTP 1982) that exists at room temperature as a white or pale-buff to yellow odorless powder. It is practically insoluble in water; freely soluble in chloroform, methylene chloride, and glacial acetic acid; soluble in benzene and ethyl acetate; and slightly soluble in methanol, ethanol, acetone, ether, and weak solutions of acetic and citric acids. It

is stable under normal storage conditions but is subject to oxidation and hydrolysis (Akron 2009). Reserpine acquires a yellow color with pronounced fluorescence, especially after the addition of acid or exposure to light. When heated to decomposition, it emits toxic fumes of nitrogen oxides (IARC 1976, HSDB 2009). Physical and chemical properties of reserpine are listed in the following table.

Property	Information
Molecular weight	608.7 <sup>a</sup>
Melting point	264.5°C <sup>a</sup>
Log $K_{ow}$	3.32 <sup>b</sup>
Water solubility	0.073 g/L at 30°C <sup>a</sup>
Vapor pressure	$4.51 \times 10^{-16}$ mm Hg at 25°C <sup>b</sup>
Dissociation constant ( $pK_a$ )	6.6 <sup>b</sup>

Sources: <sup>a</sup>HSDB 2009, <sup>b</sup>ChemIDplus 2009.

### Use

Reserpine is produced by several members of the genus *Rauwolfia*, a climbing shrub indigenous to southern and southeast Asia. It is used to lower blood pressure and reduce the heart rate and as a tranquilizer and sedative in humans. It has also been used as a radioprotective agent and experimentally as a contraceptive (Nakayama and Nakamura 1978, Chan and Tang 1984). Extracts of *Rauwolfia serpentina* have been used medicinally in India for centuries. They were used in traditional Hindu medicine for a variety of conditions, including snakebite, hypertension, insomnia, and insanity. Reserpine has also been used as a tranquilizer and sedative in animal feeds (IARC 1976).

### Production

Reserpine is extracted from the roots of *Rauwolfia serpentina* with alcohol or aqueous acid and then purified. In 1976, the volume of reserpine sold in the United States for medical use was approximately 440,000 lb. In 1974, there were six U.S. producers of reserpine (IARC 1976). In 2009, reserpine was produced by seven manufacturers, all in India (SRI 2009); it was available from 12 U.S. suppliers (ChemSources 2009), and four drug products approved by the U.S. Food and Drug Administration containing reserpine as an active ingredient were manufactured by two pharmaceutical firms (FDA 2009). In addition, over 100 discontinued drug products from over 40 pharmaceutical firms were identified as containing reserpine as an active ingredient. U.S. imports of reserpine totaled 22 lb in 1970 and 103 lb in 1983 and 1984, while U.S. exports of reserpine were negligible (HSDB 2009). No more recent information on U.S. imports or exports of reserpine was found.

### Exposure

Patients receiving therapy for hypertension may be exposed to reserpine, which is administered orally. Numerous advertisements for the sale of *Rauwolfia serpentina* and extracts from the plant as herbal products or for homeopathic medicine were identified on the Internet in 2010. The use of reserpine as a drug may result in its release to the environment in various waste streams. Occupational exposure may occur through inhalation or dermal contact at workplaces where reserpine is produced or used (HSDB 2009). Health professionals such as doctors, nurses, and pharmacists may be exposed while dispensing, preparing, or administering the drug. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 5,611 workers, including 2,414 women, potentially were exposed to reserpine (NIOSH 1990).

## Regulations

### Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

### Environmental Protection Agency (EPA)

#### Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 5,000 lb.

#### Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of reserpine = U200.

Listed as a hazardous constituent of waste.

### Food and Drug Administration (FDA, an HHS agency)

Reserpine is a prescription drug subject to labeling and other requirements.

All oral dosage drug products containing more than 1 mg of reserpine have been withdrawn from the market and may not be compounded, because such drug products were found to be unsafe or not effective.

## Guidelines

### National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

### Occupational Safety and Health Administration (OSHA, Dept. of Labor)

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